# Chapter 21: Cirrhosis and Portal Hypertension

## INTRODUCTION

- Chronic liver injury causes damage to normal liver tissue, resulting in development of regenerative nodules surrounded by dense fibrotic material, which are diagnostic hallmarks of cirrhosis.

## PATHOPHYSIOLOGY

- The distorted architecture of the cirrhotic liver impedes portal blood flow, interferes with hepatocyte perfusion, and disrupts hepatic synthetic functions such as the production of albumin. Clinical consequences of cirrhosis include increased intrahepatic resistance leading to portal hypertension, varices, and variceal bleeding; ascites; infection; hepatic encephalopathy (HE); and hepatocellular carcinoma.
- Primary causes of cirrhosis in developed countries include hepatitis C, excessive alcohol intake, and nonalcoholic fatty liver disease (**Table 21-1**).
- Cirrhosis causes changes to the splanchnic vasculature and circulation. Splanchnic vasodilation and the formation of new blood vessels contribute to increased splanchnic blood flow, formation of gastroesophageal varices, and variceal bleeding. Additionally, splanchnic vasodilation leads to hypoperfusion of the renal system, which causes activation of the renin–angiotensin–aldosterone system and, subsequently, significant fluid retention. The pathophysiologic abnormalities that cause it often result in ascites, portal hypertension and esophageal varices, HE, and coagulation disorders.
- **Portal hypertension** is noted by elevated pressure gradient between the portal and central venous pressure and is characterized by hypervolemia, increased cardiac index, hypotension, and decreased systemic vascular resistance.
- Ascites is the pathologic accumulation of fluid within the peritoneal cavity. It is one of the earliest and most common presentations of cirrhosis.

TABLE 21-1

**Etiology of Cirrhosis**

| |
|---|
| Alcoholism |
| Chronic hepatitis C |
| Metabolic liver disease<br>Hemochromatosis<br>Wilson's disease<br>Nonalcoholic fatty liver disease |
| Immunologic disease<br>Autoimmune hepatitis<br>Primary biliary cirrhosis |
| Primary biliary cholangitis<br>Vascular disease<br>Budd–Chiari |
| Drugs<br>Isoniazid, methyldopa, amiodarone, amoxicillin-clavulanate, nitrofurantoin, diclofenac, methotrexate, nevirapine, propylthiouracil, valproate |

## Portal Hypertension and Varices

- The most important sequelae of portal hypertension are the development of varices and alternative routes of blood flow resulting in acute variceal bleeding. Portal hypertension is defined by the presence of a gradient of >5 mm Hg (0.7 kPa) between the portal and central venous pressures.
- Progression to bleeding can be predicted by Child–Pugh score, size of varices, and the presence of red wale markings on the varices. First variceal hemorrhage occurs at an annual rate of about 15% and carries a mortality of 7%–15%.

## Hepatic Encephalopathy

- HE is a functional disturbance of the brain caused by liver insufficiency or portal systemic shunting that presents on a wide spectrum of symptom severity ranging from subclinical alterations to coma.
- The symptoms of HE are thought to result from an accumulation of gut-derived nitrogenous substances in the systemic circulation as a consequence of decreased hepatic functioning and shunting through portosystemic collaterals bypassing the liver. These substances then enter the central nervous system (CNS) and result in alterations of neurotransmission that affect consciousness and behavior.
- Altered ammonia, glutamate, benzodiazepine receptor agonists, aromatic amino acids, and manganese are potential causes of HE. An established correlation between blood ammonia levels and mental status does not exist.
- Type A HE is induced by acute liver failure, type B results from portal-systemic bypass without intrinsic liver disease, and type C occurs with cirrhosis. HE may be classified as episodic, persistent, or minimal.

### Coagulation Defects

- End-stage chronic liver disease is associated with decreased synthetic capability of the liver leading to decreased levels of most procoagulant factors as well as the naturally occurring anticoagulants antithrombin, protein C, and protein S.
- Antithrombin and protein C are decreased, but two procoagulant factors, factor VIII and von Willebrand factor, are actually elevated. The net effect of these events could be thrombosis or clinically significant bleeding.
- Both platelet number and function may be affected in cirrhosis. Thrombocytopenia, a common finding in cirrhosis, could promote bleeding.

