Chapter 55: Portal Hypertension and Cirrhosis

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UPDATE SUMMARY

Update Summary

May 15, 2023

The following sections were updated:

- Key Concepts: one key concept replaced with a new item
- Spontaneous Bacterial Peritonitis: new changes regarding antimicrobial therapy
- Self-Assessment Questions: edits made to questions 2, 6, and 8 and their corresponding answers

CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 21, Cirrhosis and Portal Hypertension.

KEY CONCEPTS

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1. Cirrhosis is a severe, chronic, potentially irreversible disease associated with significant morbidity and mortality. The progression of cirrhosis secondary to alcohol intake, both in those with alcoholic cirrhosis and cirrhosis due to other causes, can be interrupted by abstinence from alcohol. It is therefore imperative for the clinician to educate and support abstinence from alcohol as part of the overall treatment strategy of the underlying liver disease.

2. Patients with cirrhosis, except those screened and considered to be at low risk, should receive endoscopic evaluation looking for the presence of varices. Patients with medium to large varices, or small varices with risk factors, should receive primary prophylaxis with nonselective β-adrenergic blockade therapy to prevent variceal hemorrhage.

3. When nonselective β-adrenergic blocker therapy with propranolol or nadolol is used to prevent rebleeding, therapy should be titrated to achieve a goal heart rate of 55 to 60 beats/min, but systolic blood pressure must also be maintained above 90 mm Hg.

4. Octreotide is the preferred vasoactive agent for the medical management of variceal bleeding in the United States. Endoscopic band ligation is the primary therapeutic tool for the management of acute variceal bleeding.

5. Aldosterone antagonists and loop diuretics are recommended for the management of ascites in patients with cirrrhosis.

6. All patients who have survived an episode of spontaneous bacterial peritonitis (SBP) should receive long-term antibiotic prophylaxis.

7. The mainstay of treatment of hepatic encephalopathy (HE) involves therapy to lower blood ammonia concentrations and includes diet modifications, lactulose, and rifaximin alone or in combination with lactulose.

BEYOND THE BOOK

BEYOND THE BOOK

Watch the short Medscape video "Cirrhosis Overview Clinical Presentation" (https://www.youtube.com/watch?v=XJQn8MXnTWg). This video reviews the basic pathophysiology of cirrhosis and connects it to the most common complications of decompensated cirrhosis. Create a summary table of treatment options for each complication associated with decompensated cirrhosis: portal hypertension (primary prophylaxis against bleeding, acute bleeding, and secondary prophylaxis against bleeding), ascites, spontaneous bacterial peritonitis (SBP) (acute treatment and secondary prophylaxis), and hepatic encephalopathy. Use the below table as a guide.

Complication	Treatment/drug of choice (to include dose, route, and frequency)	Common adverse effects	Monitoring parameters	Patient counseling points/pharmacy pearls
Portal hypertension Primary prophylaxis against bleeding Acute bleeding Secondary prophylaxis of bleeding				
Ascites				
SBP Acute treatment Secondary prophylaxis				
Hepatic encephalopathy				

INTRODUCTION

Chronic liver injury causes damage to normal liver tissue resulting in the development of regenerative nodules surrounded by dense fibrotic material, which are diagnostic hallmarks of cirrhosis.[1] 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; encephalopathy; and hepatocellular carcinoma. When advanced, cirrhosis can also lead to the development of both renal and pulmonary dysfunction.

1 While cirrhosis has many causes (Table 55-1),[1–3] in industrialized countries, primary etiologies include hepatitis C, excessive alcohol intake, and nonalcoholic fatty liver disease.[1,2] Treatment strategies for managing the most commonly encountered clinical complications of cirrhosis are discussed. Fibrosis, even significant enough to have caused cirrhosis, is known to regress when anti-viral therapy for hepatitis B and C is instituted.[1] The reader is referred to Chapter 58, "Viral Hepatitis" for a detailed discussion of the treatment of cirrhosis secondary to hepatitis.

TABLE 55-1

Etiology of Cirrhosis

Alcoholism
Chronic hepatitis C
Metabolic liver disease
Hemochromatosis
Wilson disease
Nonalcoholic fatty liver disease
Immunologic disease
Autoimmune hepatitis
Primary biliary cirrhosis
Primary biliary cholangitis
Vascular disease
Budd–Chiari
Drug-induced liver injury (below list not all-inclusive)
Isoniazid, macrolides, amoxicillin-clavulanate, nitrofurantoin, fluoroquinolones, amiodarone, nonsteroidal anti-inflammatory drugs, allopurinol, sulfasalazine, methotrexate, interferon-β, interferon-α, anti-tumor necrosis factor inhibitors, valproate, lamotrigine, phenytoin, carbamazepine, green tea extract

Data from References 1–3.

EPIDEMIOLOGY

Chronic liver disease and cirrhosis were responsible for nearly 42,838 deaths in America in 2018 making it the 11th leading cause of death.[4] Acute variceal bleeding and spontaneous bacterial peritonitis (SBP) are among the immediately life-threatening complications of cirrhosis. Associated conditions causing significant morbidity include ascites and hepatic encephalopathy (HE).

PATHOPHYSIOLOGY OF CIRRHOSIS

Any discussion of cirrhosis must be based on a firm understanding of hepatic anatomy and vascular supply. Conceptually, the liver can be thought of as an elaborate blood filtration system receiving blood from the hepatic artery and the portal vein (Fig. 55-1), with portal blood originating from the small intestines.[5] Blood enters the liver via the portal triad, which contains branches of the portal vein, hepatic artery, and bile ducts. It then drains through the sinusoidal space (also known as the space of Disse) of the hepatic lobule (Fig. 55-2), which is lined by the workhorses of the liver, the hepatocytes. Individual hepatocytes are arranged in plates that are one cell thick and organized around individual central veins. The six or more surfaces of each individual hepatocyte make contact with adjacent hepatocytes, border the bile canaliculi, or are exposed to the sinusoidal space. Filtered blood travels into the terminal hepatic venules, also called central veins, and then empties into larger hepatic veins and eventually into the inferior vena cava. There are functional gradients of hepatocytes based on oxygen saturation. Hepatocytes closest to the portal triad, which contains the hepatic artery, have greater oxygen saturation than those hepatocytes nearer to the terminal hepatic venule. Blood flows past hepatocytes in zone one, then zone two, and finally zone three before entering the central vein. Hepatocytes in zone one are involved in gluconeogenesis, urea synthesis, and oxidative energy metabolism while those in zone three carry out the functions of glycolysis and lipogenesis.

