Cirrhosis

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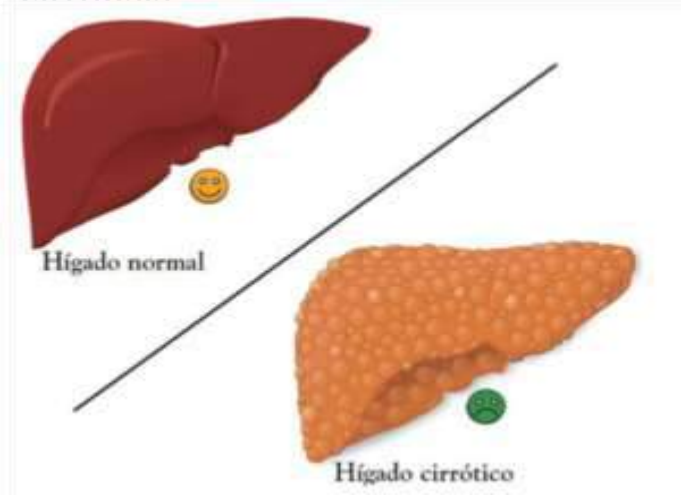
Cirrhosis

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

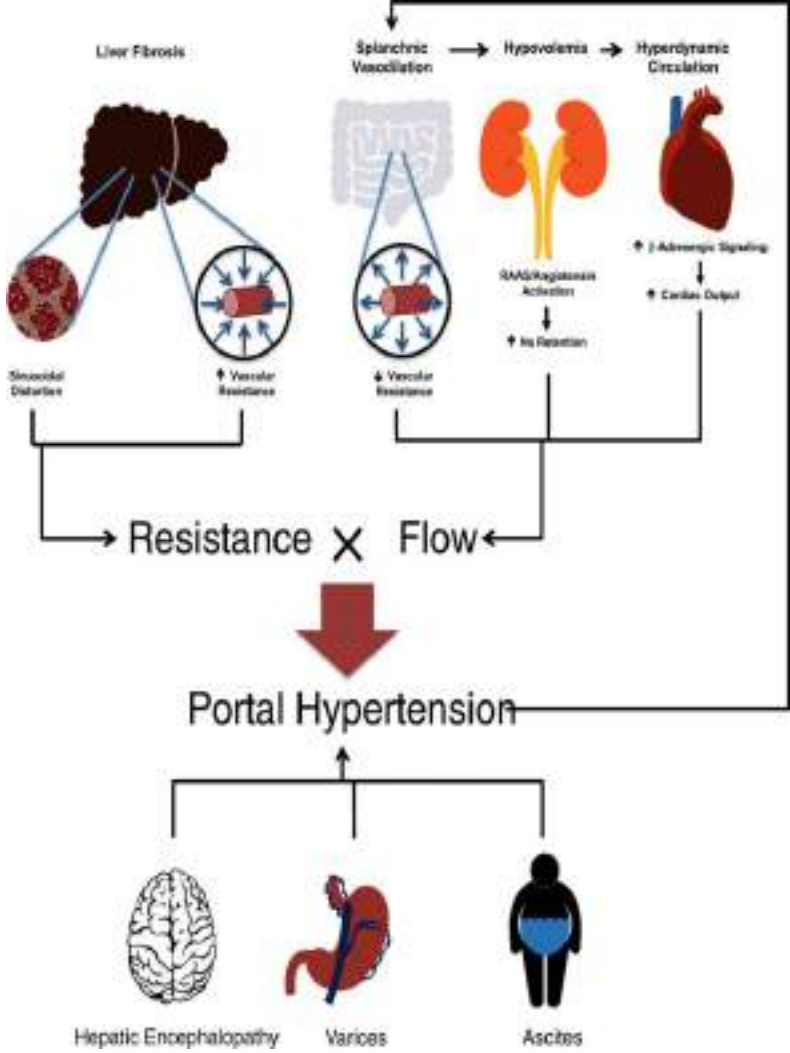


- **PATHOPHYSIOLOGY**
- The distorted architecture of the cirrhotic liver impedes portal blood flow, interferes with hepatocyte perfusion, and disrupts hepatic synthetic functions such as the production of albumin.
- Primary causes of cirrhosis in developed countries include hepatitis C, excessive alcohol intake, and nonalcoholic fatty liver disease .

