Alcoholic Liver Disease
TH 5001 Therapeutics III Fall 2003
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Required Reading

Supplemental Reading

Ability Outcomes
Assess a patient with alcoholic liver disease and complications of cirrhosis.
Evaluate a patient's current therapy for alcoholic liver disease and/or complications of cirrhosis.
Select/Recommend therapy for a patient with alcoholic liver disease and/or complications of cirrhosis.
Monitor for efficacy and side effects of therapy.
Educate a patient and/or health care professional on the management of alcoholic liver disease and complications of cirrhosis.

Content Questions
1. Describe the pathologic stages of alcoholic liver disease.
2. Identify risk factors for the development of alcoholic liver disease.
3. Know the expected laboratory findings in ALD (are not required to memorize normal values).
4. Describe typical clinical manifestations of alcoholic liver disease/complications of cirrhosis and the mechanism by which they occur (i.e. ascites due to portal hypertension, coagulopathy due to liver cell failure, gynecomastia due to increased estrogen levels).
5. Recommend appropriate therapy for all of the complications of alcoholic liver disease/cirrhosis.
6. Understand the pathophysiology of all of the complications of alcoholic liver disease/cirrhosis.
7. Discuss the rationale for the use of both aldactone and furosemide in ascites.
9. Know the significance of the SAAG.
10. List the most common pathogens in spontaneous bacterial peritonitis.
11. Explain the mechanisms of action for lactulose, neomycin and metronidazole in the treatment of hepatic encephalopathy.
12. Understand the rationale for administering vitamin K in coagulopathies associated with alcoholic liver disease/cirrhosis.
13. Discuss the indications/contraindications for corticosteroid treatment in alcoholic hepatitis.
**ALCOHOLIC LIVER DISEASE (ALD)**

**Introduction**
- In 2000, there were 26,552 deaths in the United States from chronic liver disease and cirrhosis.
- In 2000, cirrhosis was the 12th leading cause of death in the United States.
- Patients with alcoholic cirrhosis have a 5-year survival rate of 40.5% with continued drinking.
- Only 10-15% of alcoholics develop cirrhosis.

**Anatomy of the Liver**

**Pathologic Stages of ALD**
- **Hepatic steatosis (fatty liver)**
  - Benign condition
  - Can occur within hours after a large alcohol binge
  - Liver is enlarged, yellow, greasy and firm
  - Minimal or absent signs/symptoms
  - Completely reversible with abstention from alcohol
- **Alcoholic hepatitis**
  - Features
    - Liver cell necrosis
    - Mallory bodies
    - Neutrophil infiltration
    - Perivenular distribution of inflammation
- **Cirrhosis**
  - Diffuse process characterized by fibrosis and conversion of the normal hepatic architecture into structurally abnormal nodules
  - Irreversible

**Risk Factors for the Development of ALD**
Clinical Presentation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal value</th>
<th>Expected change</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST M</td>
<td>10-40 U/liter</td>
<td>Rarely exceed 500 U/liter</td>
<td>Hepatocellular injury causes leakage of AST/ALT from hepatocytes</td>
</tr>
<tr>
<td>AST F</td>
<td>9-25 U/liter</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Effects of portal hypertension
- Esophageal varices
- Hematemesis
- Gastropathy
- Melena
- Splenomegaly
- Dilated abdominal veins (caput medusae)
- Ascites
- Rectal varices (hemorrhoids)

Effects of liver cell failure
- Coma
- Fetor hepaticus (breath smells like a freshly opened corpse)
- Spider nevi
- Gynecomastia
- Jaundice
- Ascites
- Loss of sexual hair
- Testicular atrophy
- Liver "flap" (coarse hand tremor)
- Bleeding tendency (decreased prothrombin)
- Anemia
  - Macrocytic
  - Iron deficiency (blood loss)
- Ankle edema
Diagnosis

- Based on clinical and laboratory findings
  - Determine that patient is abusing alcohol
    - CAGE questionnaire
      - Have you ever thought you should cut down on your drinking?
      - Have people annoyed you by criticizing your drinking?
      - Have you ever felt bad or guilty about your drinking?
      - Have you ever drunk alcohol the first thing in the morning to steady your nerves or to try to get over a hangover (eye-opener)?
        - A threshold of 80g of alcohol taken daily (on average) for 10-12 years was once considered necessary for alcohol-mediated injury to develop but this is not absolute
        - Maximum safe dose of ethanol is __________________________
  - Rule out other causes of cirrhosis
    - Viral hepatitis
    - Hemochromatosis
    - Drugs
    - Primary biliary cirrhosis
    - Primary sclerosing cholangitis