## CLINICAL PRESENTATION

- Initial symptoms of cirrhosis may be nonspecific including fatigue, loss of appetite, and weight loss (**Table 21-2**). Patients may also present with much more significant symptoms secondary to decompensation related to cirrhosis complications such as ascites (abdominal distention), spontaneous bacterial peritonitis (SBP) (abdominal discomfort with fever), hepatopulmonary syndrome (clubbing), hepatorenal syndrome (fluid overload, oliguria, renal failure), HE (confusion, lethargy), and/or variceal bleeding (secondary to esophageal or gastric varices from portal hypertension).
- Muscle wasting, palmar erythema, spider angiomas, parotid gland enlargement, white nails, Dupuytren contracture, peripheral neuropathy, and metabolic complications including gynecomastia, testicular atrophy, and axillary hair loss are all possibly related to cirrhosis.
- A thorough history including risk factors that predispose patients to cirrhosis should be taken. Diagnostics for cirrhosis include liver function tests, coagulation tests, complete blood count, and serologic tests for viral causes including hepatitis B and C.

TABLE 21-2

**Clinical Presentation of Cirrhosis**

| |
|---|
| **Signs and Symptoms**<br>• Asymptomatic<br>• Hepatomegaly and splenomegaly<br>• Pruritus, jaundice, palmar erythema, spider angiomata, and hyperpigmentation<br>• Gynecomastia and reduced libido<br>• Ascites, edema, pleural effusion, and respiratory difficulties<br>• Malaise, anorexia, and weight loss<br>• Encephalopathy |
| **Laboratory Tests**<br>• Hypoalbuminemia<br>• Elevated prothrombin time (PT)<br>• Thrombocytopenia<br>• Elevated alkaline phosphatase<br>• Elevated aspartate transaminase (AST), alanine transaminase (ALT), and γ-glutamyl transpeptidase (GGT) |

### Laboratory Abnormalities

- There are no laboratory or radiographic tests of hepatic function that can accurately diagnose cirrhosis. Serum or plasma chemistries called “liver function tests” can be grouped into two broad categories: (1) markers of liver injury such as aspartate transaminase (AST), alanine aminotransferase (ALT), γ-glutamyl transpeptidase (GGT), and alkaline phosphatase and (2) markers of hepatocellular function such as

prothrombin time (PT), bilirubin, and albumin.

- The aminotransferases, AST and ALT, are enzymes that have increased concentrations in plasma after acute or chronic hepatocellular injury. The highest elevations (>10,000 units per liter) are most likely to occur in shock liver and drug- or toxin-induced hepatitis. The ratio of AST to ALT with AST>ALT is more likely when cirrhosis of any etiology exists but also occurs in alcoholic and ischemic liver disease.
- Elevated serum alkaline phosphatase and GGT occur in cases of liver injury with a cholestatic pattern and therefore often accompany conditions such as primary biliary cirrhosis, primary sclerosing cholangitis, drug-induced cholestasis, and bile duct obstruction.
- Elevations in serum conjugated (or direct) bilirubin indicate hepatocellular dysfunction or cholestasis. Indirect bilirubin elevations occur due to overproduction (as seen with hemolysis), decreased uptake, or decreased hepatic conjugation of bilirubin.
- Albumin and coagulation factors are markers of hepatic synthetic activity and are used to estimate hepatocyte function in cirrhosis. Reduction in albumin usually indicates a disease duration of more than 3 weeks whereas severe liver disease can cause PT elevation in less than 24 hours. Thrombocytopenia is a common feature in chronic liver disease.
- The Child–Pugh classification system uses a combination of physical and laboratory findings to assess and define the severity of cirrhosis and is a predictor of patient survival, surgical outcome, and risk of variceal bleeding (**Table 21-3**).
- The model for end-stage liver disease (MELD-Na) is a newer scoring system:

$$\text{MELD score} = 9.57 \times \log_e(\text{serum creatinine [mg/dL]}) + 3.78 \times \log_e(\text{bilirubin [mg/dL]}) + 11.20 \times \log_e(\text{INR}) + 6.43$$

MELD score=9.57×loge(serum creatinine [mg/dL])+3.78× loge(bilirubin [mg/dL])+11.20×loge(INR)+6.43

or using SI units:

$$\text{MELD score} = 9.57 \times \log_e(\text{creatinine [µmol/L]}) + 3.78 \times \log_e(\text{bilirubin [µmol/L]}) \times 0.05848) + 11.20 \times \log_e(\text{INR}) + 6.43$$

