# Management of Chronic Hepatic Failure

**Cirrhosis:** Irreversible injury of the hepatic parenchyma w/ fibrosis leading to disruption of lobular and vascular architecture.

| Types | Symptoms | Metabolic Manifestations | Manifestations of portal HTN |
|---|---|---|---|
| -Alcoholic (Laennec's cirrhosis)<br>-Biliary (due to prolonged biliary obstruction)<br>-Post-viral (hepatitis B or C)<br>-Cardiac (due to prolonged right-sided CHF) | -Anorexia / weight loss<br>-Weakness / easy fatigability<br>-N/V/D<br>-Pruritus | -Hypoalbuminemia<br>-Osteodystrophy<br>-Coagulopathy<br>-Jaundice (icteric sclera)<br>-Thyroid function abnormalities<br>-Glucose intolerance / hypoglycemia<br>-Hepatic encephalopathy | -Esophageal / gastric varices<br>-Splenomegaly (hypersplenism)<br>-Leukopenia / thrombocytopenia<br>-Ascites<br>-SBP |

**Child-Turcotte-Pugh Score:** Grading of Liver Dx

**Table 2. Child-Pugh Classification of the Severity of Cirrhosis**

| | Points* | | |
|---|---|---|---|
| | 1 | 2 | 3 |
| Encephalopathy | None | Grade 1-2 (or precipitant-induced) | Grade 3-4 (chronic) |
| Ascites | None | Mild/Moderate (diuretic-responsive) | Tense (diuretic-refractory) |
| Bilirubin (mg/dL) | <2 | 2-3 | >3 |
| Albumin (g/dL) | >3.5 | 2.3-3.5 | <2.8 |
| PT (sec prolonged) or INR | <4<br><1.7 | 4-6<br>1.7-2.3 | >6<br>>2.3 |

*5-6 points: Child A; 7-9 points: Child B; 10-15 points: Child C.

**Model for End Stage Liver Disease (MELD)**: Predicts survival for patients with advanced liver disease.

| Factors | Interpretation |
|---|---|
| • Serum bilirubin (mg/dL)<br>• INR<br>• Scr (mg/dL)<br>• Patient had dialysis at least twice in last week: yes/no | • 40 or more -- 71.3% mortality<br>• 30-39 -- 52.6% mortality<br>• 20-29 -- 19.6% mortality<br>• 10-19 -- 6.0% mortality<br>• <9 -- 1.9% mortalit |

**Hepatic Encephalopathy:** Syndrome characterized by altered mental status in pts w/ severe hepatic insufficiency

| | |
|---|---|
| **Pathophysiology** | Ammonia created by enterocytes by colonic bacterial catabolism of nitrogenous sources (protein)→ enters the circulation via the portal vein to liver for clearance--> Accumulation of ammonia in liver failure→ Production of false neurotransmitters; Activation of GABA-Benzodiazepine receptors; Altered cerebral metabolism all leading to encephalopathy sx's |
| **Precipitating factors** | 1. Drugs: benzodiazepines, narcotics, alcohol<br>2. Excess dietary intake of protein, GI bleeding, Infection, hypokalemia, constipation, metabolic alkalosis.<br>3. Dehydration: vomiting, diuretics, large volume paracentesis, diarrhea<br>4. Hepatic vein thrombosis, portal vein thrombosis. |
| **Classification** | I. Day-night reversal, restlessness, forgetfulness, mild confusion<br>II. Drowsiness, lethargic, inability to perform mental tasks, disoriented, amnesia, ataxia, asterixis<br>III. Somnolent (but arousable), unable to perform mental tasks, disoriented to time/place, incomprehensible speech, asterixis<br>IV. Comatose |

**Pharmacologic Management:**

| | Pharmacology | Formulation/dose | Side effects | Comments |
|---|---|---|---|---|
| **Lactulose** | Nonabsorbable disachharide → hydrolyzed by bacteria in the lower intestinal tract to form lactic and acetic acid→ resulting acidic environment protonates NH3 to NH4+ so that ammonia cannot be absorbed into the blood. Results in excretion of ammonia. | **Formulation:**<br>1. Syrup 10gm/15ml<br><br>**Doses-Acute Enceph:**<br>1. 25 q 1-2 hours until at least two soft or loose bowel movements per day are produced<br>2.Enema: 300ml syrup in 700ml water or 0.9% saline. Give 250-350ml as retention enema. Retain for >30min, given q4-6hrs<br>**Dose-Chronic Enceph:**<br>1. 30ml po TID. Titrate to mental status & 3-4 bowel movements/day | 1.Flatulence/bloating<br>2.Diarrhea<br>3.Hypernatremia<br>4.Bad taste (too sweet) | -First line for hepatic encephalopathy, but very limited data exists.<br>-Caution not to induce excessive diarrhea (dehydration & hypokalemia can exacerbate hepatic encephalopathy)<br>-Effect occurs w/in 12-48hrs. |
| **Rifaximin (Xifaxan)** | Synthetic ABX that kills off urease-producing bacteria in GI tract. Not systemically absorbed (~0.4% F). | Formulations:<br>550mg, 220mg tablets<br><br>Reduction of hepatic encephalopathy recurrence:<br>1. 550mg po BID<br><br>Treatment of hepatic encephalopathy (unlabeled use):<br>400mg q8hrs x 5-10 days. | 1.Headache<br>2.Flatulence<br>3.Nausea/rash<br>4.May result in bacterial superinfxns (c.diff) in pts being treated for longer than 2mos. | -Expensive (~1600/month)<br>- In rifaximan trials for HE, 91% of the patients were using lactulose concomitantly.<br>- No solid data to support use alone<br>-Also used for traveler's diarrhea (200mg po TID) |

