Management of Cirrhosis in Primary Care

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UCLA Family Medicine Grand Rounds

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Disclosures

- None

Objectives

- By the end of this lecture, you should be able to:
  - Identify high risk patient populations who need screening for cirrhosis
  - Determine the prognosis of a patient with cirrhosis
  - Educate patients on risk reduction to prevent or slow down progression of cirrhosis
  - Apply screening guidelines to patients with cirrhosis
  - Manage complications of cirrhosis in the outpatient setting

Epidemiology

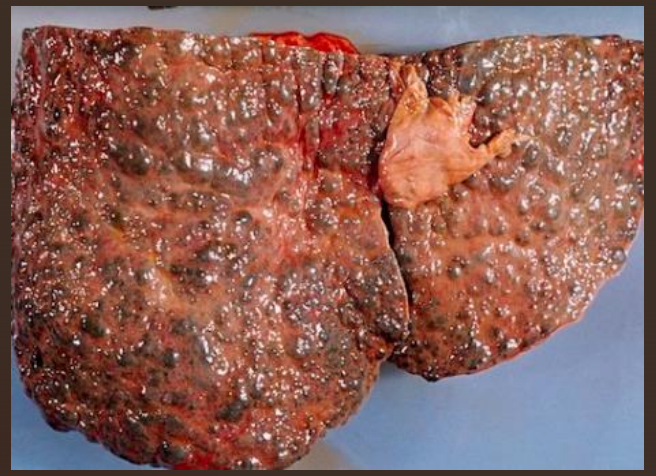
- Prevalence in US in 2015: 0.27% (633,323 people)
- 12th leading cause of death in the US
- 69% of patients who were diagnosed with cirrhosis were not aware they had liver disease
- Prevalence is higher in African-Americans, Mexican-Americans, those living below poverty level, and those with less than a 12th grade education
- Mortality: 24.6% per 2 year interval

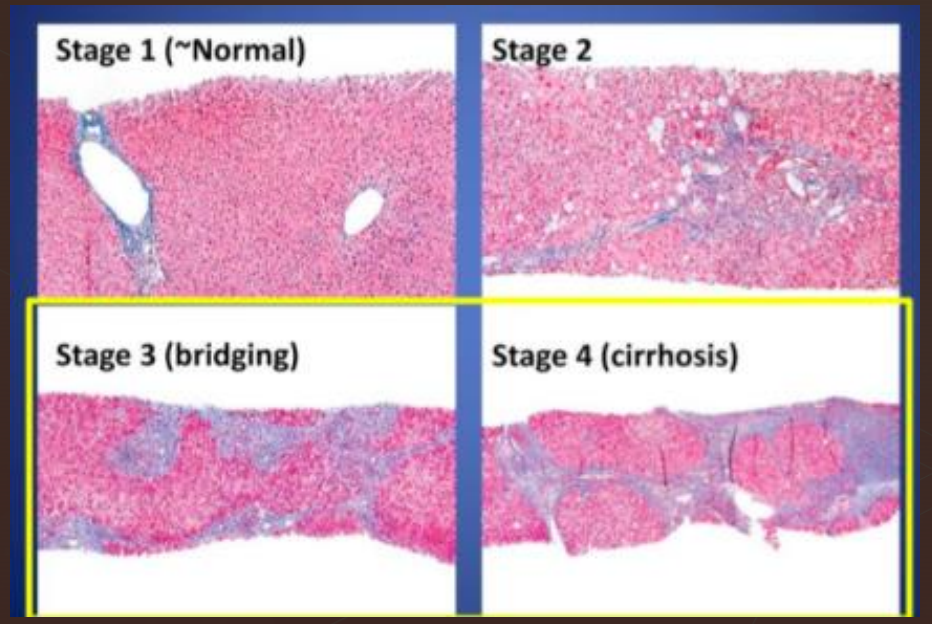
Etiologies

- Viral
  - Hepatitis B: 15%
  - Hepatitis C: 47%
- Alcohol: 18%
- Non-alcoholic fatty liver disease
- Autoimmune
- Sarcoidosis
- Medications: methotrexate, INH
- Genetic: primary biliary cirrhosis, alpha-1 anti-trypsin deficiency, hemochromatosis, Wilson’s disease
- Budd-Chiari syndrome (venoocclusive disease)
- Unknown: 14%

Pathophysiology

- Cirrhosis: end stage of chronic liver disease of different etiologies
- Characterized by bridging fibrosis and nodules on liver biopsy
- Leads to portal hypertension



