

Complications of Chronic Liver Disease

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Educational Goals

1. To understand the pathophysiology and classification of portal hypertension
2. To be able to describe the diagnosis and management of the following clinical syndromes:
 - Variceal hemorrhage
 - Ascites, Spontaneous bacterial peritonitis and hepatorenal syndrome
 - Portosystemic encephalopathy
 - Coagulopathy
3. To be familiar with two prognostic indices of liver disease: the Child-Pugh score and the MELD score

Key Words:

- ascites
- asterixis
- Child-Pugh classification
- cirrhosis
- coagulopathy
- endoscopic band ligation
- furosemide
- hepatorenal syndrome
- lactulose
- MELD (model for end-stage liver disease) score
- neomycin
- non-selective beta-blockers
- paracentesis
- peripheral arterial vasodilatation
- portal hypertension
- portal hypertensive gastropathy
- portosystemic encephalopathy
- portosystemic shunt
- refractory ascites
- rifaximin
- serum-ascites albumin gradient (SAAG)
- spironolactone
- splenomegaly
- spontaneous bacterial peritonitis (SBP)
- transvenous intrahepatic portosystemic shunt (TIPS)
- varices

I. Background

Irrespective of the etiology of chronic liver disease the complications are often the same, resulting from progressive liver injury and scarring. The majority of patients with complications already have cirrhosis. Cirrhosis is a histological diagnosis characterized by diffuse hepatic fibrosis and the conversion of normal liver architecture into regenerative nodules – islands of hepatocytes surrounded by fibrous tissue. The most significant complications of cirrhosis result from the development of portal hypertension and include (1) variceal hemorrhage, (2) ascites, (3) spontaneous bacterial peritonitis, (4) hepatorenal syndrome, and (5) portosystemic encephalopathy. Extensive replacement of the hepatic parenchyma with fibrosis leads to synthetic failure (coagulopathy) and excretory insufficiency (cholestasis and jaundice). Any of these complications may arise in severe acute liver disease, as well.

II. Pathophysiology

The liver has a dual circulation. Two-thirds of the hepatic blood supply comes from the portal vein (the confluence of the superior mesenteric vein and splenic veins) and one-third from the hepatic artery. (Figure 1) Portal hypertension results from a sequence of events that is initiated within the liver; the first step in the sequence is constriction of the hepatic microcirculation. This results from a reduction in intrahepatic nitric oxide, an endogenous vasodilator, and leads to increased resistance to portal outflow (i.e., more resistance to blood entering the liver) over time. As pressure rises in the portal circulation because of this resistance to portal outflow, nitric oxide levels *rise* in the splanchnic circulation, leading to vasodilation and increased blood flow in this

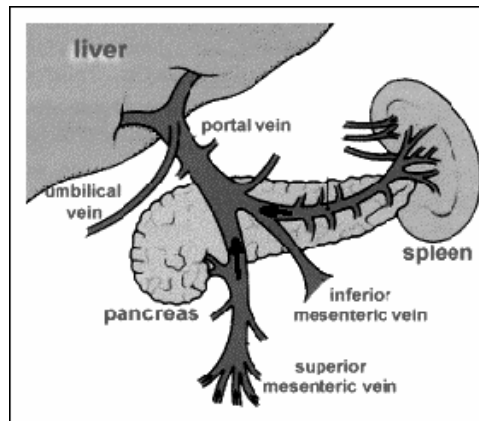
region. The result of vasodilation in the splanchnic circulation is a greater volume of blood flowing into the portal circulation. This higher volume of blood flowing into the liver meets increased resistance (within the hepatic microcirculation); the end result is high portal pressure.

As portal hypertension worsens, vasodilation becomes systemic, leading to a reduction in effective arterial blood volume (EABV). Most complications of portal hypertension, as discussed below, are the result either of the body's attempt to shunt blood away from the liver (through varices) or the *homeostatic* (anticipated) response to the reduced EABV. The homeostatic responses to reduced EABV in patients with portal hypertension include the following:

- Constriction of the renal vasculature
- Increase in renin-angiotensin
- Increase in aldosterone
- Increase in sodium and water reabsorption
- Rise in cardiac output
- Fall in systemic vascular resistance and thus drop in blood pressure

Portal hypertension can be classified as pre-hepatic, intra-hepatic and post-hepatic. Pre-hepatic causes include splenic and portal vein thrombosis. Intra-hepatic causes can be divided into pre-sinusoidal (schistosomiasis), sinusoidal (cirrhosis) and post-sinusoidal (veno-occlusive disease). Post-hepatic causes include Budd-Chiari syndrome (hepatic vein thrombosis) and right-sided heart failure.