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.

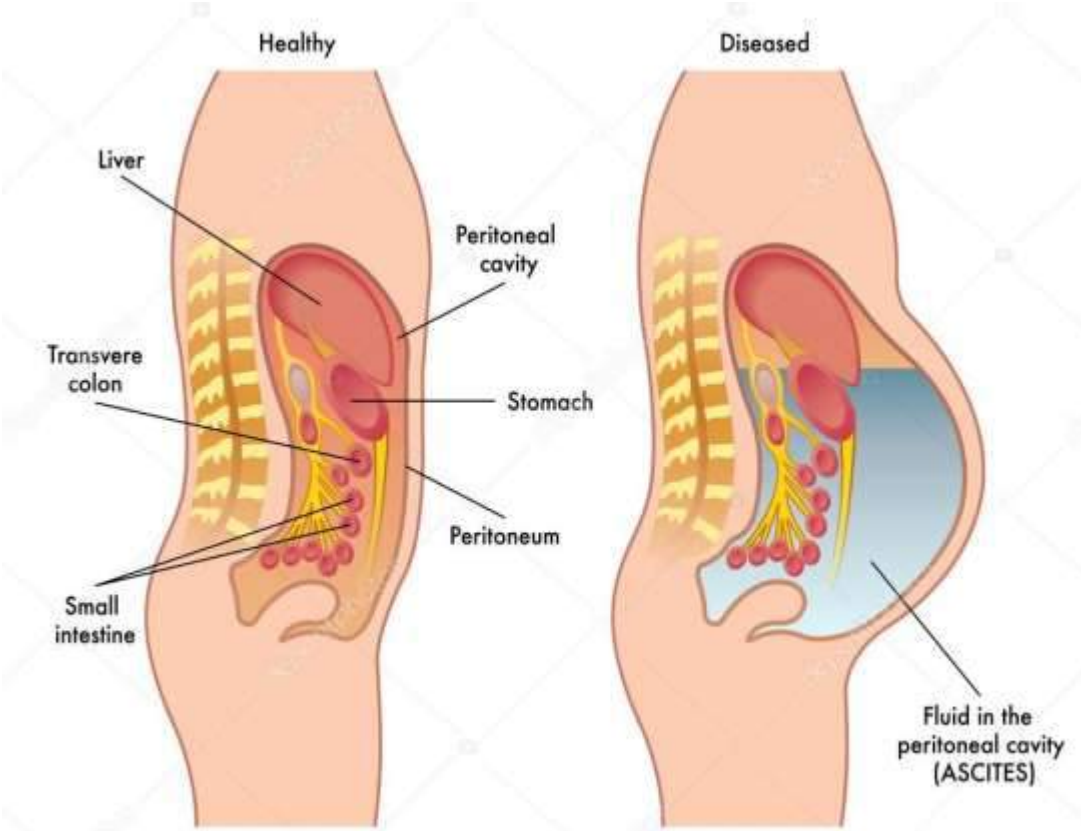
Additionally, splanchnic vasodilation leads to hypoperfusion of the renal system, which causes activation of the renin–angiotensin–aldosterone system and, subsequently, significant fluid retention.

The pathophysiologic abnormalities that cause it often result in ascites, portal hypertension and esophageal varices, HE, and coagulation disorders.