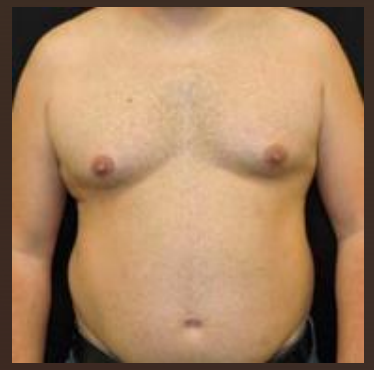


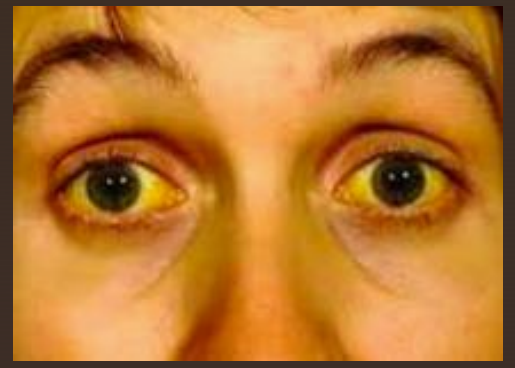
Diagnosis

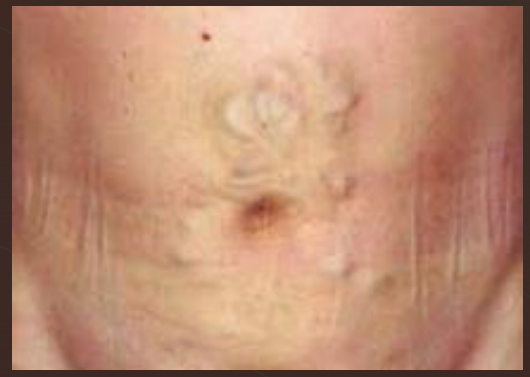
- Early cirrhosis is asymptomatic
- Suspect liver disease/cirrhosis if:
  - Risk factors: alcohol use, metabolic syndrome, family history, IV drug use, high risk sexual activity, blood transfusion before 1990
  - Lab findings: transaminitis, elevated INR, elevated bilirubin, low albumin, hyponatremia, thrombocytopenia, leukopenia, anemia
  - Physical exam findings

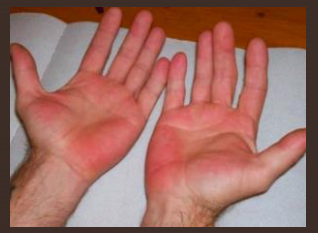
Diagnosis

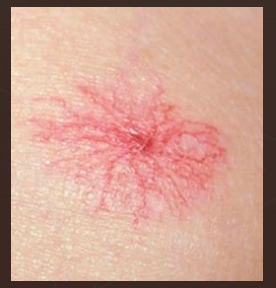
- Physical exam
  - Jaundice
  - Abdominal distension (ascites)
  - Spider angiomata
  - Gynecomastia
  - Hypogonadism
  - Caput medusae
  - Palmar erythema
  - Splenomegaly
  - Peripheral edema
  - Asterixis



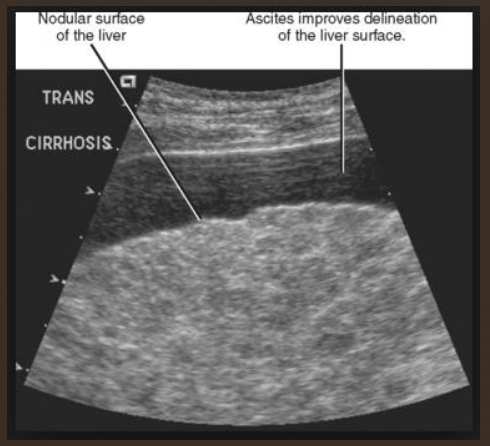








Diagnosis



- Imaging studies
  - Abdominal ultrasound: 91% sensitive, 94% specific
    - Liver is small and nodular
    - Portal hypertension, splenic enlargement, ascites
  - CT: not routinely used
  - MRI: can accurately diagnose cirrhosis and possibly severity, but limited by expense
  - Elastography: increased stiffness of tissue from scarring
- Liver biopsy (gold standard)
- Non-invasive scoring systems: APRI, FIB-4 index

Prognosis

- Compensated cirrhosis
  - Patients with cirrhosis who have not developed major complications
  - Median survival > 12 years, lower if varices present
- Decompensated cirrhosis
  - Patients who have developed complications: variceal hemorrhage, ascites, spontaneous bacterial peritonitis, hepatocellular carcinoma, hepatorenal syndrome
- Use of predictive models