FIGURE 55-1

The portal venous system.

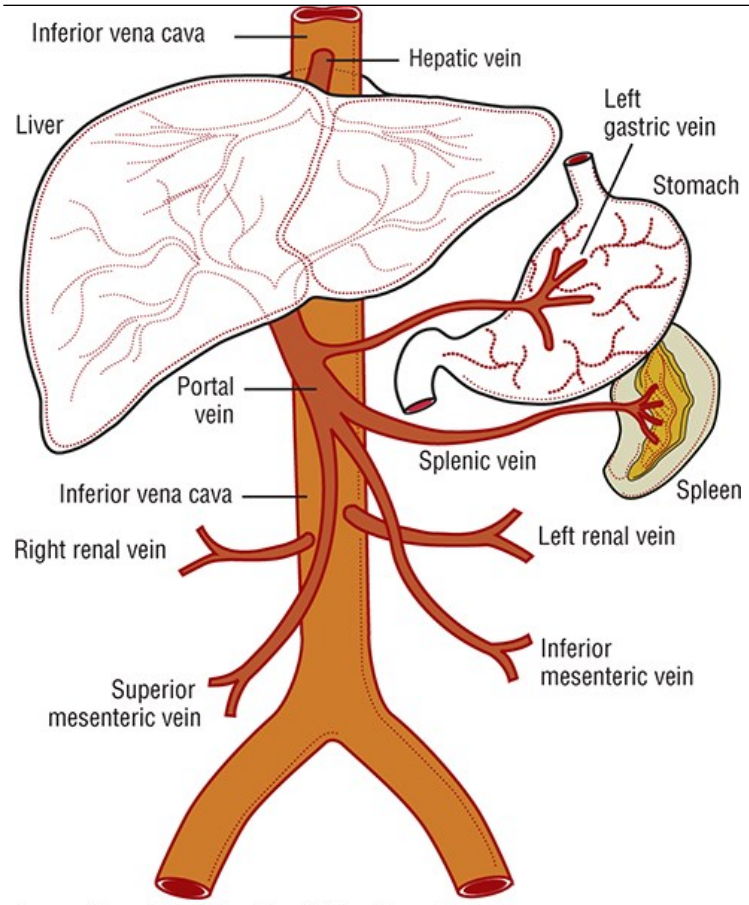
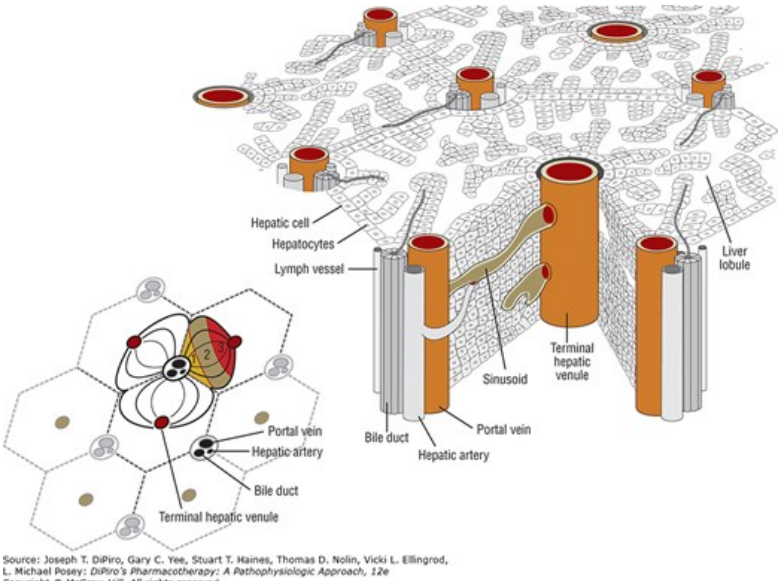


FIGURE 55-2

The hepatic lobule.



Hepatic stellate cells (HSCs), located in the space of Disse and surrounded by hepatocytes and endothelial cells, are the cell type primarily responsible

for the formation of liver fibrosis.[6] Normally, HSCs function to store vitamin A and maintain the normal matrix of the sinusoidal space. Quiescent HSCs become proliferative and transform into myofibroblasts when they are stimulated to do so by hepatocytes, Kupffer cells, platelets, leukocytes, and sinusoidal endothelial cells in reaction to exposure to toxic agents, viruses, or other insults. As myofibroblasts, HSCs lose the ability to store retinoids and upregulate synthesis of extracellular matrix components. When pro-fibrogenic triggers are persistently present, excessive extracellular matrix components accumulate which alter the liver's architecture, reduce its elasticity, and impact the flow of blood through the liver which leads to elevated sinusoidal pressure and portal hypertension, hallmarks of cirrhosis.