Figure 1: Portal Circulation



III. Syndromes

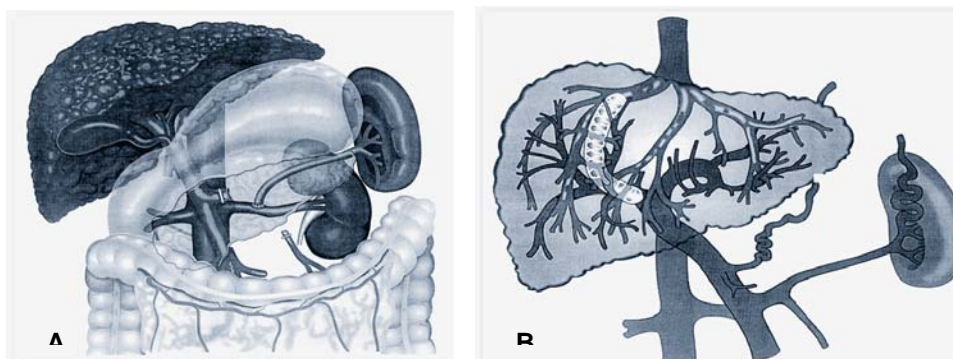
- A. Portal hypertensive hemorrhage: Progressive portal hypertension leads to the recruitment of portosystemic venous collaterals. The most important of these collaterals drain into the azygous system via the esophageal veins from the left gastric vein (coronary vein) and the splenic vein (via the short gastric veins). This altered circulation results in the development of esophagogastric varices. These varices, which can be thin-walled and under high pressure, can rupture causing significant hemorrhage. Patients with portal hypertension also may have gastric mucosal changes characterized by a macroscopic snakeskin- or mosaic-like appearance, termed "portal hypertensive gastropathy," also a cause of hemorrhage.

1. Demographics

- a) Esophageal varices are present in 60% of patients with cirrhosis
- b) Risk of bleeding from esophageal varices is about 25% within 2 years of diagnosis
- c) Mortality from initial variceal bleed is 40-70%
- d) Esophageal variceal bleeding is the leading cause of death in patients with portal hypertension

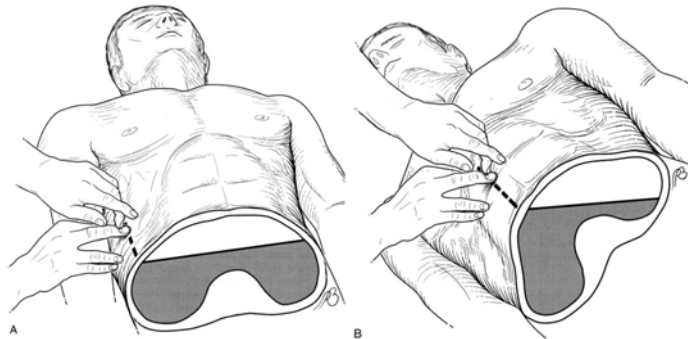
- e) Predictors of variceal rupture include
 1. Size of the varix
 2. The presence of decompensated liver disease
 3. The “red wale” (a sign of stretching epithelium)
2. Diagnosis
 - a) Patients with signs of portal hypertension such as splenomegaly, abdominal ventral wall collaterals (*caput medusae*) or ascites should be suspected of having gastroesophageal varices
 - b) Endoscopy is the diagnostic test of choice, allowing visualization and therapy
 - c) Esophageal varices are less likely to bleed if the portal pressure is < 12 mmHg. This measurement is often made indirectly by approximation of wedged hepatic vein pressure
3. Treatment
 - a) Pharmacologic: goal is lowering of portal pressures
 - Vasopressin and its analogues (octreotide, terlipressin): used in acute bleeding
 - Non-selective beta-blockers: used for prophylaxis prior to bleeding. These are also effective for prevention of re-bleeding, once an acute bleeding episode has resolved.
 - b) Endoscopic
 - Endoscopic band ligation: Small rubber bands placed at base of varices. As effective as sclerotherapy with better safety profile. Current standard of care.
 - Endoscopic sclerotherapy: irritant injected into varices. Stops bleeding >70% of cases. Complications include esophageal ulcerations, mediastinitis, infections, and rarely perforations. This therapy is falling from favor.
 - c) Decompressive (Figure 2): These shunt procedures, usually reserved for failure of endoscopic therapy, can lead to encephalopathy.
 - Surgical shunts: portocaval, mesocaval, distal splenorenal. Poorly tolerated in very ill patients, but have long-term patency.
 - Transvenous intrahepatic portosystemic shunt (TIPS): Radiologic procedure which employs a metallic stent connecting right hepatic vein to right portal vein. Can be used emergently in actively bleeding patients. Stenosis rate about 50% at 6 months, although less with newer, Teflon-coated stents.
 - d) Tamponade: Flexible tubes with esophageal and gastric balloons can be placed which, when inflated, compress bleeding varices. Although effective at achieving hemostasis, they are reserved for situations in which bleeding is too massive to permit endoscopy, or if the patient is too unstable to tolerate other interventions. These devices have a high complication rate.
 - e) Antibiotics: Patients with portal hypertensive bleeding are at risk for infection, specifically, spontaneous bacterial peritonitis. Therefore, all patients suspected of having variceal hemorrhage should be treated with antibiotics. Acceptable regimens include an intravenous 3rd generation cephalosporin (cefotaxime or ceftriaxone) or an oral quinolone.