<table>
<thead>
<tr>
<th>Test</th>
<th>Male Normal Range</th>
<th>Female Normal Range</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td>M 10-55 U/liter</td>
<td>F 7-30 U/liter</td>
<td>Same as above</td>
</tr>
<tr>
<td>AST/ALT ratio</td>
<td>1:1</td>
<td></td>
<td>Attributed to pyridoxine deficiency</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>M 45-115 U/liter</td>
<td>F 30-100 U/liter</td>
<td>Disruption of bile flow</td>
</tr>
<tr>
<td>GGT</td>
<td>M 1-94 U/liter</td>
<td>F 1-70 U/liter</td>
<td></td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>0.0-1.0 mg/dl</td>
<td>0.0-0.4 mg/dl (direct)</td>
<td>Indirect rises secondary to failure of liver to conjugate Direct rises due to impaired excretion</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.1-4.3 g/dl</td>
<td></td>
<td>Decreased synthetic activity of the liver and decreased PO intake</td>
</tr>
<tr>
<td>PT/INR</td>
<td>11-13 sec/1.0</td>
<td></td>
<td>Inability of liver to synthesize clotting factors</td>
</tr>
<tr>
<td>Hemoglobin/hematocrit</td>
<td>M 13-18 g/dl</td>
<td>F 12-16 g/dl</td>
<td>See below</td>
</tr>
<tr>
<td>MCV</td>
<td>80-100</td>
<td></td>
<td>Macrocytic anemia</td>
</tr>
<tr>
<td>Platelets</td>
<td>150-350,000/mm³</td>
<td></td>
<td>Portal hypertension results in hypersplenism</td>
</tr>
<tr>
<td>Sodium</td>
<td>135-145 mmol/liter</td>
<td></td>
<td>Likely a dilutional effect</td>
</tr>
<tr>
<td>WBC</td>
<td>4.5-11,000/mm³</td>
<td></td>
<td>Response to infection (SBP)</td>
</tr>
<tr>
<td>Ammonia</td>
<td>12-48 µmol/liter</td>
<td></td>
<td>Inability of liver to remove toxins</td>
</tr>
</tbody>
</table>
Liver biopsy can secure diagnosis (if unclear) and determine extent of liver injury
  o Associated with risks in patients with coagulopathies and/or thrombocytopenia

Child-Pugh Grading of Chronic Liver Disease

<table>
<thead>
<tr>
<th>Score</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin (mg/dl)</td>
<td>1-2</td>
<td>2-3</td>
<td>&gt;3</td>
</tr>
<tr>
<td>Albumin (mg/dl)</td>
<td>&gt;3.5</td>
<td>2.8-3.5</td>
<td>&lt;2.8</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
<td>Mild</td>
<td>Moderate</td>
</tr>
<tr>
<td>Encephalopathy (grade)</td>
<td>None</td>
<td>1 and 2</td>
<td>3 and 4</td>
</tr>
<tr>
<td>Prothrombin time (prolonged seconds)</td>
<td>1-4</td>
<td>4-6</td>
<td>&gt;6</td>
</tr>
</tbody>
</table>

Grade A - <7 points
Grade B - 7-9 points
Grade C - 10-15 points

Discriminant Function

1. \[(4.6 \times \text{prothrombin time above control in seconds}) + \text{bilirubin}]\]
   - >32 associated with a 1-month mortality rate of approximately 50%

Non-Pharmacologic Therapy of ALD

1. Major focus is ABSTINENCE from alcohol
2. Aggressive nutritional therapy with maintenance of a positive nitrogen balance
   - Goal of 1.2-1.5 g/kg of protein/day
3. Frequent meals emphasizing breakfast and a nighttime snack
4. Liver transplantation
   - 6 months of abstinence and addiction treatment required

Managing Complications of Alcoholic Liver Disease/Cirrhosis

Portal Hypertension and Varices

1. Normal portal pressure 5-10 mmHg
2. Portal hypertension exists when the portal pressure is 5 mmHg greater than the pressure in the inferior vena cava
3. Pathophysiology
   - As fibrous tissue associated with cirrhosis accumulates, resistance to blood flow increases and portal hypertension develops
   - Blood “backs up” and a substantial fraction of it finds alternative routes back to the systemic circulation, bypassing the liver
   - These alternative routes of blood flow are called varices
     - Increased risk for varices when portal pressure >12 mmHg
     - Esophageal varices most common
       - Develop at a rate of 5% per year and up to 90% of all patients with cirrhosis will develop varices
       - Hemorrhage from varices occurs in 25-40% of patients with cirrhosis and each episode of bleeding carries a 30% risk of death
4. Clinical manifestations
Primary prophylaxis
- Indicated in patients with moderate to large-sized varices
- Non-selective beta-adrenergic blockers
  - Block the adrenergic dilatory tone of the mesenteric arterioles resulting in unopposed alpha-adrenergic-mediated vasoconstriction and a decrease in portal inflow and pressure
  - Decrease cardiac output
  - Approximately 50% reduction in incidence of initial bleeding
  - Propranolol 10 mg po tid or nadolol 20 mg po qd titrated to a reduction in the resting heart rate of 25% or an absolute heart rate of 55-60 bpm
- Nitrates
  - Not recommended until further clinical research obtained