Portal hypertension leads to changes in the splanchnic vasculature and circulation.[7] Splanchnic vasodilation and the formation of new blood vessels contribute to an increased splanchnic blood flow, formation of gastroesophageal varices, and variceal bleeding. Additionally, splanchnic and systemic vasodilation leads to hypoperfusion of the renal system that causes activation of the renin-angiotensin-aldosterone system and the sympathetic nervous system which subsequently result in functional renal impairment as well as sodium and water retention presenting as ascites.[8] Therein lies the pathophysiology of ascites and renal dysfunction that often accompany chronic liver disease. Portosystemic shunting may also occur and is involved in HE and other complications.[7]

ANATOMIC AND PHYSIOLOGIC EFFECTS OF CIRRHOSIS

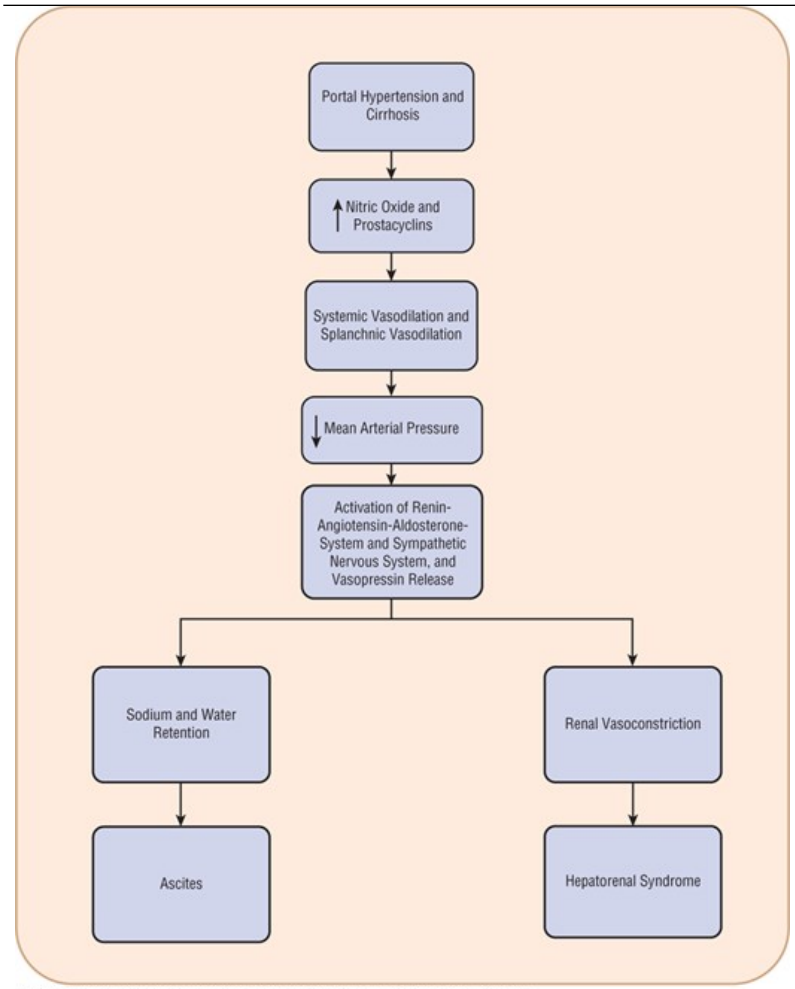
Cirrhosis and the pathophysiologic abnormalities that cause it result in the commonly encountered problems of ascites, portal hypertension, esophageal varices, HE, and coagulation disorders. Other less common problems in patients with cirrhosis include hepatorenal syndrome, hepatopulmonary syndrome, and endocrine dysfunction. These are discussed under section "Management of Portal Hypertension and Variceal Bleeding."

Ascites

Ascites is the accumulation of an excessive amount of fluid within the abdomen. It is the most common major complication of cirrhosis with approximately 20% of patients presenting with ascites at the time of their cirrhosis diagnosis.[9] As noted above, portal hypertension activates vasodilatory mechanisms leading to splanchnic and systemic vasodilation and a resultant drop in mean arterial pressure.[8] Portal hypertension is also thought to lead to bacterial translocation of gut bacteria causing local and systemic inflammation and the generation of vasodilatory nitric oxide and prostacyclins in the splanchnic vasculature which further reduces mean arterial pressure. This drop in mean arterial pressure is recognized by arterial baroreceptors activating endogenous vasoconstrictor systems including the sympathetic nervous system, the renin-angiotensin-aldosterone system, as well as a nonosmotic vasopressin release.[10] Renal vasoconstriction and sodium and water retention ensue resulting in the formation of edema and ascites. The excess fluid shifts from the intravascular compartment into the abdominal cavity. Hypoalbuminemia, which results from the decreased synthetic function of the diseased liver, contributes further to fluid leakage into the abdomen. The end result of this complex process is the sustained peritoneal ascites of end-stage liver disease (Fig. 55-3).

FIGURE 55-3

Pathogenesis of ascites.



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Portal Hypertension and Varices

Sinusoidal portal hypertension is most often caused by cirrhosis.[11] It is associated with acute variceal bleeding, a medical emergency that is among the most severe complications of cirrhosis.[12] Portal hypertension is defined by the presence of a gradient of greater than 5 mm Hg (0.7 kPa) between the portal and central venous pressures (see Fig. 55-1).[11] This gradient is called the hepatic venous pressure gradient (HVPG). Esophageal and gastric varices and variceal bleeding may arise after an HVPG pressure gradient of 10 mm Hg (1.3 kPa) is reached.

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% to 15%. Rebleeding is common following initial hemorrhage with a median rate of 60% and carries a mortality rate as high as 33%. Prevention of bleeding is a major goal in the therapy of portal hypertension, and strategies include both pharmacologic and surgical approaches.

Hepatic Encephalopathy

Hepatic encephalopathy 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.[13] Symptoms of HE result from an accumulation of gut-derived nitrogenous substances in the systemic circulation as a consequence of decreased hepatic functioning.[14] Once these substances enter the CNS, they cause alterations of neurotransmission that affect consciousness and behavior. Ammonia is the most commonly cited culprit in the pathogenesis of HE, but glutamine, benzodiazepine receptor agonists, and aromatic amino acids are also potential causes.[13,14] Arterial ammonia levels are commonly

increased in both acute and chronic liver diseases, but an established correlation between blood ammonia levels and mental status does not exist.[14] A normal ammonia level finding brings the diagnosis of HE into question.[13] Interventions to lower blood ammonia levels remain the mainstay of treatment for HE.[13,14]

Hepatic encephalopathy is categorized as type A, B, or C.[13] Type A is HE induced by acute liver failure, type B is due to portal-systemic bypass without associated intrinsic liver disease, and type C is HE that occurs in patients with cirrhosis. The severity of HE symptoms, time course (whether episodic, recurrent, or persistent), and whether incited by precipitating factors (such as infection, GI bleeding, an electrolyte disorder, or constipation) are additional ways in which HE is classified. The majority of episodic cases of HE secondary to cirrhosis are associated with a precipitant. It is important that precipitating factors be sought and treated when present.