Prognosis

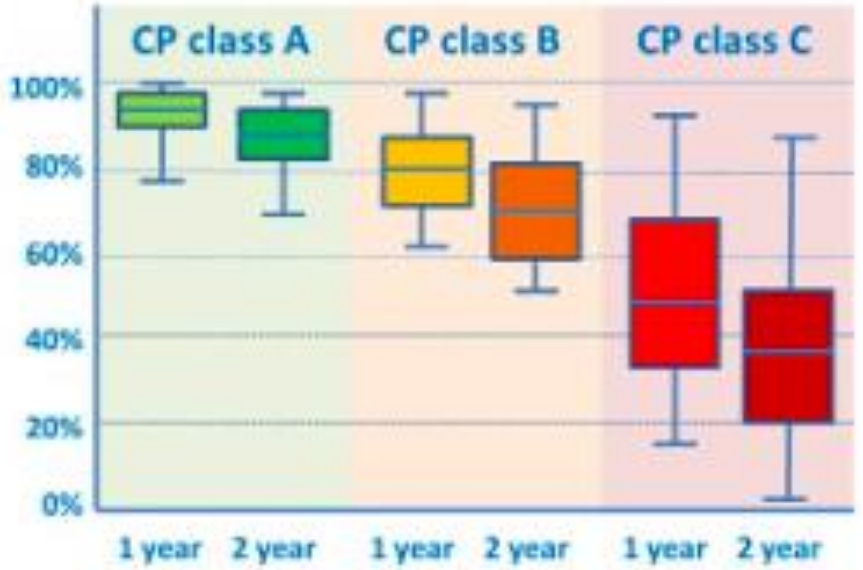
- Child-Pugh classification

Child Pugh Score

Criteria	1	2	3
Encephalopathy	None	Mild	Severe
Ascites	None	Controlled	Uncontrolled
Bilirubin	≤ 33	34-50	≥ 51
Albumin	≥ 36	28-35	≤ 27
INR	≤ 1.6	1.7-2.2	≥ 2.3

Class	A = 5-6 pts	B = 7-9 pts	C = 10-15 pts

Survival by Child Pugh Class



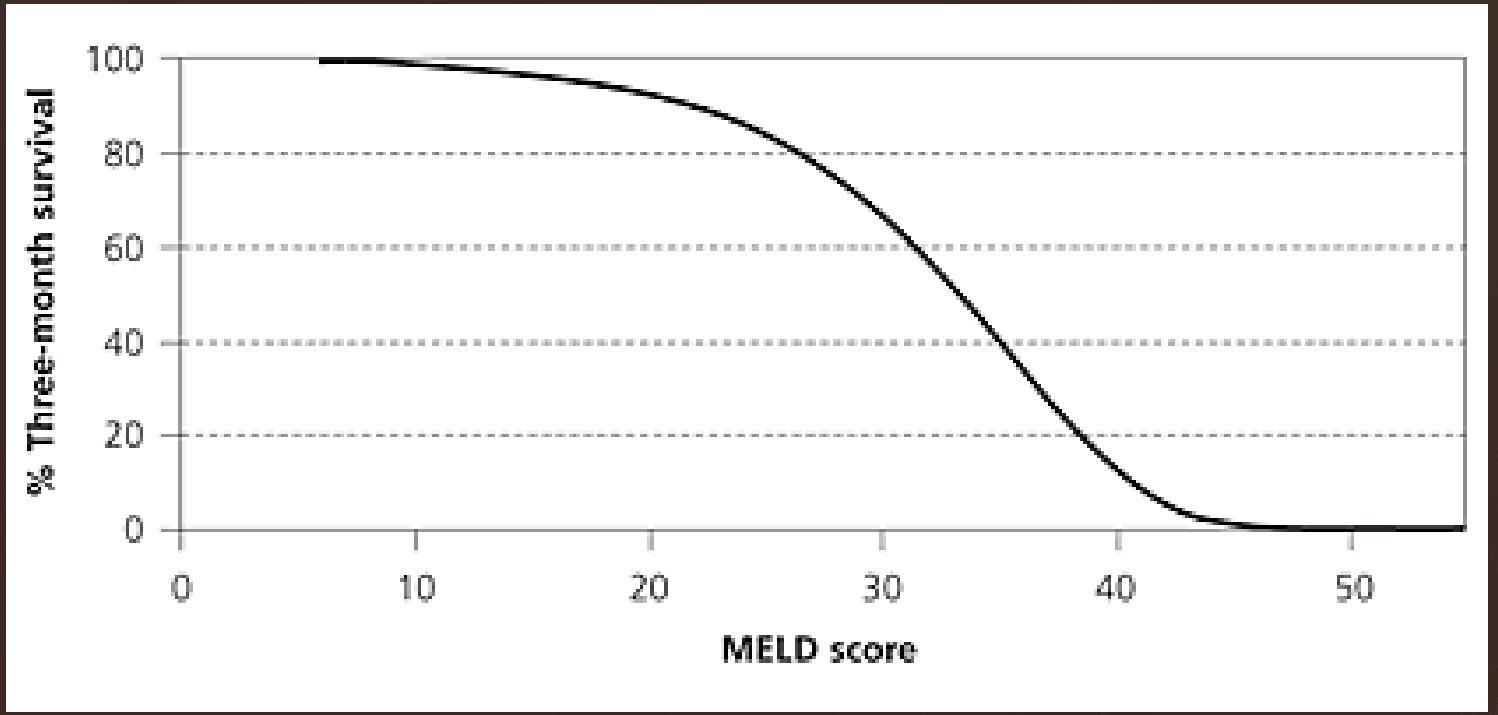
Pooled analysis on prognosis from 118 studies (n=23,797)

Adapted from D'Amico G, et al. J Hepatol 2006; 44: 217-231.