Acute variceal hemorrhage (covered in TH IV)

Secondary prophylaxis
- Endoscopy management
  - Endoscopic band ligation (EBL) or endoscopic injection sclerotherapy (EIS) every 2 weeks until varices are gone, re-scope at 3 and 6 months
    - EBL
      - Rubberbands placed around the varix
      - Varix will slough off after 48 to 72 hours
    - EIS
      - Injection of a sclerosing agent into the lumen of the varix to tamponade blood flow
- Pharmacologic management
  - Non-selective beta-adrenergic blockers
    - 21% reduction in rebleeding and a 7.4% reduction in death as a consequence of rebleeding
    - Same dosing regimen as primary prophylaxis
  - Non-selective beta-adrenergic blocker plus nitrate
    - Indicated for nonresponders to beta-blocker monotherapy
    - Isosorbide mononitrate 20 mg po qd-bid; titrate up to 40mg po bid if tolerated
      - Causes smooth muscle vasodilation thus decreasing portal hypertension
  - TIPS (transjugular intrahepatic portosystemic shunting)
- Placement of one or more stents between the hepatic vein and portal vein
- Complications include hepatic encephalopathy and stent occlusion

- Monitoring

**Ascites**
- Pathologic accumulation of lymph fluid within the peritoneal cavity
- Approximately 50% of patients with cirrhosis will develop ascites within 10 years

**Pathogenesis**

- Cirrhosis/portal hypertension
  - ↑ Nitric oxide
  - Systemic/splanchnic vasodilation
  - ↓ Effective arterial blood volume
  - Activation of renin angiotensin aldosterone system
  - Hyperdynamic circulation
  - Sodium/water retention
  - Renal vasoconstriction

- **Clinical manifestations**

- **Treatment**
  - Therapeutic paracentesis
    - Removal of 4-6 liters if tense ascites present
      - Volume expansion after paracentesis
        - Albumin vs. synthetic plasma expander (controversial)
  - Diagnostic paracentesis
    - Rule out spontaneous bacterial peritonitis
• Determine if ascites a result of portal hypertension
  • SAAG = serum albumin concentration - ascitic albumin concentration
    o If >1.1 g/dl, portal hypertension present with 97% accuracy
  o Sodium restriction (2g/day)
  o Fluid restriction only if serum sodium <120 mEq/L
  o Diuretics
    • Spironolactone 100 mg po qd alone in mild to moderate ascites
    • Spironolactone 100mg po qd PLUS furosemide 40 mg po qd in severe ascites
    • RATIONALE for combination therapy
      • Spironolactone
        o Aldosterone antagonist, 14-day delay in onset of action, potassium-sparing
      • Furosemide
        o Less effective when used alone, fast onset of action, balances potassium-sparing effects of spironolactone
    • Maintain 100:40 ratio when titrating diuretics
    • Maximum daily dose of 400mg spironolactone and 160mg furosemide
    • Monitoring

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**Spontaneous Bacterial Peritonitis**

- Infection of ascitic fluid in the absence of a primary intra-abdominal source of infection
- In-hospital mortality of an episode of SBP is approximately 20% with a 1-year recurrence rate of 70%
- Risk factors
  - Low ascitic fluid protein levels (<1.0 g/dl)
  - Variceal hemorrhage
  - Prior SBP
- Pathogenesis
  - Unknown but presumably results from hematogenous seeding of the ascitic fluid which offers a favorable growth medium
- Most common pathogens (etiology)
Clinical manifestations
- Fever
- Leukocytosis
- Abdominal pain
- Guarding
- Hypoactive or absent bowel sounds
- Rebound tenderness
- Some patients have no symptoms at all
- Ascitic fluid analysis
  - Absolute polymorphonuclear leukocyte count of \( \geq 250 \text{ cells/mm}^3 \)
  - Positive ascitic fluid culture