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.[15] However, two procoagulant factors, factor VIII and von Willebrand factor, are actually elevated in chronic liver disease. It was thought that chronic liver disease induced an acquired bleeding disorder owing to the decrease in most procoagulant factors, but it is now believed that these patients actually live in a tenuous state of rebalanced hemostasis. This is due to increased levels of factor VIII and von Willebrand factor and the decreased levels of natural anticoagulants (antithrombin, protein C, and protein S). The rebalanced homeostasis seen in chronic liver disease can be tipped toward either thrombosis or clinically significant bleeding at any time depending on the circumstances experienced by the patient at the time. The prothrombin time (PT) is a standard component of the Child-Pugh scoring system and the international normalized ratio (INR) is utilized in the model for end-stage liver disease, a prognostic evaluation tool. The ability of the PT and INR to accurately measure bleeding risk and assist with estimation of the severity of a patient's liver disease has been called into question.[15]

Both platelet number and function may be affected in cirrhosis. Thrombocytopenia, a common finding in cirrhosis, could promote bleeding. However, von Willebrand factor, the binding site for platelets, is not decreased by cirrhosis and thrombin generation assays show that platelet procoagulant activity is actually preserved in patients with cirrhosis. Fibrinolysis is another process that is likely rebalanced in cirrhosis. While α-2-antiplasmin and thrombin-activatable fibrinolysis inhibitor levels are reduced, tissue plasminogen activator levels are increased. These changes would be expected to increase the risk for bleeding. However, procoagulant changes, including reduced plasminogen levels and normal to increased platelet activator inhibitor levels, occur concurrently, which provide a homeostasis in the fibrinolysis process.

CLINICAL PRESENTATION

CLINICAL PRESENTATION: Cirrhosis

Signs and Symptoms

- Asymptomatic
- Splenomegaly
- Jaundice, palmar erythema, and spider nevi
- Gynecomastia
- Ascites and edema
- 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)

Portal Hypertension

Patients with compensated cirrhosis are usually asymptomatic.[16] Initial symptoms may be nonspecific including fatigue, loss of appetite, and weight loss. Patients may also present with much more significant symptomatology secondary to decompensation related to cirrhosis complications such as ascites (abdominal distention) and HE (confusion, lethargy).

The approach to a patient with suspected liver disease begins with a thorough history and physical examination. In addition to fatigue, loss of appetite, and weight loss, patients may also experience other nonspecific signs. Muscle wasting, palmar erythema, spider nevi, parotid gland enlargement, white nails, Dupuytren contracture, asterixis and metabolic complications including gynecomastia, testicular atrophy, and axillary hair loss are all possibly related to cirrhosis.

Diagnostics for cirrhosis include liver function tests, coagulation tests, complete blood count, and serologic tests for viral causes including hepatitis B and C. A thorough history is key in determining if alcoholism is the likely cause of a patient's cirrhosis. A basic history and physical may also uncover the presence of obesity and history of diabetes that are suggestive of nonalcoholic fatty liver disease. Additional testing may include an antinuclear antibody titer to evaluate for the presence of autoimmune hepatitis; serum iron and transferrin saturation, possibly in conjunction with genetic testing, to look for hemochromatosis; and alpha-1 antitrypsin level and genotyping to test for alpha-1 antitrypsin deficiency, a rare disease, but one that can lead to liver disease as well as lung damage. When the underlying cause is still unable to be elucidated, additional testing for antimitochondrial antibodies or a magnetic resonance cholangiopancreatography to look for strictures and dilations of the bile ducts indicating primary biliary cholangitis may be completed. Wilson disease can be screened for using serum ceruloplasmin and copper levels.

Liver Chemistries

Liver chemistries are part of the initial evaluation of a patient with symptoms or signs suggestive of cirrhosis.[17] Liver chemistries are actually markers

of liver injury rather than function, though they are commonly referred to as liver function tests.[18] A comprehensive metabolic profile includes AST, ALT, alkaline phosphatase, bilirubin, and albumin. Additionally, the PT and GGT are needed. The use of liver function tests in the diagnosis and management of cirrhosis is discussed in the following sections. It may be useful to group the tests into two broad categories: (1) markers of liver injury such as AST, ALT and alkaline phosphatase and (2) markers of hepatocellular function such as PT, bilirubin, and albumin.[18]

Aminotransferases

The aminotransferases, AST and ALT, are enzymes involved in the transfer of amino groups of aspartate and alanine to ketoglutaric acid. Also referred to as transaminases, their presence in serum is a marker of hepatocellular injury. While AST is present in the liver, cardiac tissue, skeletal muscle, kidney, and brain, ALT is primarily in the liver. Liver injury, whether acute or chronic, results in increases in the serum concentrations of the aminotransferase enzymes. The degree of elevation, rate of rise, and whether AST > ALT or ALT > AST are helpful in suggesting possible etiologies.

Transaminases will typically be severely elevated as a result of acute insults including conditions like acute viral hepatitis, autoimmune hepatitis, ischemic hepatitis/shock liver, acute Budd-Chiari syndrome, hepatic artery occlusion, diffuse infiltration of cancer into the liver, acute biliary obstruction, liver trauma, eclampsia, and Wilson disease. The highest elevations (>10,000 units per liter [167 μkat/L]) are most apt to occur in shock liver and drug- or toxin-induced hepatitis. Borderline and mild transaminase elevations are seen in a variety of liver and nonliver disease states.