MELD score=9.57×loge(creatinine [µmol/L])+3.78× loge(bilirubin [µmol/L])×0.05848)+11.20×loge(INR)+6.43

where international normalized ratio (INR) is TK.

$$\text{MELD-Na score} = \text{MELD} - (\text{sodium [mEq/L]}) - (0.025 \times \text{MELD} \times (140 - \text{sodium [mEq/L]})) + 140$$

MELD-Na score=MELD −(sodium [mEq/L])−(0.025×MELD×(140−sodium [mEq/L]))+140

or using SI units:

$$\text{MELD-Na score} = \text{MELD} - (\text{sodium [mmol/L]}) - (0.025 \times \text{MELD} \times (140 - \text{sodium [mmol/L]})) + 140$$

MELD-Na score=MELD −(sodium [mmol/L])−(0.025×MELD×(140−sodium [mmol/L]))+140

- In MELD, laboratory values less than 1 are rounded up to 1. The formula's score is multiplied by 10 and rounded to the nearest whole number.

TABLE 21-3

**Criteria and Scoring for the Child–Pugh Grading of Chronic Liver Disease**

| Score | 1 | 2 | 3 |
|---|---|---|---|
| Total bilirubin (mg/dL) | <2 (34.2 µmol/L) | 2–3 (34.2–51.3 µmol/L) | >3 (51.3 µmol/L) |
| Albumin (g/dL) | >3.5 (35 g/L) | 2.8–3.5 (28–35 g/L) | <2.8 (28 g/L) |
| Ascites | None | Mild | Moderate |
| Encephalopathy (grade) | None | 1 and 2 | 3 and 4 |
| Prothrombin time (seconds prolonged) | <4 | 4-6 | >6 |

Grade A, <7 points; grade B, 7–9 points; grade C, 10–15 points.

# TREATMENT

- Goals of Treatment: *Resolution of acute complications* such as tamponade of bleeding and resolution of hemodynamic instability for an episode of acute variceal hemorrhage and *prevention of complications* through lowering of portal pressure with medical therapy using non-selective β-adrenergic blocker therapy or supporting abstinence from alcohol.

## General Approach to Treatment

- Approaches to treatment include the following:

  ✔ Identify and eliminate the causes of cirrhosis (eg, alcohol abuse).

  ✔ Assess the risk for variceal bleeding and begin pharmacologic prophylaxis where indicated, reserving endoscopic therapy for high-risk patients or acute bleeding episodes as well as patients with contraindications or intolerance to nonselective β-adrenergic blockers.

  ✔ Evaluate the patient for clinical signs of ascites and manage with pharmacologic treatment (eg, diuretics) and paracentesis. SBP should be carefully monitored in patients with ascites who undergo acute deterioration.

  ✔ HE is a common complication of cirrhosis and requires clinical vigilance and treatment with dietary restriction, elimination of CNS depressants, and therapy to lower ammonia levels.

  ✔ Frequent monitoring for signs of hepatorenal syndrome, pulmonary insufficiency, and endocrine dysfunction is necessary.

## Management of Portal Hypertension and Variceal Bleeding

- The management of varices involves three strategies: (1) primary prophylaxis to prevent first bleeding episode, (2) treatment of variceal hemorrhage, and (3) secondary prophylaxis to prevent rebleeding in patients who have already bled.

### Primary Prophylaxis

- All patients with cirrhosis and portal hypertension should be screened for varices on diagnosis.
- The mainstay of primary prophylaxis is the use of a nonselective β-adrenergic blocking agent such as **propranolol, nadolol,** or **carvedilol.** These agents reduce portal pressure by reducing portal venous inflow via two mechanisms: decrease in cardiac output and decrease in

splanchnic blood flow.

- Patients with small varices plus risk factors for variceal hemorrhage including red wale marks or Child–Pugh grade C should receive prophylactic therapy with a nonselective β-adrenergic blocker.
- Therapy for medium or large varices that have not bled should be initiated with propranolol 20 mg twice daily, nadolol 20–40 mg once daily and titrate every 2–3 days to maximal tolerated dose or to a heart rates of 55–60 beats/min, or, rather than propranolol or nadolol, carvedilol could be chosen and started at 3.125 mg twice daily with slow titration at intervals of 1–2 weeks. β-Adrenergic blocker therapy should be continued indefinitely. Endoscopic vein ligation (EVL) is an alternative to β-adrenergic blockers. If EVL is chosen, it will be performed every 2–4 weeks until the obliteration of varices.
- Monitor patients for development of contraindications to β-adrenergic blockers such as renal impairment and hypotension that may accompany end-stage liver disease.

