Management of Cirrhosis in Primary Care

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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
Prognosis

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

\[
\text{MELD score}^* = 9.6 \times \log_{e} (\text{creatinine mg/dL}) + 3.8 \times \log_{e} (\text{bilirubin mg/dL}) + 11.2 \times \log_{e} (\text{INR}) + 6.4
\]

\[
\text{MELD-sodium}^\dagger = \text{MELD} + 1.59 \times (135 - \text{Na [mEq/L]})
\]
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

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

Indicated to receive 1 dose of PPSV23 at 19 through 64 years

PPSV23 (at 19–64 years) → At least 1 year apart → PCV13 (at ≥ 65 years) → At least 1 year apart → PPSV23 (at ≥ 65 years)

Includes adults with:
- chronic heart or lung disease
- diabetes mellitus
- alcoholism
- chronic liver disease

Also includes adults who smoke cigarettes

For those who have not received any pneumococcal vaccines, or those with unknown vaccination history:
- Administer 1 dose of PPSV23 at 19 through 64 years.
- Administer 1 dose of PCV13 at 65 years or older. This dose should be given at least 1 year after PPSV23.
- Administer 1 final dose of PPSV23 at 65 years or older. This dose should be given at least 1 year after PCV13 and at least 5 years after the most recent dose of PPSV23.

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

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

* 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/mm³
  - 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/mm³, 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:

.cirrhosisrhm
References

“Any questions?”