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. Seventy percent of patients with alcoholic liver disease had ratios greater than two and 92% of patients had ratios greater than one.[19]

Alkaline Phosphatase and γ-Glutamyl Transpeptidase

Elevated serum levels of 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.[18] Alkaline phosphatase is not found solely in the liver. When elevations of alkaline phosphatase occur with subsequent elevations of transaminases, confirmation of hepatic origin is not needed. When alkaline phosphatase is elevated without other concurrent liver test abnormalities, the GGT is evaluated since combined elevations of both alkaline phosphatase and GGT levels increase clinical suspicion of hepatic etiology.

A mixed pattern liver injury is evidenced by elevations of both AST/ALT levels and alkaline phosphatase. An R ratio can be calculated in these cases which is achieved by utilization of the following formula: R = (ALT value/ALT upper limit of normal)/(alkaline phosphatase value/alkaline phosphatase upper limit of normal). An R ratio above 5 indicates hepatocellular injury. An R ratio below 2 indicates cholestatic disease. Ratios between 2 and 5 represent a mixed pattern.

Bilirubin

Bilirubin is the product of the breakdown of hemoglobin molecules.[18] Elevations in serum conjugated (or direct) bilirubin indicate hepatocellular dysfunction or cholestasis. When total bilirubin elevation exists, it should be fractionated into direct (conjugated) and indirect (unconjugated) levels. Indirect bilirubin elevations occur due to over-production (as seen with hemolysis), decreased uptake, or decreased hepatic conjugation of bilirubin and can be found in conditions like Gilbert's syndrome. Direct hyperbilirubinemia is the result of liver injury or biliary obstruction and is associated with a number of hepatic diseases including cirrhosis. When cirrhosis has been established, the degree of bilirubin elevation has prognostic significance and is used as a component of the Child-Pugh and MELD scoring systems for quantifying the severity of cirrhosis.[20,21]

Albumin and Coagulation Factors

Albumin and coagulation proteins are markers of hepatic synthetic activity and are therefore used to estimate the level of hepatic functioning in cirrhosis. Albumin and PT are used in the Child-Pugh system for quantifying liver disease, and the INR is used in the MELD scoring system as a marker of coagulation.[20,21] 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. These tests are not specific to liver disease as any significant illness can reduce albumin levels and the PT can be elevated for a variety of reasons including anticoagulation with warfarin, vitamin K deficiency, and steatorrhea.

Thrombocytopenia

Thrombocytopenia is a common feature of chronic liver disease.[15] The platelet count is rarely below 30,000/mm^3 to 40,000/mm^3 (30 × 10^9/L to 40 × 10^9/L) though. When liver abnormality is suspected, a complete blood cell count that includes platelets should be evaluated.

Child-Pugh Classification and Model for End-Stage Liver Disease Score

The Child-Pugh classification system has gained widespread acceptance as a means of quantifying the myriad of effects of the cirrhotic process on the laboratory and clinical manifestations of this disease.[20] Recommended drug dosing adjustments for patients in liver failure are normally based on the Child-Pugh score. The newer MELD-Na scoring system is now the accepted classification scheme used by the Organ Procurement and Transplantation United Network for Organ Sharing (OPTN/UNOS) in the allocation livers for transplantation.[16] The Child-Pugh classification system employs a combination of physical and laboratory findings (Table 55-2), whereas the MELD score calculation takes into account a patient's serum creatinine, bilirubin, INR, and etiology of liver disease, omitting the more subjective reports of ascites and encephalopathy used in the Child-Pugh system.

TABLE 55-2

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.

Data from Reference 20.

The MELD scoring calculation is as follows[21]:

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

or using SI units:

$$\text{MELD score}^* = 9.57 \times \log_e(\text{creatinine [µmol/L]} \times 0.01131) + 3.78 \times \log_e(\text{bilirubin [µmol/L]} \times 0.05848) + 11.20 \times \log_e(\text{INR}) + 6.43$$

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

or using SI units:

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

These classification systems are important because they are used to assess and define the severity of cirrhosis, and predict patient survival, surgical outcome, and risk of variceal bleeding.

Imaging and Biopsy

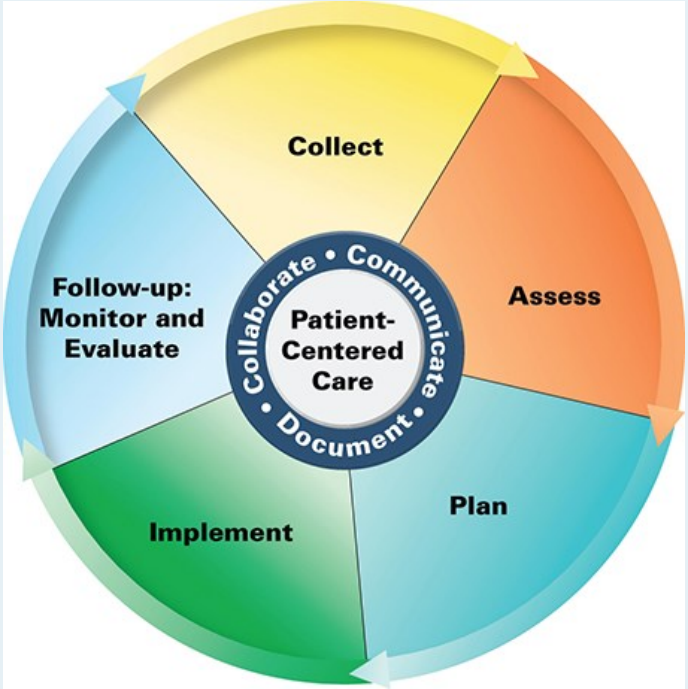
Ultrasound technology can be used to detect more advanced cirrhosis as well as to evaluate the presence of portal hypertension and ascites. A liver in

the stage of advanced cirrhosis will appear nodular on ultrasound.[17] Ultrasound may also be used to evaluate the presence of portal hypertension and ascites. Elastography via ultrasound or magnetic resonance may be useful in early cirrhosis or when other imaging is not definitive. Sometimes a liver biopsy is required when less invasive testing is inconclusive or when the results of biopsy may dictate the most appropriate management for the patient.