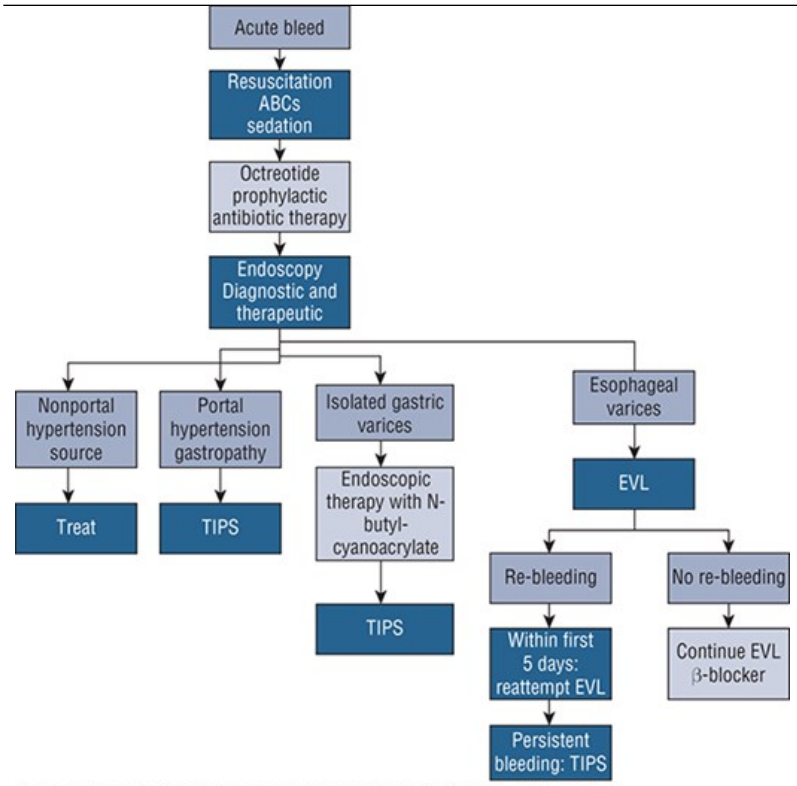
## Acute Variceal Hemorrhage

- **Figure 21-1** presents an algorithm for managing variceal hemorrhage. Evidence-based recommendations for select treatments are presented in **Tables 21-4** and **21-5**.
- Treatment of acute variceal bleeding includes general stabilizing and assessment measures as well as specific measures to control the acute hemorrhage and prevent complications.
- Initial treatment goals include: (1) adequate blood volume resuscitation, (2) protection of the airway from aspiration of blood, (3) prophylaxis against SBP and other infections, (4) control of bleeding, (5) prevention of rebleeding, (6) preservation of liver function of HE, and (7) prevention of acute kidney injury.
- Prompt stabilization of blood volume to maintain hemoglobin of 7 g/dL (70 g/L; 4.34 mmol/L) to 8 g/dL (80 g/L; 4.97 mmol/L) is recommended.
- Combination pharmacologic therapy plus EVL (preferred) or sclerotherapy (when EVL is not technically feasible) is the most rational approach to treatment of acute variceal bleeding.
- Vasoactive drug therapy is used to stop or slow bleeding as soon as a diagnosis of variceal bleeding is suspected and is started before endoscopy. Treatment with **octreotide** should be initiated early to control bleeding and facilitate endoscopy. Octreotide is administered as an IV bolus of 50 mcg followed by a continuous infusion of 50 mcg/hr. It should be continued for 2–5 days after acute variceal bleeding. Vasoactive therapy discontinuation can be considered once the patient is free of bleeding for at least 24 hours.
- Prophylactic antibiotic therapy to prevent SBP and other infections should be implemented upon admission. For all patients with cirrhosis and acute variceal bleeding, intravenous ceftriaxone 1 g/24 hours is recommended or oral **ciprofloxacin** 500 mg twice daily, or **trimethoprim–sulfamethoxazole** one double-strength tablet twice daily. A 250-mg dose of **erythromycin** intravenously prior to endoscopy may be used to accelerate gastric emptying of clots and improve visibility during the endoscopic procedure.
- Child–Pugh Class C patients and those in Class B with active hemorrhage at the time of diagnostic endoscopy are at high risk for failing standard therapy with EVL plus octreotide. In these patients early transjugular intrahepatic portosystemic shunt (TIPS) may be considered instead of standard therapy. The TIPS procedure involves the placement of one or more stents between the hepatic vein and the portal vein.

