PORTAL HYPERTENSION AND CIRRHOSIS

Raed Abughazaleh, PharmD, BCPS
PHAR 551: Pharmacotherapy I
Birzeit University

Background

- Cirrhosis: advanced stage of liver fibrosis due to chronic liver injury
- Fibrosis: replacement of injured tissue collagenous scar due to abnormal healing
- "Cirrhosis": orange-yellow
- Cirrhosis is irreversible, progressive, and leads to various complications: portal HTN, hepatocellular carcinoma, impaired hepatic function, hepatorenal syndrome, variceal bleeding, ascites, hepatic encephalopathy, SBP..

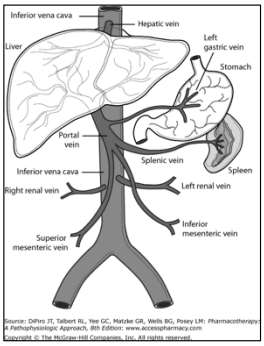
Epidemiology & Etiology

- Common causes: chronic alcohol consumption, chronic viral hepatitis (B, C, D), immunologic disorders (e.g., autoimmune hepatitis), metabolic disorders (e.g., Cystic fibrosis), vascular disease (e.g., CHF), drugs (e.g., INH, amiodarone, MTX, retinol)..
- Western world → primary causes are excessive alcohol intake and Hepatitis C
- Rest of world → hepatitis B is the primary cause for liver cirrhosis

Epidemiology & Etiology

- Acute vs. Chronic viral hepatitis
- Clinical signs of chronic liver damage typically occur after the 4th decade of life
- Once it develops, disease progression course is the same regardless of initial cause
- Main mortality-related complications: SBP and variceal bleeding
- Approx. 50% of pts with cirrhosis will develop ascites within 10 years
- Approx 30-40% will experience variceal bleeding
- Nearly half of those who develop ascites will die within 2 years

Pathophysiology



Pathophysiology

- Sinusoidal damage from cirrhosis is the most common cause for portal HTN
  - Normal portal pressure = 5-10 mmHg
  - Portal HTN: > 10-12 mmHg
- Reduced hepatic flow consequences
  - Reduced metabolic and detox capacity → consequence on drug metabolism
  - Reduced protein synthesis
  - Bilirubin accumulation
  - Changes in steroid hormone production → decreased libido, gynecomastia, feminization in men..
  - Splenomegaly → thrombocytopenia
  - RAAS activation → Na and H_2O retention

Pathophysiology

- Ascites
  - Accumulation of fluid in peritoneal space
  - Decompensated cirrhosis, poor prognosis
  - ↓ Albumin, ↑ RAAS, ↑ portal/splanchnic pressure, renal compensation via ↑ RAAS
- Hepatorenal syndrome (HRS)
  - Rapid decline in renal fcn in decomp. cirrhosis
  - Untreated 14-d mortality = 50%
  - Renal hypoperfusion leads to compensation mechanisms that eventually gets overwhelmed
  - Type 1 Vs. Type 2
  - SBP and NSAIDs are common triggers

Pathophysiology

- Varices
  - Collateral vessels that develop in esophagus, stomach, and rectum as shunting mechanism
  - Decreased first pass metabolism
  - Increased bleeding risk (e.g., esophageal)
- SBP
  - Isolated (spontaneous) ascitic bacterial infection
  - Intestinal bacterial translocation via lymph nodes Vs. hematogenous translocation
  - Most common bugs: *Kleb pneumoniae*, *E. coli, pneumococci*
  - 10-30% incidence in ascitis

Pathophysiology

- Hepatic encephalopathy (HE)
  - Toxin build-up 2/2 hepatic bypass mechanisms can lead to encephalopathy
  - Ammonia (NH_3) is one of the toxins with a strong association with encephalopathy
  - S/S: AMS, confusion, behavioral changes, asterixis, elevated NH_3 levels
  - Precipitating factors usually exist
  - Acute HE is reversible, chronic is not

Pathophysiology

- Coagulopathies
  - Signal end-stage liver disease
  - Failure of liver to synthesize pro- and anti-coagulation factors
  - Increased PT/INR, elevated INR (fixed INR)
  - Thrombocytopenia 2/2 splenic sequestration and reduced PLT production by bone marrow
  - Macrocytic anemia 2/2 poor diet and low storage of folate and vitamin B_{12}
  - Ethanol is toxic to bone marrow and may independently cause blood abnormalities

Clinical Presentation

- May be asymptomatic till complications develop
- S/S related to specific complications
  - Symptoms: weakness, hormonal changes, hematochezia, hempotysis, abdominal pain, nausea, tight abdomen..
  - Signs: AMS, jaundice, bruising, splenomegaly, gynecomastia, ascites, signs of infection..