Prognosis

MELD score*	9.6 * $\log_e$ (creatinine mg/dL) + 3.8 * $\log_e$ (bilirubin mg/dL) + 11.2 * $\log_e$ (INR) + 6.4
MELD-sodium†	MELD + 1.59 * (135-Na [mEq/L])

- MELD (model for end stage liver disease): used to prioritize patients for transplant



Management

Interventions to Reduce Progression

- Establish etiology
- Evaluate for co-morbidities: HIV, Hepatitis B, Hepatitis C
- Abstinence/cessation of alcohol consumption
- Treat obesity
- Vaccination
- Avoid herbal supplements
- Counsel on nutrition

Treatment of Underlying Cause

Diagnostic tests, suggested etiology, and current treatment for the most frequent forms of liver cirrhosis in adult patients

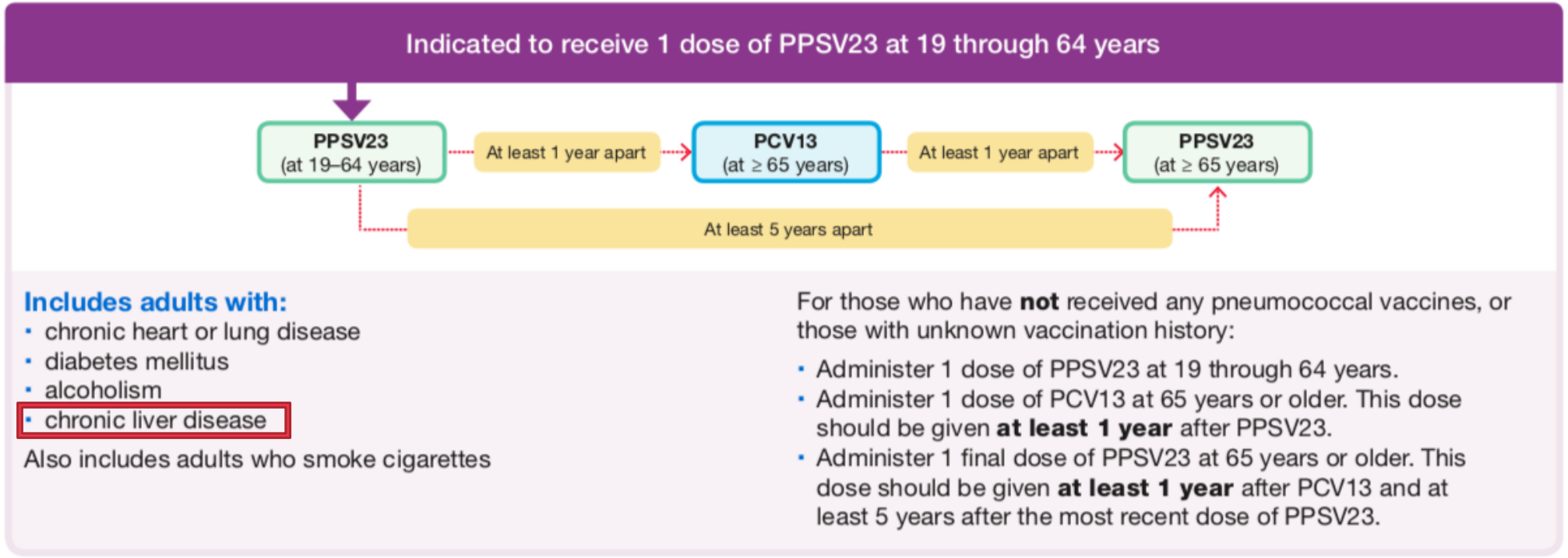
Abnormal test(s)	Etiology	Treatment
γGT (high), MCV (high)	Alcohol	Abstinence
HBsAg, HBV-DNA, HBc-IgM, HDV-RNA (positivity)	HBV + Delta virus infection	Interferon α-2b, nucleoside (Lamivudine, Telbivudine, Entecavir) and nucleotide (Adefovir, Tenofovir) analogues
HCV-RNA (positivity)	HCV infection	Interferon plus ribavirin
γGT (high), alkaline phosphatase (high), AMA (positivity)	Primary biliary cirrhosis	Ursodeoxycholate
ANA, ASMA, LKM (positivity)	Autoimmune hepatitis	Prednisone, azathioprine
Ferritin (high), transferring saturation index (> 45%), liver iron content (high), *HFE* gene mutation for hereditary hemochromatosis (C282Y, H63D)	Hemochromatosis	Phlebotomy, deferoxamine
Ceruloplasmin (low), serum (low) and 24 h urine copper excretion (high)	Wilson's disease	D-penicillamine, zinc
HDL-cholesterol (low), glucose (high), triglycerides (high)	NAFLD/NASH	Low caloric diet, exercise, drugs lowering insulin-resistance