TREATMENT

Patient Care Process

Patient Care Process for Cirrhosis



Collect

- Patient medical history
  - Recent history of anorexia or weight loss
  - Risk factors for hepatitis B and C
  - Personal and family history of autoimmune or hepatic diseases
- Social history (specifically ethanol use—quantity and duration)
- Current medications including nonprescription medications
- Objective data
  - Blood pressure (BP), heart rate (HR), respiratory rate (RR), height, weight, O_2-saturation
  - Laboratory findings including albumin, bilirubin, complete blood count (CBC) with platelets, prothrombin time (PT), international normalized ratio (INR), alkaline phosphatase, aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transpeptidase (GGT)

Assess

- Presence of jaundice, palmar erythema, and spider nevi
- Presence of medications that can cause cirrhosis (see Table 55-1)
- Presence of complications of cirrhosis (ascites, portal hypertension, esophageal varices, hepatic encephalopathy, coagulation disorders)
- Child-Pugh score (see Table 55-2) for need for medication dosage adjustments
- Patient's willingness to stop drinking alcohol

Plan*

- Identify and treat possible causes of cirrhosis (ie, hepatitis C)
- Remove offending medications that may cause or exacerbate cirrhosis or complications of cirrhosis
- Create a plan to treat acute complications of cirrhosis, if present
  - Ascites: sodium restriction and furosemide + spironolactone (see Table 55-3)
  - Portal hypertension

    Primary prevention of esophageal varices: beta-blocker (nadolol, propranolol, or carvedilol) and/or EVL for prevention

    Treatment of acute variceal bleeding: octreotide + EVL, SBP prophylaxis (eg, ceftriaxone) × 7 days (see Fig. 55-4 and Table 55-4)

    Secondary prevention: nadolol or propranolol + EVL
  - Spontaneous bacterial peritonitis

    Treatment: empiric antibiotic therapy with appropriate antibiotic (eg, cefotaxime) based on ascitic fluid PMN count and/or symptoms (see Table 55-3)

    Secondary prevention: ciprofloxacin daily (see Table 55-3)
  - Hepatic encephalopathy: dietary protein restriction and lactulose +/− rifaximin

Implement

- Provide patient education and assistance for achieving abstinence from alcohol, if applicable
- Discuss all elements of treatment plan (medications and dietary modifications) with patient
- Provide vaccines as indicated
- Adjust medication doses as needed based on major organ function and patient characteristics
- Plan to assess progress of treatment including efficacy and adverse effects of treatments (see Table 55-5)

Follow-up: Monitor and Evaluate

- Monitor for long-term efficacy and adverse effects
- Patient's adherence to alcohol abstinence, prescribed medications, and dietary modifications
- Resolution of complications of cirrhosis

- Evaluate for possibility of liver transplant and need for dietitian (ie, sodium and protein restriction)

Collaborate with patient, caregivers, and other healthcare professionals.

General Approaches to Treatment

General approaches to therapy in cirrhosis should include the following:

1. Identify and eliminate, where possible, the causes of cirrhosis (eg, alcohol misuse).
2. Assess the risk for variceal bleeding and begin pharmacologic prophylaxis when indicated. Prophylactic endoscopic therapy can be used for patients with high-risk medium and large varices as well as in patients with contraindications or intolerance to nonselective β-adrenergic blockers. Endoscopic therapy is also appropriate for patients suffering acute bleeding episodes. Variceal obliteration with endoscopic techniques in conjunction with pharmacologic intervention is the recommended treatment of choice in patients with acute bleeding.
3. Evaluate the patient for clinical signs of ascites and manage with pharmacologic therapy (eg, diuretics) and paracentesis. Careful monitoring for SBP should be used in patients with ascites who experience acute deterioration of their clinical status.
4. Recognize that HE is a common complication of cirrhosis that requires clinical vigilance and treatment with dietary restriction, elimination of precipitating factors, and therapy to lower ammonia levels.
5. Monitor patients for signs of hepatorenal syndrome, pulmonary insufficiency, and endocrine dysfunction.

Desired Outcomes

Portal hypertension and cirrhosis can be classified as compensated versus decompensated.[22] In compensated portal hypertension, though HVPG may be elevated and varices may be present, the patient does not experience complications of cirrhosis such as variceal bleeding, ascites, SBP, or encephalopathy. The desired therapeutic outcomes during the compensated stage include *prevention of complications* through therapeutic modalities such as lowering of portal pressure with medical therapy using nonselective β-adrenergic blocker therapy and supporting abstinence from alcohol. In patients with decompensated cirrhosis, *resolution of acute complications* becomes the desired therapeutic outcome. Treatment modalities and therapeutic goals are presented below for each of the primary complications of decompensated portal hypertension. Recommended therapies and therapeutic goals are discussed.

Management of Portal Hypertension and Variceal Bleeding

The management of varices involves three strategies: (a) primary prophylaxis (prevention of the first bleeding episode), (b) treatment of acute variceal hemorrhage, and (c) secondary prophylaxis (prevention of rebleeding in patients who have previously bled).[11] It is also possible for a patient to have been diagnosed with cirrhosis and portal hypertension but have no varices. These patients would be considered to be in a preprimary prophylaxis stage. No specific treatment is recommended for preprimary prophylaxis and, for that reason, the focus of this chapter will be primary prophylaxis, treatment of acute variceal bleeding, and secondary prophylaxis.

Primary Prophylaxis

β-Adrenergic Blockade

The mainstay of primary prophylaxis is the use of nonselective β-adrenergic blocking agents such as propranolol, nadolol, or carvedilol.[11,12,22] These agents reduce portal pressure by reducing portal venous inflow via two mechanisms: a decrease in cardiac output through β_1-adrenergic blockade and a decrease in splanchnic blood flow through β_2-adrenergic blockade that results in unopposed α-1 activity.[11]

Endoscopic Variceal Ligation (EVL)

Endoscopic variceal ligation is an endoscopic therapy that consists of placing rubber bands around varices until the varices are obliterated.