Figure 2: (A) Distal splenorenal shunt and (B) TIPS



- B. Ascites/Spontaneous Bacterial Peritonitis/Hepatorenal Syndrome: Ascites refers to the accumulation of excessive fluid within the peritoneal cavity. It is most commonly caused by cirrhosis and portal hypertension, but it can be a consequence of neoplasm, congestive heart failure and infection (e.g. tuberculosis).
1. Pathogenesis: The accumulation of peritoneal fluid results, most prominently, from a homeostatic (i.e., physiologically expected) response to the reduction in EABV, as described above. That is, the reduction in EABV leads to an expected upregulation in the renin-angiotensin, aldosterone system. This leads to renovascular constriction and sodium and water retention. However, the intensity of EABV is so great in portal hypertension that the retention of salt and water does not limit itself, and fluid accumulates in potential spaces, such as the peritoneal cavity (ascites) and subcutaneous tissues (edema). The over-expression of anti-diuretic hormone leads to the absorption of water, and thus hyponatremia (dilutional) is commonly seen. The onset of ascites in cirrhosis is associated with a 50% 2-year survival.
 2. Diagnosis: abdominal distension in patient with portal hypertension
 - a) Flank dullness by percussion has 90% accuracy for the presence of ascites
 - b) Shifting dullness is confirmatory. Shifting dullness is elicited by percussion of the abdomen in the recumbent position, then repeated in a partially decubitus position in order to elicit a change in the level of dullness (Figure 3)

Figure 3: Shifting dullness test for ascites: shifting dullness is elicited by percussion in the recumbent position, marking the most medial site of dullness (A). If, when percussion is repeated in a partially recumbent position, (B), the level of dullness has shifted medially, ascitic fluid is likely to be present.



3. Etiology: ascites may result from non-hepatic causes
 - a) Examine for stigmata of chronic liver disease
 - Jaundice
 - Caput medusae
 - Small arteriovenous communications on the upper body
 - Gynecomastia
 - Other signs of portal hypertension
 - b) Heart failure: distended neck veins, third heart sound
 - c) Cancer: weight loss, muscle wasting, lymphadenopathy, palpable mass
 - d) Pelvic exam: ovarian cancer is common cause of malignant ascites
 - e) Paracentesis is the best test to assess the etiology of ascites. The serum-ascites albumin gradient (SAAG) can differentiate ascites resulting from portal hypertension from non-portal hypertensive causes. SAAG is the arithmetic difference between serum and ascites albumin concentrations. Essentially, the SAAG reflects the protein in ascites, relative to the serum. Processes which are likely to exude protein into the fluid, such as infections or malignancies, will

demonstrate a smaller difference between the ascites and serum protein level. In portal hypertension, the ascites is low in protein concentration.

$$\text{SAAG} = (\text{serum albumin}) - (\text{ascites albumin})$$

If SAAG \geq 1.1, ascites is very likely the result of portal hypertension. Table 1 lists the major components of the differential diagnosis of ascites based on the SAAG

Table 1: Differential diagnosis of ascites based on serum-ascites albumin gradient

| SAAG \geq 1.1 | SAAG < 1.1 |
|--------------------------|------------------------------|
| Cirrhosis | Peritoneal carcinomatosis |
| Alcoholic hepatitis | Tuberculous peritonitis |
| Budd-Chiari syndrome | Pancreatic ascites |
| Cardiac ascites | Bowel obstruction/infarction |
| Massive liver metastases | Nephrotic syndrome |
| Myxedema | Serositis |