Immunizations

- Hepatitis A
- Hepatitis B
- Pneumococcal vaccination (PCV13 and PPSV23)
- Influenza yearly

https://www.cdc.gov/vaccines/adults/rec-vac/health-conditions/liver-disease.html

Pneumococcal vaccine timing for adults with certain medical conditions



https://www.cdc.gov/vaccines/adults/rec-vac/health-conditions/liver-disease.html

Nutrition

- 20% of patients with compensated cirrhosis and 60% of patients with decompensated cirrhosis have malnutrition (especially EtOH cirrhosis)
- Assess nutrition with the Subjective Global Assessment (SGA)
- Protein: 1.2-1.5 g/kg/day
- If cirrhosis and ascites present, Na restriction to < 2g a day
- Fluid restriction if hyponatremia present (Na < 125)
- MVI to prevent micronutrient deficiency
- Calorie (but not protein) restriction if overweight with NASH

Management of Complications of Cirrhosis

Osteoporosis

- Pathophysiology unclear, thought to be multifactorial from toxic effects, chronic inflammation and hormone imbalances
- Patients with cirrhosis have a 2x higher fracture risk compared to patients without cirrhosis
- Patients with cirrhosis are susceptible to fractures of different bones: vertebrae, femoral neck, and distal radius
- Only complication that worsens after transplant (due to immunosuppression)

Osteoporosis

- Screening
  - Get DEXA once upon diagnosis of cirrhosis and then repeat every 2-3 years
  - Bone density can be falsely elevated by presence of ascites -> get DEXA after paracentesis
  - Study showed patients with cirrhosis from PBC had increased fracture risk with T score <-1.5

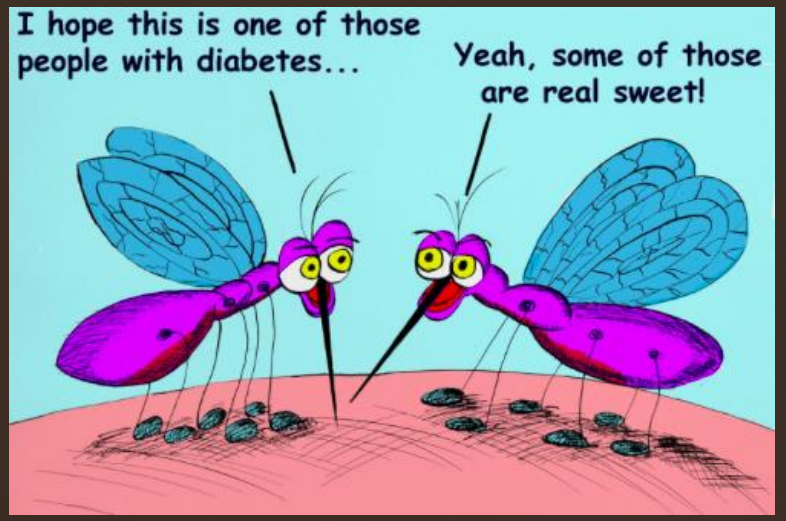
Osteoporosis

- Treatment
  - Tobacco and alcohol cessation
  - Increasing weightbearing exercises
  - Calcium: 1.0-1.5 grams a day, preferably in food
  - Vitamin D: recommend calcitriol, unclear dose
  - Calcitonin: controversial
  - Hormone replacement
    - 33 post-menopausal women 2 years after OLT given transdermal estradiol with increase in lumbar BMD by 5.3%

Osteoporosis

- Bisphosphonates
  - Concern for theoretical risk of ulceration on esophageal varices with oral bisphosphonates (low)
  - Millonig et al: 136 patients with osteoporosis and cirrhosis took alendronate 70 mg weekly after OLT, showed improvement in BMD
  - Bodingbauer et al: 96 patients after OLT received monthly zoledronic acid 4 mg x 1 year, showed decrease in vertebral fractures but no difference in BMD
  - Bansal at al: 47 cirrhotic patients before transplant (most were decompensated cirrhotic patients with ascites and varices, most were EtOH cirrhosis) received ibandronate 150 mg PO monthly -> only 19 patients completed the study but had significant increase in T-scores