Treatment Recommendations: Variceal Bleeding—Primary Prophylaxis

2 All patients with cirrhosis should be screened for varices at the time of diagnosis.[11,12] Transient elastography that shows liver stiffness below 20 kPa in patients with platelets over 150,000/mm^3 (150 × 10^9/L) do not require screening endoscopy.[12,22] Others should undergo screening endoscopy to identify and evaluate varices. β-Adrenergic blocker therapy is not indicated in patients without varices to prevent the formation of varices.[11,12,22] 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. β-Adrenergic blocker therapy is recommended preferentially to EVL in this situation due to the technical difficulty of EVL in the treatment of small varices. β-Adrenergic blocker therapy is optional for patients with small varices in the absence of risk factors, but additional studies to confirm benefit in this population are needed. All patients found to have medium to large varices that have not bled should receive primary prophylaxis therapy with a nonselective β-adrenergic blocker or EVL. The choice of treatment should be based on a consideration of resources and expertise as well as patient preferences and characteristics with a particular emphasis on side effects and contraindications.[12] If β-adrenergic blocker therapy is chosen, initiate therapy with oral propranolol 20 to 40 mg twice daily or nadolol 20 to 40 mg once daily and titrate every 2 to 3 days to a resting heart rate of 55 to 60 beats/min.[22] The daily dose of propranolol should not exceed 320 mg for patients without ascites or 160 mg for patients with ascites. The maximum daily dose of nadolol should not exceed 160 mg for patients without ascites or 80 mg for those with ascites. Systolic blood pressure should be maintained above 90 mm Hg. Rather than propranolol or nadolol, carvedilol could be chosen and started at 3.125 mg twice daily with titration to 6.25 mg twice daily after 3 days. In addition to β-adrenergic blockade, carvedilol also provides anti-α-adrenergic activity and enhances the release of nitric oxide.[23,24] Carvedilol may be considered in patients unable to tolerate propranolol or nadolol due to side effects like fatigue, weakness, and shortness of breath as it is perceived to be better tolerated than the pure nonselective β-adrenergic blockers.[22] Unlike propranolol and nadolol, titration of carvedilol is not guided by resting heart rate measurement, though systolic blood pressure should be maintained above 90 mm Hg while on carvedilol as well. β-Adrenergic blocker therapy should generally be continued indefinitely, but the patient must be monitored for development of contraindications such as renal impairment and hypotension that may accompany end-stage liver disease.[12] Following initiation and appropriate titration of the β-adrenergic blocker, further endoscopic surveillance is not needed.[11,22] If EVL is chosen, it will be performed every 2 to 8 weeks until the obliteration of varices.[22] Follow-up surveillance will occur at 3 to 6 months and again every 6 to 12 months thereafter.

Fifteen percent of patients have absolute contraindications to nonselective β-adrenergic blockers (ie, those with asthma or those with hypoglycemia unawareness while receiving antihyperglycemic therapy) and another 15% have common side effects such as fatigue, weakness, and shortness of breath that contribute to medication nonadherence.[11] Patients who qualify for β-adrenergic blocker therapy as primary prophylaxis, but who are unable to take or continue it, should be considered for alternative therapy with EVL.[12,22] Also, EVL may be considered as a possible first option for primary prophylaxis in patients with high-risk medium to large varices.

Acute Variceal Hemorrhage

Variceal hemorrhage is a medical emergency that carries a mortality rate of 7% to 15%, requires admission to an intensive care unit, and is one of the most feared complications of cirrhosis.[11] Treatment of acute variceal bleeding includes general stabilizing and assessment measures as well as specific measures to control the acute hemorrhage and prevent complications.

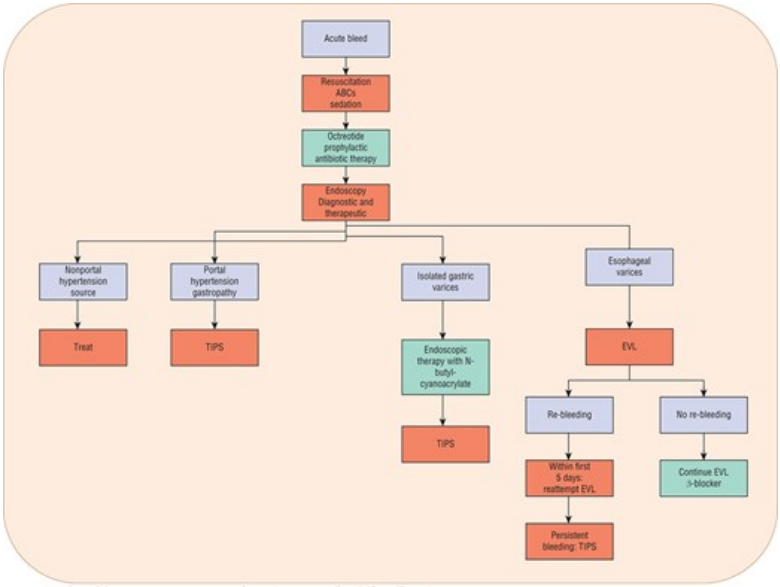
Initial treatment goals include (a) adequate blood volume resuscitation, (b) protection of airway from aspiration of blood, (c) prophylaxis against SBP and other infections, (d) control of bleeding, (e) prevention of re-bleeding, (f) preservation of liver function/prevention of HE, and (g) prevention of acute kidney injury.[24] Prompt stabilization of blood volume, with administration of packed red blood cells at a hemoglobin threshold of 7 g/dL (70 g/L; 4.34 mmol/L) and a goal hemoglobin of 7 g/dL (70 g/L; 4.34 mmol/L) to 9 g/dL (90 g/L; 5.59 mmol/L), should be undertaken.[22] Use of recombinant factor VIIa therapy is not recommended in patients with cirrhosis with GI hemorrhage.[11,22] Combination pharmacologic therapy plus endoscopic therapy with EVL (preferred), or sclerotherapy if EVL is not technically feasible, is considered the most rational approach to the treatment of acute variceal bleeding.[11,22,24] Endoscopy should be performed as soon as possible, but at least within 12 hours of admission.