Clinical Presentation

- Labs
  - ALT/AST elevation early in disease
  - ALT/AST = 1:2 in alcoholic cirrhosis
  - Total and direct bilirubin
  - Platelets
  - Anemia
  - PT/INR- one of the best markers of progression
  - Serum albumin
  - Blood ammonia
  - SCr
  - Diagnostic paracentesis if SBP suspected

Diagnosis

- Definitive diagnosis needs biopsy however is presumed based on presenting complications
- Ascites or varices confer a diagnosis of portal HTN
- Ultrasound and CT reveal small nodular liver
- Child-Pugh Classification
  - Variables: T. Bil., albumin, PT/INR, ascites, HE
  - Used to determine disease severity
  - Grade A, B, C (increasing severity)

Diagnosis

- MELD Score
  - Variables: Cr, T. Bil, INR
  - More objective than Child-Pugh (omits HE, ascites)
  - Used to evaluate need for transplantation
  - Predicts 3 month mortality
    - < 9: 1.9%
    - ≥ 40: 71.3% mortality

Treatment

- Goals: treat any acute complications, prevention of complications and further liver damage
- Non-pharmacologic therapy
  - Alcohol abstinence (even if non-alcoholic etiology)
  - Avoiding any other hepatic insult (including hepatotoxic drugs)
  - Na restriction with ascites
  - NG suction in variceal bleeding
  - Endoscopic band ligation for variceal bleeding

Treatment

- Non-pharmacologic therapy/cont
  - Temporary protein restriction during acute episodes of HE
  - Vaccines: Hep A, Hep B, pneumococcal, influenza
  - TIPS: transjugular intrahepatic portosystemic shunts

Pharmacologic Therapy
Portal Hypertension

- *Non-selective* β-blockers (nadolol, propranolol) are first line therapy
- Effective for primary and secondary prophylaxis of variceal bleeding and reduce mortality but don't prevent variceal formation
- Start at low doses
  - Propranolol 10-20 mg BID
  - Propranolol is metabolized hepatically
  - Titrate to maximal tolerated dose
  - Continue lifelong
- Nitrates may be added to β-blockers as 2nd line

Pharmacologic Therapy
Ascites

- Goal is to minimize discomfort, reduce ascites, and prevent SBP
- Symptoms include dyspnea, distention
- Treatment is with diuretics and Na restriction
  - Spironolactone and furosemide (100 : 40 ratio)
  - Starting dose: 100/40 QD
  - Continued lifelong
- Symptomatic relief → therapeutic paracentesis
  - For large taps (> 5L), give albumin 8-10 g/L otherwise high risk for HRS and HoTN
  - No significant effect on mortality

Pharmacologic Therapy
Variceal Bleeding

- Variceal bleeding
  - Emergency, mortality 15-20%
- Acute bleeding → octreotide IV infusion and endoscopic therapy/TIPS
- Octreotide
  - Synthetic somatostatin analog
  - Splanchnic vasoconstriction and ↓ portal pressure
  - Continued x 1-5 days post bleeding cessation
- SBP prophylaxis x 7 days with norfloxacin or ciprofloxacin or 3rd gen CP

Pharmacologic Therapy
Spontaneous Bacterial Peritonitis

- If suspected, broad spectrum abx should be started empirically until cultures back
  - 3rd gen CP (1st line), FQ, Zosyn, etc. (all IV)
  - Avoid FQ if pt was on it for long-term px.
  - Narrow therapy once cultures back
  - 5-10 days of therapy
- Secondary SBP prophylaxis in all pts
  - Decreases mortality
  - Norfloxacin 400 mg/d, trimethoprim-sulfamethoxazole DS/d

Pharmacologic Therapy
Hepatic Encephalopathy

- Lactulose
  - Standard therapy, available PO or enema
  - Lowers colonic pH, which converts NH_3 to NH_4^+ (ammonium) which cannot be absorbed and gets excreted with feces
  - 15-30 mL BID-TID, titrate to 2-4 soft BMs/day
- Rifaximin
  - Can be used as first line therapy
  - Decreases urease-producing gut bacteria thus reducing ammonia production
  - Efficacious, well-tolerated, but expensive
  - Neomycin and metronidazole have similar mechanism but toxicity with chronic use → not recommended

Pharmacologic Therapy
Hepatorenal Syndrome

- Maximize renal perfusion
  - D/C diuretics
  - Albumin infusion
  - Treat any precipitating factors i.e. SBP
  - TIPS procedure
  - Liver transplant is the ultimate solution
- Coagulopathies
  - SQ Vitamin K (phytonadione) may partially reverse INR
  - In acute bleeding PLT may be given for thrombocytopenia and FFP for elevated INR