FIGURE 21-1

**Management of acute variceal hemorrhage.**

(ABCs, airway, breathing, and circulation; EVL, endoscopic vein ligation; TIPS, transjugular intrahepatic portosystemic shunt.)




Source: Terry L. Schwinghammer, Joseph T. DiPiro, Vicki L. Ellingrod, Cecily V. DiPiro: *Pharmacotherapy Handbook, 11e*


TABLE 21-4

**Evidence-Based Table of Select Treatment Recommendations: Variceal Bleeding in Portal Hypertension**

| Recommendation | Grade |
|---|---|
| Prevention of variceal bleeding | |
| Nonselective β-blocker therapy should be initiated in: | |
| Patients with small varices and criteria for increased risk of hemorrhage | 1b |
| Patients with medium/large varices | 1a |
| EVL may be recommended for prevention in patients with medium/large varices at high risk of hemorrhage instead of nonselective β-blocker therapy | 1a |
| Treatment of variceal bleeding | |
| Short-term antibiotic prophylaxis should be instituted on admission | 1a |
| Vasoactive drugs should be started as soon as possible, prior to endoscopy, and maintained for up to 5 days | 1a |
| Endoscopy should be performed to diagnose variceal bleeding and treat bleeding with EVL | 1b |
| Endoscopy should be performed within 12 hours of presentation | 5 |
| Unless contraindicated, erythromycin 250 mg IV should be administered 30–120 minutes prior to endoscopy | 1b |
| Secondary prophylaxis of variceal bleeding | |
| Nonselective β-blocker therapy plus EVL is the best therapeutic option for prevention of recurrent variceal bleeding | 1a |

Recommendation grading:

1a: Systematic review (with homogeneity) of randomized controlled trials.

1b: Individual randomized controlled trial with narrow confidence interval.

1c: All or none.

2a: Systematic review (with homogeneity) of cohort studies.

2b: Individual cohort study (including low-quality randomized controlled trial).

2c: Outcomes research; ecological studies.

3a: Systematic review (with homogeneity) of case-controlled studies.

3b: Individual case-control study.

4: Case-series (and poor quality cohort and case-control studies).

5: Expert opinion.

TABLE 21-5

**Evidence-Based Table of Selected Treatment Recommendations: Ascites and Spontaneous Bacterial Peritonitis**

| Recommendation | Grade |
|---|---|
| Ascites | |
| Paracentesis should be performed in patients with apparent new-onset ascites | IC |
| Sodium restriction of 2000 mg/day should be instituted as well as oral diuretic therapy with spironolactone and furosemide | IIaA |
| Diuretic-sensitive patients should be treated with sodium restriction and diuretics rather than serial paracentesis | IIaC |
| Refractory ascites | |
| Serial therapeutic paracenteses may be performed | IC |
| Postparacentesis albumin infusion of 6–8 g/L of fluid removed can be considered if more than 5 L is removed during paracentesis | IIaA |
| Treatment of SBP | |
| If ascitic fluid PMN counts are >250 cells/$mm^3$ ($0.25 \times 10^9$/L), empiric antibiotic therapy should be instituted (cefotaxime 2 g every 8 hours) | IA |
| If ascitic fluid PMN counts are <250 cells/$mm^3$ ($0.25 \times 10^9$/L), but signs or symptoms of infection exist, empiric antibiotic therapy should be initiated while awaiting culture results | IB |
| Ofloxacin 400 mg twice daily may be substituted for cefotaxime in patients without vomiting, shock, grade II or higher encephalopathy, or serum creatinine >3 mg/dL (265 µmol/L) and if there is no prior exposure to quinolones | IIaB |
| If ascitic fluid polymorphonuclear leukocyte counts are >250 cells/$mm^3$ ($0.25 \times 10^9$/L), clinical suspicion of SBP is present, and the patient has a serum creatinine >1 mg/dL (88 µmol/L), blood urea nitrogen >30 mg/dL (10.7 mmol/L), or total bilirubin over 4 mg/dL (68.4 µmol/L), 1.5 g/kg albumin should be infused within 6 hours of detection and 1 g/kg albumin infusion should also be given on day 3 | IIaB |
| Prophylaxis against SBP | |
| Short-term antibiotic prophylaxis should be used for 7 days to prevent SBP in cirrhosis patients with GI hemorrhage | IA |
| Patients who survive an episode of SBP should receive long-term prophylaxis with either daily ciprofloxacin or trimethoprim–sulfamethoxazole | IA |
| Patients with low-protein ascites (<1.5 g/dL [15 g/L]) plus at least one of the following: serum creatinine ≥1.2 mg/dL (106 µmol/L), blood urea nitrogen ≥25 mg/dL (8.9 mmol/L), serum sodium ≤130 mEq/L (mmol/L), or Child–Pugh score of ≥9 with bilirubin ≥3 mg/dL (51.3 µmol/L) may also justifiably receive long-term ciprofloxacin or sulfamethoxazole/trimethoprim as prophylaxis | IA |