Diabetes



- Types
  - Conventional type 2 diabetes mellitus
  - Hepatogenous diabetes: chronic liver disease causes diabetes
- Pathophysiology
  - Liver maintains glucose metabolism by storing glucose and producing endogenous glucose from glycogen stores
  - Decreased hepatocytes leads to hyperinsulinemia, which causes downregulation of insulin receptors in cells and increase in pancreatic activity leading to burn out
- Higher prevalence of diabetes in Hepatitis C cirrhosis

Diabetes

- Diagnosis
  - HgbA1C: may be falsely low in cirrhosis due to red blood cell turnover due to hypersplenism
  - Fasting blood sugar: cutoff of >126, patients with cirrhosis more likely to have elevated postprandial glucose levels and normal fasting levels
  - Recommend oral glucose tolerance test (OGTT) for diagnosis of diabetes if high suspicion

Hepatocellular Carcinoma

- HCC is the major cause of liver-related death in patients with compensated cirrhosis
- Risk of HCC is dependent on the underlying cause of cirrhosis (5 year cumulative risks in the US)
  - Hemochromatosis: 21%
  - HCV cirrhosis: 17%
  - HBV cirrhosis: 10%
  - Alcoholic cirrhosis: 8-12%
  - Primary biliary cirrhosis: 4%
- Increased risk in HBV/HCV and HBV/HDV co-infections

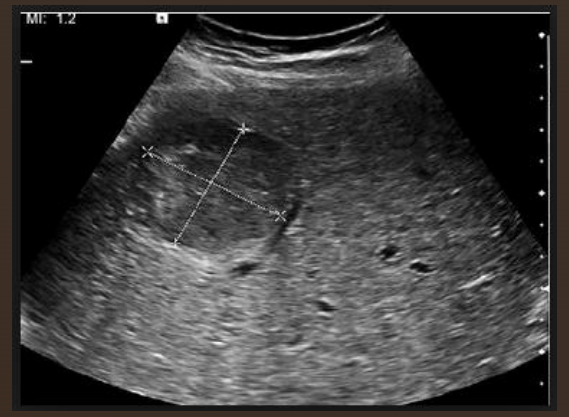
Hepatocellular Carcinoma

Burden of the main risk factors for HCC in United States.

	Prevalence in general US population	Risk estimate of HCC*	Current prevalence in HCC cases	Population attributable fraction
HBV	0.5–1%	20–25	10–15%	5–10%
HCV	1–2%	20–25	30–60%	20–25%
Alcoholic liver disease	10–15%	2–3	20–30%	20–30%
Metabolic syndrome	30–40%	1.5–2.5	20–50%	30–40%

* Compared to controls without risk factor

Hepatocellular Carcinoma



- All patients with cirrhosis should be screened for HCC every 6-12 months
- AASLD surveillance guidelines
  - Abdominal ultrasound: 94% sensitive for identifying HCC at all stages and 63% for early stage
    - Study of 163 patients at the VA comparing US with CT showed US was just as effective at HCC detection
  - AFP: NOT recommended alone or in combination with ultrasound
    - 2009 meta-analysis: not better at detecting HCC, higher false positive rate and not cost-effective

Ascites

- Pathophysiology
  - Portal hypertension in cirrhosis causes increase in hydrostatic pressure within the splanchnic bed
  - Decreased protein synthesis causes decreased oncotic pressure
- New onset ascites should undergo diagnostic paracentesis
  - Check ascitic fluid cell count and differential, ascitic total protein, and serum-ascites albumin gradient, ascitic LDH, culture
  - SAAG: >1.1 g/dL confirms portal hypertension or heart-failure associated cirrhosis
  - Rule out alternate cause of ascites such as inflammatory causes or peritoneal carcinomatosis

Ascites

- Treatment
  - Sodium restriction: < 2g Na a day
  - Fluid restriction: only if hyponatremia present (Na < 125)
  - Diuretic-sensitive
    - Small volume ascites: spironolactone 50 mg daily + furosemide 20 mg daily
    - Large volume ascites: titrate dose upward every 3-5 days as tolerated, maintain 100/40 ratio
  - Diuretic-refractory
    - Serial therapeutic paracenteses
    - Transjugular intrahepatic portosystemic stent-shunt (TIPS)
    - Expedited referral for liver transplant

Ascites

- Consider stopping beta-blockers in patients with refractory ascites as it may shorten survival
- Avoid ACE-I and ARBs: lower arterial blood pressure, which decreases survival rates
- Avoid NSAIDs: decrease response to diuretics
- Can use oral midodrine to help with blood pressure: improves clinical outcomes and survival in patients with refractory ascites