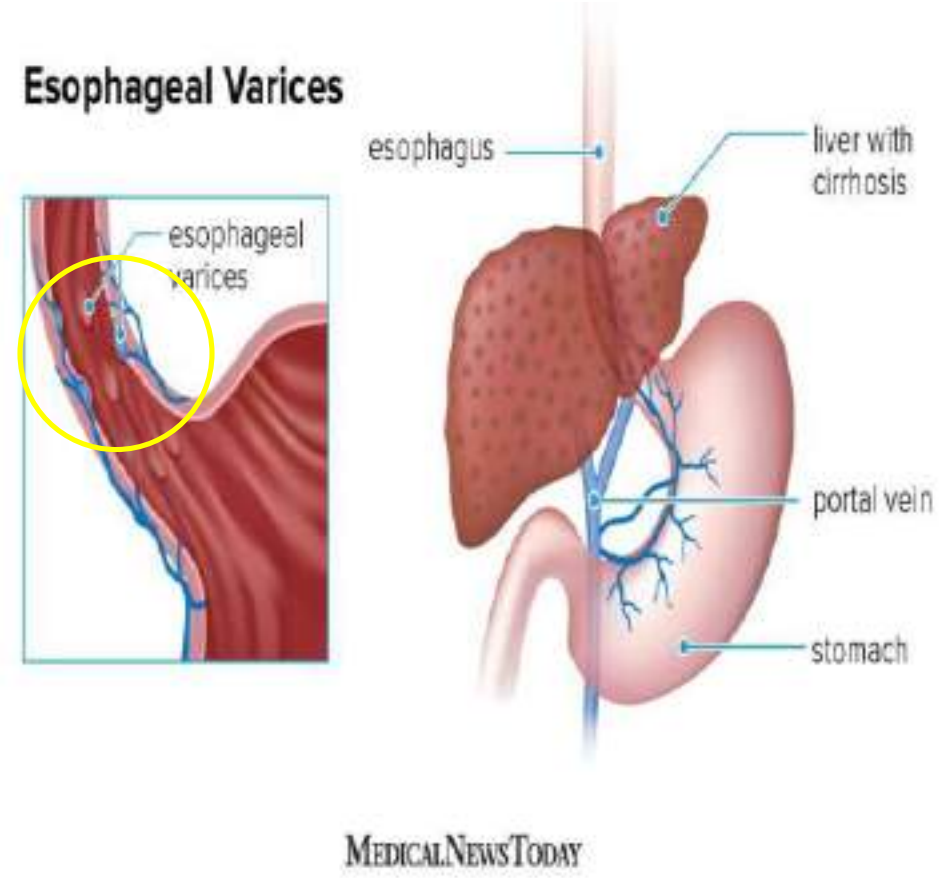
Ascites

- is the pathologic accumulation of fluid within the peritoneal cavity. It is one of the earliest and most common presentations of cirrhosis



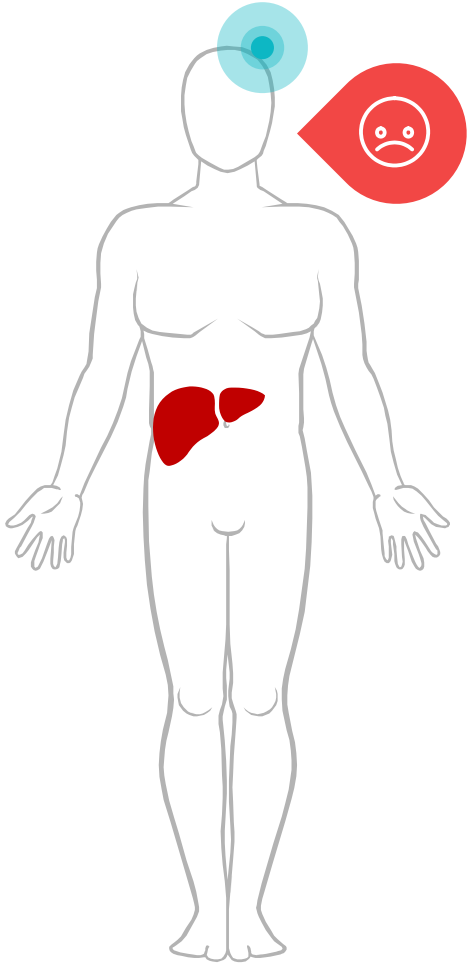
Portal Hypertension and Varices

- Portal hypertension is noted by elevated pressure gradient between the portal and central venous pressure (Portal hypertension is defined by the presence of a gradient of >5 mm Hg (0.7 kPa) between the portal and central venous pressures.) and is characterized by hypervolemia, increased cardiac index, hypotension, and decreased systemic vascular resistance.
- The most important sequelae of portal hypertension are the development of varices and alternative routes of blood flow resulting in acute variceal bleeding
- Progression to bleeding can be predicted by Child–Pugh score, size of varices, and the presence of red wale markings on the varices.