Treatment
- Broad spectrum antibiotics
  - Third generation non-pseudomonal cephalosporins
    - Cefotaxime 2g IV q8h
    - Ceftriaxone 2g IV q24h
  - Fluoroquinolones
    - Levofloxacin 500mg IV/PO q24h
    - Gatifloxacin/moxifloxacin 400mg IV/PO q24h
    - Ofloxacin 400mg po q12h
- Duration of therapy
  - 5 days if repeat paracentesis (at 48 hours) reveals sterile ascitic fluid with < \( 250/\text{mm}^3 \) PMNs
  - 10-14 days if no follow-up paracentesis performed

Prevention of recurrence (secondary prophylaxis)
- Norfloxacin 400mg po qd
- SMX/TMP 800/160mg po bid
- Ciprofloxacin 750mg po qweek

Primary prophylaxis
- Only indicated in cirrhotic patients admitted with the following:
  - Low ascitic fluid protein levels (<1.0 g/dl)
  - Variceal hemorrhage
- Norfloxacin 400mg po bid x 7 days
- Ciprofloxacin 500mg po bid x 7 days

Monitoring
- Follow-up paracentesis usually not necessary
- WBC, temperature, signs and symptoms of SBP

Hepatic Encephalopathy (HE)
- Waxing and waning alterations in mental status that occur as a consequence of hepatic insufficiency or portal-to-systemic shunting
- 1-year survival rate of 40% in patients that develop overt hepatic encephalopathy
- Pathophysiology
o Accumulation of nitrogenous substances derived from the gut (ammonia)
o Impairment of the normal blood-brain barrier
o Increased levels of GABA and/or endogenous benzodiazepine-like metabolites
o Increased levels of short-chain fatty acids
o Increased synthesis of “false” neurotransmitters (increased aromatic amino acids in CNS)

☑ Classified as acute (< 4 weeks), chronic (≥ 4 weeks) or subclinical

☐ Clinical manifestations
  o Cognitive changes
    ▪ Range from mild confusion, apathy, agitation, euphoria, restlessness and insomnia/reversal of the day-night sleep pattern to somnolence, marked confusion and coma
  o Motor changes
    ▪ Range from fine tremor, slowed coordination and asterixis to decerebrate posturing and flaccidity

☐ Precipitating factors
  o Gastrointestinal bleeding
  o Infection
  o Excessive dietary protein intake
  o Constipation
  o Electrolyte abnormalities
  o Azotemia/dehydration/ overdiuresis
  o Sedative ingestion
  o Non-compliance
  o Portosystemic shunts
  o Superimposed acute liver disease

☐ Grading system

<table>
<thead>
<tr>
<th>Grade</th>
<th>Level of Consciousness</th>
<th>Personality/Intellect</th>
<th>Neurologic Abnormalities</th>
<th>EEG abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
<td>Normal</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Subclinical</td>
<td>Normal</td>
<td>Normal</td>
<td>Psychomimetic only</td>
<td>None</td>
</tr>
<tr>
<td>Grade 1</td>
<td>Inverted sleep patterns/restless</td>
<td>Forgetful; mild confusion; agitation; irritable</td>
<td>Tremor; apraxia; incoordination; impaired handwriting</td>
<td>Triphasic waves (5 cycles/second)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Lethargic, slow responses</td>
<td>Disorientation for time; amnesia; decreased inhibitions; inappropriate behavior</td>
<td>Asterixis; dysarthria; ataxia; hypoactive reflexes</td>
<td>Triphasic waves (5 cycles/second)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Somnolent but rousable, confused</td>
<td>Disorientation for place; aggressive</td>
<td>Aterixis; hyperactive reflexes; Babinski’s sign; muscle rigidity</td>
<td>Triphasic waves (5 cycles/second)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Coma, unarousable</td>
<td>None</td>
<td>Decerebrate</td>
<td>Delta activity (2-3 cycles/second)</td>
</tr>
</tbody>
</table>

☐ Treatment
  o Treat any precipitating factors
  o Nutritional management
    ▪ Avoid prolonged periods of dietary protein restriction
    ▪ Patients should receive the maximum tolerable protein intake with a goal of 1.2g/kg/day (range 1-1.5)
In cases of deep encephalopathy, oral intake can be held for 24-48 hours and IV glucose provided until improvement. Begin protein intake at 0.5g/kg/day, with a progressive increase to 1-1.5g/kg/day

- Vegetable and dairy sources preferable to animal protein
- Oral branched chain amino acids can be considered for individuals intolerant of all protein

- High fiber diet
  - Acidifies the colon and stimulates evacuation of colonic contents (including ammonia)