Spontaneous Bacterial Peritonitis

- Rule out spontaneous bacterial peritonitis with any signs or symptoms of infection
  - Paracentesis: ascitic fluid PMN > 250 cells/mm^3
  - If positive, patients should receive antibiotics within 6 hours if hospitalized and within 24 hours if ambulatory
- Consider empiric antibiotics with one or more of the following:
  - Temperature > 38 C
  - Abdominal pain/tenderness
  - Mental status change
- Treatment: third-generation cephalosporin

Spontaneous Bacterial Peritonitis

- Prophylaxis
  - Diuretic therapy: decreases ascitic fluid
  - Early recognition and treatment of localized infections: cellulitis, cystitis
  - Restrict PPI use: linked to increased risk of SBP
  - Antibiotic prophylaxis: for select groups of patients

Spontaneous Bacterial Peritonitis

- Acute (inpatient)
  - *Patients with cirrhosis and GI bleeding*
    - Ceftriaxone 1g IV daily
    - Switch to oral once bleeding controlled and tolerating food
      - Trimethoprim-sulfamethoxazole DS daily
      - Ciprofloxacin 500 mg daily
    - Treat for total of 7 days
  - *Patients with cirrhosis admitted with no GI bleeding and ascitic fluid protein < 1.0 g/dL* -> treat while inpatient, discontinue at discharge
    - Trimethoprim-sulfamethoxazole DS daily
    - Ciprofloxacin 500 mg daily

Spontaneous Bacterial Peritonitis

- Chronic (outpatient)
  - *Patients with one or more episodes of SBP* (1 yr recurrence 70%)
  - *Patients with cirrhosis and ascitic fluid protein < 1.5 (g/dL)* ***AND*** *one of the following:*
    - Creatinine > 1.2
    - BUN > 25
    - Serum Na < 130
    - Child-Pugh score > 8 AND bilirubin > 3
  - Antibiotic therapy
    - Trimethoprim-sulfamethoxazole DS daily
    - Ciprofloxacin 500 mg daily

Hepatic Encephalopathy

- Pathophysiology
  - Toxic compounds (ammonia) generated by gut bacteria are transported by portal vein to the liver, which is unable to metabolize it in cirrhosis
- West Haven Criteria Grading System of Hepatic Encephalopathy
  - Grade I: changes in behavior, mild confusion, slurred speech, sleeping but arousable, mild asterixis
  - Grade II: lethargy, moderate confusion, pronounced asterixis
  - Grade III: marked confusion (stupor), incoherent speech, sleeping but arousable, pronounced asterixis
  - Grade IV: coma, unresponsive to pain
- Patients with hepatic encephalopathy should be counseled about no driving

Hepatic Encephalopathy

- Management
  - Rule out alternate causes of altered mental status
  - Evaluate for precipitating cause
    - Gastrointestinal bleeding
    - Infection: SBP, urinary tract infections
    - Electrolyte abnormalities
    - Renal failure
    - Hypovolemia
    - Hypoxia
    - Medications/drugs
    - Hypoglycemia

Hepatic Encephalopathy

- Treatment: lower blood ammonia levels
  - Treatment of hypokalemia: low K increases renal ammonia production
  - Lactulose
    - Non-absorbable disaccharide that decreases absorption of ammonia and modifies colonic flora to non-urease producing bacterial strains
    - 30-45 mL (20-30 grams) PO BID to QID, titrate to 2-3 soft stools a day
    - Can give lactulose enema if patient cannot take it orally
  - Rifaximin
    - Antibiotic to decrease intestinal ammonia-producing bacterial strains
    - Also can help decrease SBP
    - 550 mg PO BID or 400 mg PO TID

Hepatic Encephalopathy

- L-ornithine-L-aspartate
  - Used outside US
  - Lowers plasma ammonia levels by enhancing the metabolism of ammonia to glutamine
  - Zhu GQ et al: meta-analysis of four trials showed patients with overt hepatic encephalopathy who received L-ornithine-L-aspartate were more likely to improve clinically compared to those receiving placebo (OR 3.71, 95% CI 1.98-6.98)

Hepatic Encephalopathy

- Branched-chain amino acids (BCAA)
  - Thought that cirrhosis leads to increased ratio of plasma aromatic amino acids (AAA) to branched-chain amino acids (BCAA) , which causes increased AAA precursors for monoamine neurotransmitter production, which contributes to neuronal excitability
  - Gluud LL et al: meta-analysis of 16 trials with 827 participants with hepatic encephalopathy showed no improvement in mortality but did show improvement in manifestations of hepatic encephalopathy (RR 0.7, 95% CI 0.6-0.9)

Hepatic Encephalopathy

- Probiotics
  - Favor colonization of gut with non-urease producing bacteria
  - Dalal et al: meta-analysis of 21 trials with 1420 patients showed improvement in recovery and reduced plasma ammonia concentrations compared to placebo, but not compared to lactulose