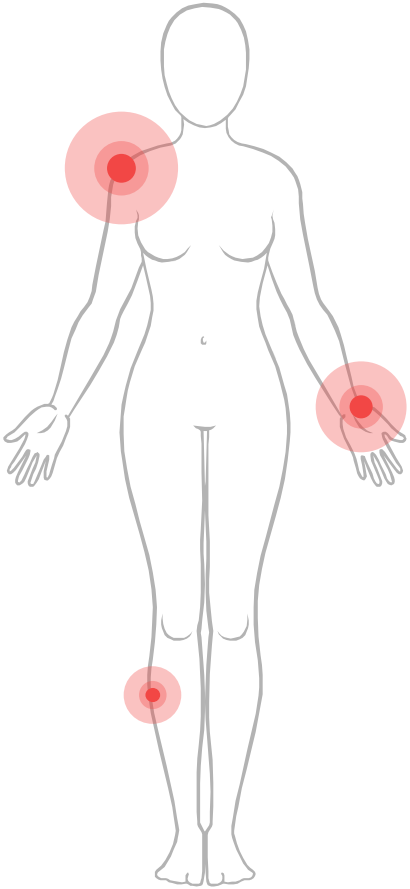
Hepatic Encephalopathy

- 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.



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.



Signs and Symptoms

- Asymptomatic
- Hepatomegaly and splenomegaly
- Pruritus, jaundice, palmar erythema, spider angiomata, and hyperpigmentation
- Gynecomastia and reduced libido
- Ascites, edema, pleural effusion, and respiratory difficulties
- Malaise, anorexia, and weight loss
- Encephalopathy

Laboratory Tests

- Hypoalbuminemia
- Elevated prothrombin time (PT)
- Thrombocytopenia
- Elevated alkaline phosphatase
- Elevated aspartate transaminase (AST), alanine transaminase (ALT), and γ-glutamyl transpeptidase (GGT)

Review the stigmata of chronic liver disease

A70-year-old white man (height 72 inches, weight 75 kg) with a history of intravenous drug abuse and he had metastatic prostate cancer with life expectance about 7 months and he is seen today for a new diagnosis of chronic HCV, genotype 1a. Pretreatment laboratory values include AST 350 IU/mL, ALT 420 IU/mL, HCV RNA 950,000 IU/mL, SCr 1 mg/dL, hemoglobin 12 g/dL, and WBC 12 × 103 cells/mm3.

As a clinical pharmacist what is your suggestion for your patient?

A38-year-old white man (height 72 inches, weight 75 kg) with a history of intravenous drug abuse with no history of other disease and he is seen today for a new diagnosis of chronic HCV. Pretreatment laboratory values include AST 350 IU/mL, ALT 420 IU/mL, HCV RNA 950,000 IU/mL, SCr 1 mg/dL, hemoglobin 12 g/dL, and WBC 12 × 103 cells/mm3. As a clinical pharmacist what is your suggestion for your patient?

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.

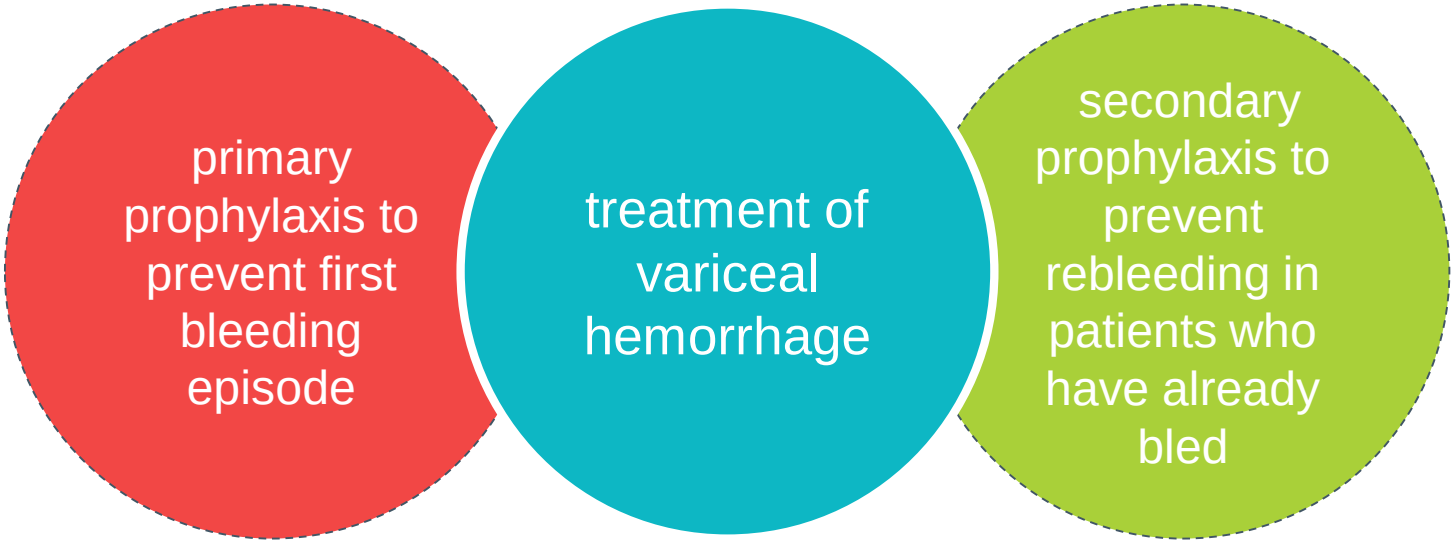
✔ Evaluate the patient for clinical signs of ascites and manage with pharmacologic treatment (eg, diuretics) and paracentesis. SBP should be carefully monitored in patients with ascites who undergo acute deterioration.