- Lactulose
  - FIRST LINE THERAPY
  - Urease-producing bacteria metabolize dietary protein and endogenous protein substrates producing ammonia
  - Fermentation of lactulose acidifies the colon thus inhibiting the viability of urease-producing bacteria and decreasing the production of ammonia
  - Acidification also enhances the net movement of ammonia from the blood into the bowel
  - Cathartic effect eliminates ammonia and protein substrates
  - Acutely give 30-60ml po q 1-2 h until catharsis begins; then decrease to 15-30ml po qid and titrate to produce 2-4 soft acidic stools/day
  - Can also give retention enema acutely (300ml lactulose syrup in 700ml water, held for 30-60 minutes)
  - Give 30-60ml/day and titrate to the same endpoint in patients with chronic HE

- Neomycin
  - Inhibits the activity of urease-producing bacteria
  - Give 2-8g/day in 4 divided doses (use lowest effective dose)
  - Ototoxicity and nephrotoxicity limit use
  - May give in combination with lactulose in refractory patients

- Metronidazole
  - 500mg po BID
  - Inhibits the activity of urease-producing bacteria
  - May give in combination with lactulose in refractory patients
  - Gastrointestinal side effects and peripheral neuropathies limit use

- Lactobacillus acidophilus
  - Attempt to replace urease-producing bacteria with nonurease-producing bacteria

- Eradication of *Helicobacter pylori*

- L-ornithine L-aspartate
  - Enhances ureagenesis

- Zinc supplementation
  - Required cofactor for ammonia metabolism
  - 600mg po qd in patients who are zinc deficient

- Flumazenil
  - Inhibition of GABA-benzodiazepine receptors

- Branched chain amino acids (BCAAs)
  - May have a role in the malnourished cirrhotic patient who is intolerant of standard protein supplementation

- Subclinical HE requires **NO** treatment
Coagulopathies

- Increased risk of bleeding
- Pathophysiology
  - Reduction in synthesis of coagulation factors
    - Vitamin K dependent clotting factors affected early
  - Thrombocytopenia due to hypersplenism
- Treatment
  - Vitamin K 10mg sq qd x 3 days
    - Corrects vitamin K deficiency if one exists
  - Platelet transfusions for thrombocytopenia if actively bleeding
  - Fresh frozen plasma for prolongation of PT/INR if actively bleeding
- Monitoring
  - PT/INR, platelets
  - Signs and symptoms of bleeding

Hepatorenal Syndrome

- Functional renal failure (no intrinsic renal disease) in the setting of cirrhosis
  - Characterized by progressively rising serum creatinine and diminished urine volume
  - >95% of patients die within a few weeks of onset of azotemia
- Pathophysiology
  - Poorly understood but occurs as a result of intense renal vasoconstriction
- Precipitating factors
  - Overly aggressive diuresis/large volume paracentesis
  - GI bleeding
- Treatment
  - Discontinue potential nephrotoxins (NSAIDs, aminoglycosides, etc.)
  - Withhold diuretics and administer a fluid challenge to rule out prerenal azotemia
  - Liver transplantation
- Monitoring
  - Renal function (BUN/SCr)
  - I/Os
  - Electrolytes

Endocrine Dysfunction

- Feminization/hypogonadism
  - Decreased testosterone and increased estrogen levels
    - Loss of libido, gynecomastia, testicular atrophy, diminished axillary and pubic hair, spider angiomas, palmar erythema, Dupuytren’s contractures
    - Consider testosterone replacement
- Hypothyroidism
  - Central and peripheral defects in thyroid secretion
  - Direct toxic effects of alcohol
o Replace thyroid hormone

**Peripheral Edema**
- Occurs secondary to hypoalbuminemia which reduces plasma oncotic pressure permitting leakage of fluid from the vascular space
- Treat with diuretics (see ascites section)

**Jaundice (icterus)**
- Yellow discoloration of the scleras and skin
- Occurs secondary to the inability of liver cells to conjugate and excrete bilirubin
- Treat underlying liver disease

**Anemia**
- Macrocytic in nature
  - Occurs secondary to alcohol toxicity, vitamin B₁₂/folic acid deficiency, and/or increased lipid deposition on red blood cell membranes
- Treat the nutritional deficiency if one exists

**Alcoholic Hepatitis**
- Confirm diagnosis by biopsy (if benefits outweigh risks)
- Treatment
  - Corticosteroids should be considered in patients with a discriminant function > 32 and/or hepatic encephalopathy in the absence of infection, GI bleeding, renal failure and/or pancreatitis
  - Prednisolone 40mg po qd x 4 weeks, followed by a taper
  - Avoid prednisone because it requires conversion to prednisolone in the liver