Recommendation grading: Class I—conditions for which there is evidence and/or general agreement; Class II—conditions for which there is conflicting evidence and/or a divergence of opinion; Class IIa—weight of evidence/opinion is in favor of efficacy; Class IIb—efficacy less well established; Class III—conditions for which there is evidence and/or general agreement that treatment is not effective and/or potentially harmful; Level A—data from multiple randomized trials or meta-analyses; Level B—data derived from single randomized trial or nonrandomized studies; Level C—only consensus opinion, case studies, or standard of care.

## Prevention of Rebleeding

- A nonselective β-adrenergic blocker along with EVL is the best treatment option for prevention of rebleeding.
- **Propranolol** may be given at 20 mg twice daily (or **nadolol** 40 mg once daily) and titrated weekly to achieve a goal of heart rate 55–60 beats/min or the maximal tolerated dose. Patients should be monitored for evidence of bradycardia, bronchospasm, and hypoglycemia, particularly in patients with insulin-dependent diabetes, as well as symptoms of heart failure and excessive sodium and water retention.
- Patients who cannot tolerate or who fail pharmacologic and endoscopic interventions can be considered for tips or surgical shunting to prevent bleeding.

## Ascites

- The therapeutic goals for patients with ascites are to control the ascites, prevent or relieve ascites-related symptoms (dyspnea, abdominal pain, and distention), and prevent SBP and hepatorenal syndrome.
- For patients with ascites, a serum–ascites albumin gradient should be determined. If the gradient is ≥1.1 g/dL (11 g/L), the patient almost certainly has portal hypertension.
- The treatment of ascites secondary to portal hypertension includes abstinence from alcohol, sodium restriction (to 2 g/day), and diuretics. Fluid loss and weight change depend directly on sodium balance in these patients. A goal of therapy is to increase urinary excretion of sodium to >78 mmol/day.
- Diuretic therapy should be initiated with single morning doses of **spironolactone** 100 mg and **furosemide** 40 mg, titrated every 3–5 days (or spironolactone alone), using the 100:40 mg dose ratio (spironolactone to furosemide) with a goal of 0.5 kg maximum daily weight loss. The dose of each can be increased together, maintaining the 100:40 mg ratio, to a maximum daily dose of 400 mg spironolactone and 160 mg furosemide.
- Diuretic therapy should be discontinued in patients who experience uncontrolled or recurrent encephalopathy, severe hyponatremia (serum sodium <120 mEq/L [mmol/L]) despite fluid restriction, or renal insufficiency (serum creatinine >2 mg/dL [177 µmol/L]).
- If tense ascites is present, paracentesis should be performed prior to institution of diuretic therapy and salt restriction.
- Liver transplant should be considered in patients with refractory ascites.

## Spontaneous Bacterial Peritonitis

- Patients with documented or suspected SBP should receive broad-spectrum antibiotic therapy to cover *Escherichia coli, Klebsiella pneumoniae,* and *Streptococcus pneumoniae*.
- **Cefotaxime** 2 g every 8 hours IV or a similar third-generation cephalosporin for 5 days is considered the drug of choice. Oral **ofloxacin** 400 mg every 12 hours for 8 days is an alternative for patients without vomiting, shock, significant HE, or serum creatinine >3 mg/dL (265 µmol/L).
- Patients who survive an episode of SBP should receive long-term antibiotic prophylaxis with daily ciprofloxacin 500 mg or double-strength trimethoprim–sulfamethoxazole.