Esophageal Varices

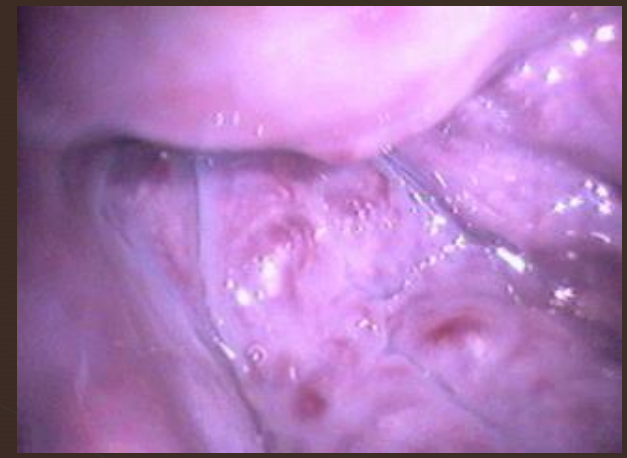
- Screening for esophageal varices: endoscopy
  - Compensated cirrhosis
    - Screening endoscopy should be performed within 12 months of diagnosis
    - No varices: repeat every 2-3 years
  - Decompensated cirrhosis
    - Screening endoscopy should be performed within 3 months of diagnosis
    - No varices: repeat every year

Esophageal Varices

- Prophylaxis
- Pre-primary prophylaxis
  - No evidence to start beta blockers in patients with portal hypertension who have not yet developed varices
- Primary prophylaxis
  - Pharmacological: non-selective beta blocker
  - Endoscopic: endoscopic variceal ligation (EVL)

Esophageal Varices

- Patients who should get primary prophylaxis
  - Child B or Child C cirrhosis
  - Medium or large varices
  - Small varices with red signs
- Patients with Child A cirrhosis with small varices without red signs should be monitored with routine endoscopy every 1-2 years



Esophageal Varices

- Non-selective beta blockers
  - Mechanism
    - Decrease portal venous inflow
    - NNT to prevent one episode of bleeding = 11
    - Cardio-selective beta blockers do not reduce portal venous pressure as much and have not been validated in large-scale clinical trials
  - Factors leading to beta blockers not being as effective
    - Younger age
    - Large varices
    - Advanced liver failure
    - Lower doses of beta-blockers

Esophageal Varices

- Medications
  - Propranolol 20 mg BID
  - Nadolol 40 mg daily
  - Carvedilol 6.25 mg BID
    - Non-selective beta blocker with mild anti-alpha 1 adrenergic activity
    - Reduces hepatic vascular tone and hepatic resistance which also reduces portal pressure
    - Usually not tolerated by patients due to drops in blood pressure

Esophageal Varices

- Side effects from beta blockers
  - Bronchoconstriction
  - Hypotension
  - Increased mortality if used in patients with refractory ascites
    - Serste T et al: prospective study of 151 patients with cirrhosis and refractory ascites showed median survival was 20 months without propranolol versus 5 months with propranolol
    - Mechanism: reduce cardiac output which is a strong predictor of hepatorenal syndrome, or worsen hypotension with sepsis/SBP

Key Recommendations for Practice

- Screening and prevention
  - All patients should be screened for alcohol abuse (SORT B)
  - All pregnant women should be screened for Hepatitis B (SORT A)
  - Patients who have cirrhosis associated with a MELD score of 15 or more, or with any complications of cirrhosis should be referred to a transplant center (SORT A)
  - Patients with cirrhosis should be screened for hepatocellular carcinoma every 6-12 months (SORT B)

Key Recommendations for Practice

- Ascites
  - Treat ascites with salt restriction and diuretics (SORT A)
  - Patients with new-onset ascites should receive diagnostic paracentesis consisting of cell count, total protein, albumin level and bacterial culture and sensitivity (SORT C)
  - If ascitic fluid PMN count is greater than 250 cells/mm^3, the patient should receive antibiotics within six hours if hospitalized and within 24 hours if ambulatory (SORT A)

Key Recommendations for Practice

- Hepatic encephalopathy
  - Patients with hepatic encephalopathy should have paracentesis performed during the hospitalization in which the encephalopathy is diagnosed (SORT C)
  - Persistent hepatic encephalopathy should be treated with disaccharides or rifaximin (SORT B)
  - Patients with hepatic encephalopathy should be counseled about not driving (SORT C)

Key Recommendations for Practice

- Esophageal varices
  - Screening endoscopy for esophageal varices should be performed within 12 months in patients with compensated cirrhosis, and within three months in patients with decompensated cirrhosis (SORT B)
  - Patients with cirrhosis and medium or large varices should receive beta blockers and/or have endoscopic variceal ligation performed (SORT A)

Dotphrase on Care Connect for Cirrhosis Routine Health Maintenance:

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"Any questions?"