**Non-Pharmacologic Management:** Limit protein intake (1.2-1.5 g/kg/day); Avoid red meat, fish, etc (vegetable-based protein is ideal). Daily energy intakes should be 35-40 kcal/kg ideal body weight

**Spontaneous Bacterial Peritonitis:** in pts w/ ascites in the absence of recognized secondary causes (bowel perforation, intra-abdominal abscess)

**Pathophysiology:**
-Bacterial Translocation Hypothesis: Enteric bacteria cross intestinal barrier, infect mesenteric lymph nodes, blood stream, and ascites fluid.

| Common Pathogens | Diagnosis | Predisposing factors | Findings |
|---|---|---|---|
| E. coli (43%)<br>Klebsiella pneumoniae 11%<br>Streptococcus penumoniae 9%<br>Other streptococcus species 19%<br>Enterobacteriaceae 4%<br>Staphylococcus 3%<br>Pseudomonus 1% | >250 neutrophils/mm3 in ascetic fluid<br>-Positive ascetic fluid cx | -Previous hx of SBP<br>-GI hemorrhage<br>-UTI<br>-Bladder/IV catherization<br>-Repeated large volume paracentesis | -Abdominal pain<br>-worsened renal fx<br>-fever<br>-leukocytosis<br>-increased ascites<br>-Percipitation of hepatic encephalopathy |

**Indications for empiric treatment**
-Convincing signs of infxn (fever, abdominal pain, unexplained encephalopathy)
-Ascitic flid cell count: Polymorphonuclear leukocyte (PMN) ≥250 cells/$mm^3$
-Ascitic fluid should be sent for culturing.

**Treatment:**
-1st line tx: 3rd generation cephalosporins: cefotaxime 2g IV q8hrs OR ceftriaxone 1g q24hrs PLUS Albumin 1.5gm/kg IV day 0 and 1g/kg on day 3
-PCN allergy: Bactrim SS 1 po BID OR Norfloxacin 400mg po BID.
-If oral preferred: Oxafloxacin 400 mg po BID UNLESS prior exposure to FQ, vomiting, shock, grade II or higher HE, or Scr>3.

**Duration of treatment:** 5-10 days. RCT (Runyan BA, et al.): 5 day vs 10 day antibiotic tx of SBP shows no difference in cure rates and mortality.

**Albumin:** For pts w/ Scr>1, BUN>30, or T.bili>4
-Dosing: 1.5 g/kg within 6 hrs and 1g/kg on day 3
-Purpose: maintains oncotic pressure and perfusion to kidneys.

**Prophylaxis:**

Indications:

1. Cirrhosis with GI bleed
    - Ceftriaxone 1g q24 hrs OR norfloxacin 400mg BID x 7 days
2. Ascitic fluid protein <1.5g/dL with impaired renal or liver dysfunction
3. 1+ episode of SBP→ life-long
    - Norfloxacin 400mg po daily
    - Bactrim 1 SS tab po daily

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## Esophageal Varices:

**Pathophysiology**
Portal pressure increases d/t increased resistance to flow (fibrotic liver). Ultimately, blood flow is diverted from the liver to low-resistance collateral channels through the coronary vein, into the esophagus and proximal stomach. Can then lead to vein rupture and bleeding.

**Diagnosis**
Esophagogastroduodenoscopy (EGD)= Gold standard.

**Screening**
-Patients with cirrhosis must have varices screening via EGD. Those with medium or large varices should be placed on prophylactic therapy.
-In those with small varices and increased risk of hemorrhage (Child B/C or presence of red wale marks on varices) prophylactic therapy should also be started.