## Hepatic Encephalopathy

- The general approach to the management of HE is four pronged and includes the following: care for patients with altered consciousness, identify and treat any other causes besides HE for altered mental status, identify and treat any precipitating factors, and begin empirical HE treatment.
- The grading system for HE is shown in **Table 21-6**.
- Treatment approaches include: (1) reduction in blood ammonia concentrations by dietary restrictions, with drug therapy aimed at inhibiting ammonia production or enhancing its removal (non-absorbable disaccharides such as lactulose and antibiotics); and (2) inhibition of γ-aminobutyric acid-benzodiazepine receptors by **flumazenil**.

- To reduce blood ammonia concentrations in patients with episodic HE, protein intake is limited or withheld (while maintaining caloric intake) until the clinical situation improves. Protein intake can be titrated back up based on tolerance to a total of 1.2–1.5 g/kg/day. Vegetable-source and dairy-source protein may be preferable to meat-source protein because the latter contains a higher calorie-to-nitrogen ratio.
- To reduce blood ammonia concentrations in episodic HE, lactulose is initiated at a dose of 25 g (16.7 g) orally every 1–2 hours (or by retention enema: 300 mL lactulose syrup in 1 L water every 6–8 hours) until catharsis begins and the patient experiences one to two bowel movements. The dose is then decreased to 15–45 mL orally every 8–12 hours and titrated to produce two to three soft stools per day for chronic therapy.
- **Rifaximin** 550 mg twice daily plus lactulose is superior to lactulose alone in patients with a history of recurrent HE. Rifaximin is now considered the next line of therapy for recurrent HE over either metronidazole or neomycin.

TABLE 21-6

**Grading System for Hepatic Encephalopathy**

| Grade | Level of Consciousness | Personality/Intellect | Neurologic Abnormalities |
|---|---|---|---|
| Unimpaired | Normal | Normal | Normal |
| Minimal | No clinical evidence of change | No clinical evidence of change/alterations identified on psychometric or neuropsychological testing | No clinical evidence of change |
| I | Trivial lack of awareness; shortened attention span | Euphoria or anxiety; impairment of addition or subtraction | Altered sleep rhythm |
| II | Lethargic | Obvious personality changes; inappropriate behavior; apathy | Asterixis; dyspraxia; disoriented for time |
| III | Somnolent but arousable | Bizarre behavior | Responsive to stimuli; confused; gross disorientation to time and space |
| IV | Coma/unarousable | None | Does not respond to stimuli |

## EVALUATION OF THERAPEUTIC OUTCOMES

- **Table 21-7** summarizes the drug monitoring guidelines for patients with cirrhosis and portal hypertension, including monitoring parameters and therapeutic outcomes.

TABLE 21-7

**Drug Monitoring Guidelines**

| Drug | Adverse Drug Reaction | Monitoring Parameter | Comments |
|---|---|---|---|
| Nonselective β-adrenergic blocker | Heart failure, bronchospasm, glucose intolerance | BP, HR<br>Goal HR: 55–60 beats/min or maximal tolerated dose | Nadolol, propranolol, carvedilol |
| Octreotide | Bradycardia, hypertension, arrhythmia, abdominal pain | BP, HR, EKG, abdominal pain | |
| Spironolactone/furosemide | Electrolyte disturbances, dehydration, renal insufficiency, hypotension | Serum electrolytes (especially potassium), SCr, blood urea nitrogen, BP<br>Goal sodium excretion: >78 mmol/day | Spot urine sodium concentration greater than potassium concentration correlates well with daily sodium excretion >78 mmol/day |
| Lactulose | Electrolyte disturbances | Serum electrolytes<br>Goal number of soft stools per day: 2–3 | |
| Neomycin | Ototoxicity, nephrotoxicity | SCr, annual auditory monitoring | |
| Metronidazole | Neurotoxicity | Sensory and motor neuropathy | |
| Rifaximin | Nausea, diarrhea | | |

BP, blood pressure; beats/min, beats per minute; EKG, electrocardiogram; HR, heart rate; SCr, serum creatinine; mmol, millimole.

*See Chapter 54, Portal Hypertension and Cirrhosis, authored by Julie M. Sease and Alyson G. Wilder, for a more detailed discussion of this topic.*