4. Treatment of Ascites

- a) Determine underlying cause
- b) Alcohol cessation
- c) Sodium restriction: chance of successful diuretic therapy can be inferred by measurement of spot urinary sodium
 - Urinary sodium \geq 30 mEq/day: diet may be sufficient
 - Urinary sodium < 10 mEq/day: diuretics necessary
 - The usual sodium restriction is 2.0 g/day. Restrictions of less than 1.0 g/day are unpalatable
 - Fluid restriction not necessary unless serum Na^+ < 120 mEq/L
- d) Diuretics
 - K^+ sparing (spironolactone, amiloride, triamterene): aldosterone antagonists which act on distal tubule. These drugs have a mechanism based rationale for use; the reduced EABV leads to the homeostatic increase in renin-angiotensin, aldosterone system). Delayed onset of action compared to loop diuretics. Side effects include: gynecomastia, loss of libido, menstrual irregularities, azotemia, hyperkalemia. Loop diuretics (furosemide, bumetanide, torasemide): Inhibit Na^+ transport in ascending loop. Potent, rapid acting, synergistic with K^+ sparing diuretics. Thiazides: not indicated; can induce hepatic encephalopathy.
- e) High volume paracentesis: considered safe, despite stormy history. Indicated in refractory ascites, which is defined as massive ascites, not responsive to maximal conventional therapy:
 - Na^+ restriction of 1.0 g/day
 - Spironolactone 400 mg/day
 - Furosemide 160 mg/day
 - 3 or more episodes tense ascites over 9 months *requiring* paracentesis
 - Only 5-10% of patients with ascites meet these criteria
- f) Shunting: mesocaval shunt and TIPS can be successful in alleviating ascites in the majority of refractory patients, but these procedures are associated with risk, especially hepatic encephalopathy, hemolysis, acceleration of liver failure and renal insufficiency.
- g) Liver transplantation

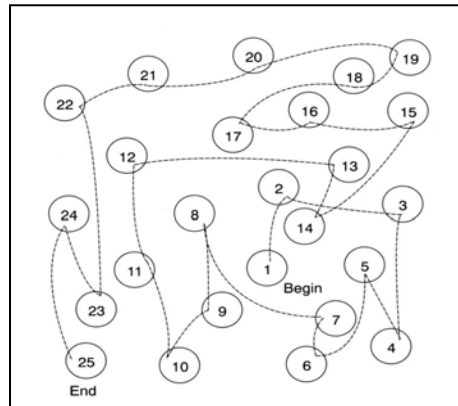
C. Spontaneous Bacterial Peritonitis (SBP): As name implies, intra-abdominal infection without apparent underlying cause. SBP is associated with a 50% 6-month survival.

- 1) Pathophysiology

- a) Abnormal gut permeability to bacteria leads to infection of mesenteric nodes and portal blood. Infected lymph then enters ascitic fluid.
 - b) Patients with cirrhosis have a relative inability to clear infection: serum and ascites complement deficiency, poor ascites opsonic activity.
 - c) Microbiology: monomicrobial infection, usually E. Coli, Klebsiella, pneumococcus
 - 2) Clinical findings: fever, abdominal pain, and worsening ascites or any worsening in a patient with stable cirrhosis.
 - 3) Diagnosis made by paracentesis:

If ascites contains > 250 neutrophils/mm³, SBP is diagnosed
 - 4) Mortality is 78-100% without treatment and 30% with treatment.
 - 5) First line therapy is third generation cephalosporin (eg., ceftriaxone, cefotaxime).
- D. Hepatorenal Syndrome: renal failure characterized by profound sodium retention, uremia, and oliguria, in the setting of end stage liver disease and portal hypertension.
- 1) Etiology: unknown, but suspected to be the result of intensive peripheral arterial vasodilatation (reduced EABV) with compensatory increased renal vasoconstriction. May represent an imbalance between vasoconstrictors (angiotensin II, norepinephrine) and vasodilators (prostacyclin – PGI₂).
 - 2) Diagnosis: worsening renal function, low urine sodium (or fractional excretion of sodium), adequate intravascular volume.
 - 3) Without liver transplantation, a pre-morbid event.
 - 4) Classification:
 - a) Type I: anuric, relentlessly progressive, high mortality. This probably evolves from Type II hepatorenal syndrome, after some trigger, such as infection.
 - b) Type II: fluctuating renal failure, at least partially responsive to restoration of EABV (through volume resuscitation) and other interventions.
 - 4) Therapy has focused on reversal of peripheral vasodilatation with intravenous vasoconstrictors (midodrine), inhibitors of vasoconstriction (octreotide), and aggressive volume replacement. In general, patients with hepatorenal syndrome can only be adequately treated with liver transplantation.
- E. Portosystemic encephalopathy: changes in mental status that are directly related to hepatic dysfunction. Varies in severity from sleep disturbance through confusional states and coma.
1. The pathogenesis of portosystemic encephalopathy has not been definitively elucidated: diversion of portal blood from the liver (portal hypertension with portosystemic shunting) appears to be necessary. May result from impaired hepatic metabolism of gut-derived neuroactive substances. The most likely candidate is ammonia, which has been shown to lead to astrocyte swelling/dysfunction; also, aromatic amino acids, gamma-aminobutyric acid (GABA) may be candidates.
 2. Diagnosis: changes in state of arousal in a patient with chronic liver disease
 - a) Other causes of changing mental status must be explored (alcohol, trauma, stroke, intracranial bleed, etc.)
 - b) Arterial ammonia (and the more variable venous ammonia) are used to help establish the diagnosis, but levels correlate poorly with clinical signs and symptoms (i.e., the ammonia level may be normal in patients with hepatic encephalopathy).
 - c) Stages:
 1. Confusion
 2. Drowsiness
 3. Somnolence
 4. Coma
 - d) EEG findings: diffuse slowing and d waves; non-specific.
 - e) Neuropsychiatric testing: appearance of signature, trail making test, other specific visual and special tasks. (Figure 6)

Figure 4: Trail making test used in diagnosis of hepatic encephalopathy



3. Treatment of portosystemic encephalopathy
 - a) Correct underlying precipitating factors such as electrolyte disturbances, infection, uremia, neuropsychiatric or hepatotoxic medications, gastrointestinal bleeding or overzealous protein ingestion
 - b) Exclude other causes for altered mentation, including CNS lesions or bleeding
 - c) Patients with cirrhosis have increased dietary protein requirements so absolute protein restriction should be avoided. However, manipulation of protein intake can decrease frequency and severity of bouts of encephalopathy
 - Decrease dietary protein from animal sources
 - Increased dietary protein from vegetable sources
 - Commercial supplements high in branched-chain amino acids are available, but expensive and unpalatable
 - d) Oral lactulose: hydrolyzed by colonic bacteria to acetic and lactic acids, reducing colonic pH, “trapping” nitrogenous waste and inducing an osmotic diarrhea. Goal of therapy: two to three semi-solid bowel movements/day to keep colonic pH < 5.5. Although widely used, there are no data to show that lactulose is better than correction of underlying precipitating factors (as above).
 - e) Nonabsorbable oral antibiotics, including rifaximin and neomycin eradicate colonic bacteria implicated in generating ammonia and toxic amines. Neomycin has potential for nephrotoxicity and ototoxicity

- F. Coagulopathy/Thrombocytopenia: Bleeding tendency in cirrhosis is multifactorial: deficient production of clotting factors, diminished synthesis and degradation of fibrinolytic factors, impaired clearance of activated clotting factors, abnormal fibrinogen, and thrombocytopenia due to splenic sequestration.
 1. Factors I (fibrinogen), II (prothrombin), V, VII, IX, XI and XII are reduced
 2. Diagnosis: clinical bleeding, bruising and elevation of prothrombin time (INR)
 3. Treatment: oral Vitamin K will correct nutritional deficiencies, but not synthetic failure. Subcutaneous Vitamin K can correct malabsorption, but not synthetic failure. In case of bleeding with elevated INR, parenteral fresh frozen plasma (FFP) can be administered. Platelet transfusions can provide brief improvement in hemostasis in cases of thrombocytopenia and bleeding.

IV. Prognostic Indices in Cirrhosis

The Child-Pugh classification (see Table below) is a useful scoring system to help determine prognosis in patients with cirrhosis. Patients with a score of 10 or greater (Class C) have a 1-year survival of 50%. Patients with Class A and B have a better prognosis (5-year survival 70-80%).