✔ 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



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 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

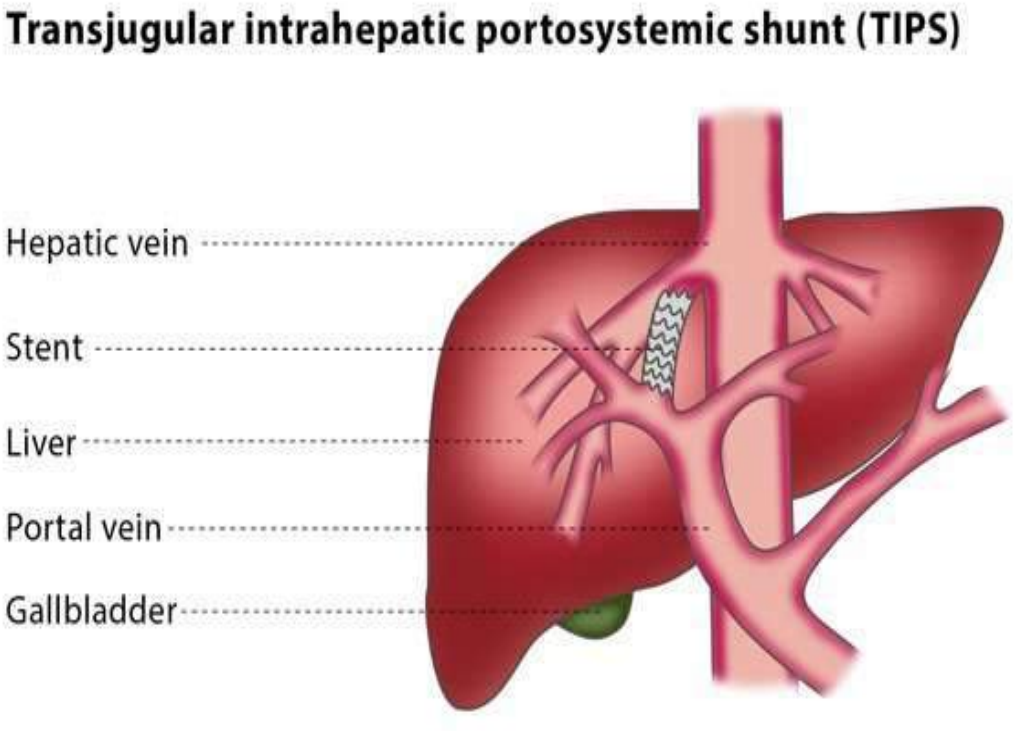
Treatment of acute variceal bleeding includes general stabilizing and assessment measures as well as specific measures to control the acute hemorrhage and prevent complications. Initial treatment goals include:

- adequate blood volume resuscitation
- protection of the airway from aspiration of blood
- Prophylaxis against SBP and other infections
- control of bleeding
- prevention of rebleeding
- preservation of liver function of HE, and 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.



Ascites

The therapeutic goals for patients with ascites are to
1. control the ascites,
2. prevent or relieve ascites-related symptoms and
3. 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

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.

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