**Pharmacologic Management:** Should be started as soon as bleed suspected prior to EGD confirmation.

| | Pharmacology/MOA | Dosing | Adverse Effects | Comments |
|---|---|---|---|---|
| **Octreotide** | -More potent/longer lasting synthetic analog of somatostatin<br>-Vasoconstrictor of splanchnic bed, resulting in decreased portal venous flow/pressure | LD: 50 mcg IV push<br>Infusion: 50-100mcg/hr | -Bradychardia w/ large IV bolus<br>-Ileus<br>-Cholestasis<br>-Hypo/hyperglycemia | -Comparable in efficacy w/ fewer side effects for controlling acute variceal bleeding to vasopressin and balloon tamponade<br>-Can be used for 5 days |
| **Vasopressin** | -Anterior pituitary hormone. Antidiuretic hormone<br>-At doses greater than for antidiuretic effects, causes vasoconstriction of small arterioles/capillaries, resulting in decreased blood flow to splanchnic bed, coronary arteries, GI, skin/muscles | 0.2—0.4unit/min IV infusion and increased qhr by 0.2/min until control of bleeding (max dose=0.8unit/min) | -Myocardial ischemia<br>-Bowel ischemia<br>-Arrhythmias<br>-Hypertension<br>-Water intoxication / hyponatremia | -Use of central line over peripheral IV infusion preferred b/c of tissue necrosis risk.<br>-Not used much anymore due to SEs<br>-Should always be accompanied by IV NTG at 40 mcg/minute. Can be increased to max of 400mcg/minute, adjusted to maintain SBP> 90 mmHg.<br>-Max duration at highest effective dose of 24hrs. |
| **PPI or H2 blocker (Adjunctive agent)** | Suppress acid secretion | Pantoprazole 80mg IVx1 then 8mg/hr infusion OR Omeprazole 20mg PO daily to BID<br>Famotidine 20mg po daily-BID | | |
| **Short term Abx (7 days)** | Prevent SBP | 1.Norfloxacin 400mg BID<br>2.Ciprofloxacin IV or PO<br>3.Ceftriaxone 1g IV | | -Should be started in any pt with cirrhosis and suspected GI hemorrhage.<br>-Ceftriaxone= superior to FQs (possibly d/t FQ resistance in pt population studied). |
| **Primary Prophylaxis:** Prevents first bleeding episode by reducing portal HTN | | | | |
| **Propranolol** | Nonselective B-blocker (reduces portal blood flow):<br>-Reduces portal pressure by decreasing cardiac output (B-1 effect)<br>-Produces splanchnic vasoconstriction (B-2 effect). | Starting dose: 20mg po BID-TID | -Bradychardia<br>-Fatigue<br>-lightheadedness | -Titrate to maximum tolerated doses.<br>-Prevent bleeding in >50% of pts with medium and large varices.<br>-Risk of bleeding recurs when tx stopped. Continue indefinitely. |
| **Nadolol** | Same as above. | Starting dose: 40mg po daily | Same as above | Same as above |
| **Nitrates** | Vasodilation causes venous pooling, inducing splanchnic vasoconstriction resulting in decreased portal pressure | Isosorbide dinitrate:5-10mg po TID<br>Isosorbide mononitrate: 15-30mg po daily | -Hypotension<br>-Wheezing<br>-Bradycardia<br>-Confusion | -Normally used in conjunction w/ beta-blockers.<br>-Efficacy with monotherapy not proven. Can lead to increase mortality in those >50 yrs old. |
| **Non-pharmacologic management:** Balloon tamponade, endoscopic variceal ligature/sclerotherapy | | | | |

## Ascites: Accumulation of fluid in peritoneal cavity from increased production and/or decreased absorption of peritoneal fluid

| Pathophysiology | Diagnosis | Presentation | Complications |
|---|---|---|---|
| -Portal HTN→Splanchnic vasodilation→Decreased effective circulatory volume→ Renin-Angiotensin-Aldosterone System (RAAS) activation→ Na and water retention | -Paracentesis (cell count and differential, albumin and total protein concentration)<br><br>Portal HTN: Serum-albumin gradient≥1.1g/dL | -Increased abdominal girth<br>-Jugular venous distension<br>-Edema<br>-Low urinary sodium<br>-Decreased UOP | -Spontaneous bacterial peritonitis<br>-Impaired pulmonary fxn<br>-GERD<br>-Hernia |

**Pharmacologic Management:**

| | Dose | Adverse effects |
|---|---|---|
| **Loop diuretics** | Furosemide 40mg PO daily<br>Furosemide 20mg PO daily for pts w/o edema | -Hypokalemia<br>-Hypotension<br>-Hyponatremia |
| **Potassium sparing diuretics** | Spironolactone 100mg PO daily (Can be titrated q3-5 days if weight loss and natriusis is inadequate. Maintain furosemide: spironolactone ratio of 40:100mg) | -Hyperkalemia<br>-Dehydration<br>-Gynecomastia (amelioride = substitute that avoids SE but not as effective; epleronone not studied in liver pts) |
| **Albumin** | 6-8g/L of ascetic fluid removed during paracentesis or 50 g total for >5L. | -Decreases mortality |

**Non-pharmacological:** Bed rest (increased renin activity when standing), Na restriction to 2gm/day, no alcohol, fluid restriction not necessary unless serum Na <125, avoid ACE, ARBs, NSAIDs.
**Goals of therapy:** 0.5kg/day weight loss for pts w/o edema; 1kg/day weight loss for pts w/ edema