Modified Child-Pugh Classification

| | 1 | 2 | 3 |
|---|--------------|------------------|-----------------|
| Encephalopathy | none | mild | severe |
| Ascites | none | slight | moderate/severe |
| Total bilirubin (mg/dL) | < 2.0 | 2.0-3.0 | > 3.0 |
| Albumin (g/dL) | > 3.5 | 2.8-3.5 | < 2.8 |
| Prothrombin time (seconds prolonged) or (INR) | < 4 < 1.7 | 4 - 6 1.7-2.3 | > 6 > 2.3 |

score: A=5-6 B=7-9 C=10-15

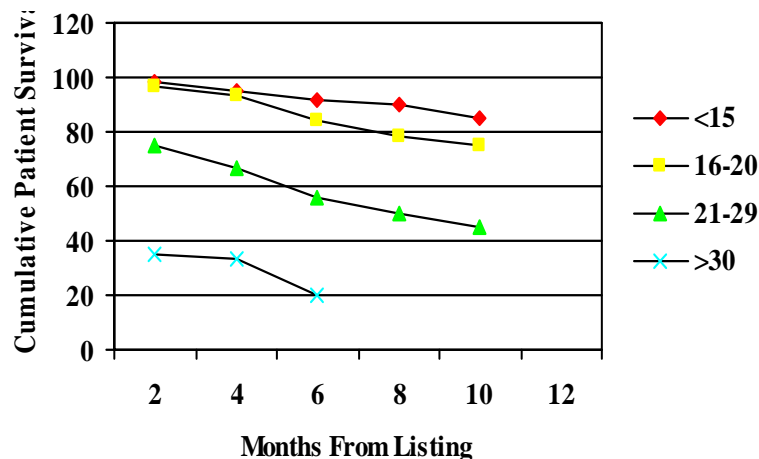
MELD (model for end-stage liver disease)score

The MELD score was originally determined to predict survival in cirrhotic patients undergoing surgery. Using retrospective multivariate analysis this rather unwieldy formula was obtained:

$$\text{MELD Score} = 10 \{0.957 \text{Ln(Scr)} + 0.378 \text{Ln(Tbil)} + 1.12 \text{Ln(INR)} + 0.643\}$$

This score, which can be calculated with handheld devices or via internet sites (<http://www.unos.org/resources/MeldPeldCalculator.asp?index=98>), has been prospectively validated to correlate with 3 month survival in cirrhotic patients (see Figure 8). It is now used to assign priority for liver transplantation.

Figure 5: Survival probability depending upon the MELD Score.



V. References

Garcia-Tsao G, Sanyal AJ, Grace ND, Carey W. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. *Hepatology*. 2007;46:922-38.

Lizardi-Cervera J, Almeda P, Guevara L, Uribe M. Hepatic encephalopathy: a review. *Ann Hepatol*. 2003;2:122-30.

Nietsch HH. Management of portal hypertension. *J Clin Gastroenterol*. 2005;39:232-6.

Runyon B. Management of adult patients with ascites due to cirrhosis. *Hepatology*. 2004;39:1-16.

VI. Study Questions

1. A 55 year old man with a history of chronic hepatitis C infection presents to the emergency department vomiting blood. He is hypotensive, tachycardic and poorly responsive to verbal stimuli. Examination is notable for scleral icterus, spider angiomas on the chest, ascites, splenomegaly and peripheral edema.
 - What is the most likely cause of the GI bleed?
 - What is the first step in management?
 - What is the most effective endoscopic treatment of this disorder?
 - What therapies can be considered if endoscopic therapy fails to achieve hemostasis?

2. A 62 year old woman with a history of primary biliary cirrhosis notes progressively increasing abdominal girth despite sodium restriction and the use of spironolactone and furosemide in high dose. Paracentesis yields straw-colored fluid with the following laboratory characteristics: albumin 0.6 g/dL, total protein 1.0 g/dL, WBC 800/mm³, neutrophils 15%. Serum analysis: albumin 2.4 mg/dL, sodium 132 mEq/dL, creatinine 1.6 mg/dL, total bilirubin 4.6 mg/dL.
 - Does this patient have portal hypertension?
 - Does this patient have spontaneous bacterial peritonitis?
 - Should you increase the diuretics?
 - Should you introduce a water restriction?
 - (For fun): calculate the MELD score. Does this patient need a liver transplant?

3. A 66 year old man with cirrhosis due to remote alcohol use is noted by his family to be more forgetful and sleepy. His medications include propranolol, spironolactone, furosemide, lactulose and zolpidem. Exam is notable for temporal wasting, jaundice, gynecomastia, no ascites or peripheral edema.
 - What might be causing worsening of encephalopathy?
 - What therapeutic measures are available?
 - What other causes of mental status change should be considered?
 - What dietary recommendations are most appropriate?