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.[11,22]

The vasoactive drug used to manage acute variceal bleeding in the United States is the somatostatin analogue octreotide. Antibiotic therapy to prevent SBP and other infections should be implemented upon admission.[12] Intravenous ceftriaxone 1 g/24 hours is recommended.[12,22] A 250 mg dose of intravenous erythromycin prior to endoscopy may be used to accelerate gastric emptying of clots and improve visibility during the endoscopic procedure.[12,24] Should episodic HE occur secondary to acute GI bleeding, lactulose may be utilized. Figure 55-4 presents an algorithm for the management of variceal hemorrhage.

FIGURE 55-4

Management of acute variceal hemorrhage. (ABCs, Airway Breathing Circulation; EVL, endoscopic variceal ligation; TIPS, transjugular intrahepatic portosystemic shunt.)



Octreotide

The splanchnic vasoconstriction from octreotide therapy is due to inhibition of the release of vasodilatory peptides such as glucagon; however, a local vasoconstrictive effect also exists.[25] Somatostatin analogues, including octreotide, are associated with fewer side effects as compared with the most potent splanchnic vasoconstrictor, vasopressin. The primary side effects of octreotide therapy are hyperglycemia, vomiting, bradycardia, hypertension, arrhythmia, and abdominal pain.[11,24] The recommended dosing of octreotide for variceal bleeding consists of an initial IV bolus of 50 µg followed by a continuous IV infusion of 50 µg/h.[11,22] Octreotide can be continued for 2 to 5 days after acute variceal bleeding in an effort to prevent re-bleeding. Vasoactive therapy discontinuation can be considered once the patient is free of bleeding for at least 24 hours.

Prevention of Spontaneous Bacterial Peritonitis

Patients with cirrhosis with active bleeding are at high risk of severe bacterial infections.[22] Short-term prophylactic antibiotic therapy to reduce the risk of infection during episodes of bleeding not only reduces the likelihood of infections but also reduces the incidence of rebleeding and increases survival.[26] For these reasons, a short course (7 days maximum) of IV ceftriaxone 1 g daily is recommended.[12,26,27] Oral norfloxacin was once recommended as an alternative to IV ceftriaxone in cases where the patient had not been previously receiving quinolone therapy and when the prevalence of quinolone-resistant bacteria was low, but norfloxacin is no longer available.[22] Oral ciprofloxacin could be considered instead, but ceftriaxone is typically used today and is preferred in patients with advanced cirrhosis, in areas of high quinolone resistance, and in patients who have received quinolone therapy for ongoing SBP prophylaxis.

Endoscopic Interventions: Sclerotherapy and Band Ligation

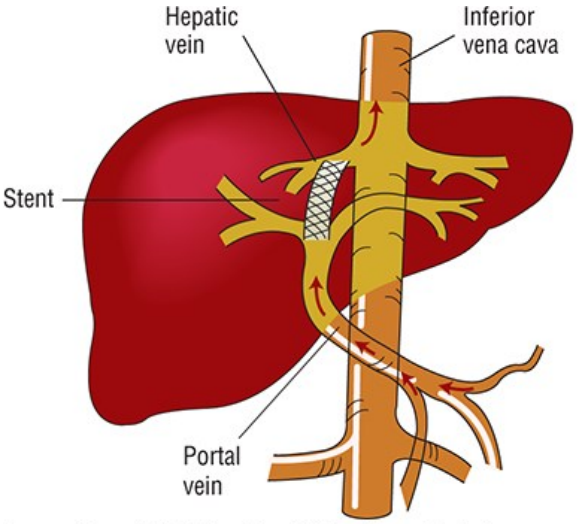
Guidelines recommend that endoscopy be performed within 12 hours of admission in cases of upper GI bleeding.[12,22] Endoscopy is used to diagnose variceal bleeding, and endoscopic techniques, particularly EVL, are used to stop variceal bleeding. EVL can be repeated if hemorrhage is not controlled or in the event of early recurrence of bleeding (within the first 5 days).[12] EVL is more effective than sclerotherapy with greater control of hemorrhage, less risk for rebleeding, lower likelihood of adverse events, and lower mortality.[11] Consensus recommendation calls for EVL (in conjunction with pharmacologic therapy) as the recommended form of endoscopic therapy for acute variceal bleeding.[12] Endoscopic injection of the tissue adhesive *N*-butyl cyanoacrylate is recommended to control acute *gastric* variceal bleeding from isolated gastric varices and gastroesophageal varices type 2 that extend beyond the cardia. EVL or tissue adhesive can be used for bleeding from gastroesophageal varices type 1. A pre-endoscopy infusion of erythromycin 250 mg IV, 30 to 120 minutes prior to the procedure, is recommended in the absence of QT interval prolongation.

Interventional and Surgical Treatment Approaches

Child-Pugh Class C patients and those in Class B with active hemorrhage at the time of diagnostic endoscopy make up less than 20% of patients admitted with variceal hemorrhage, but these patients do comprise a group who are at high risk for failing standard therapy with EVL plus octreotide.[11] In these cases, early transjugular intrahepatic portosystemic shunt (TIPS) may be considered instead of standard therapy.[22] The TIPS procedure involves the placement of one or more stents between the hepatic vein and the portal vein (Fig. 55-5). TIPS (preferably with polytetrafluoroethylene-covered stents) is also recommended for patients who fail to achieve or maintain hemostasis despite combined endoscopic and pharmacologic therapy.[22]

FIGURE 55-5

Transjugular intrahepatic portosystemic shunt.



Balloon tamponade may be used as a bridge therapy to control variceal bleeding temporarily (maximum of 24 hours).[12,22] It should be reserved as a temporizing measure until a more definitive treatment, such as TIPS, can be performed.

Treatment Recommendations: Variceal Hemorrhage

4 Patients require cautious resuscitation with blood products to correct intravascular losses.[22] Drug therapy with octreotide should be initiated early to control bleeding and facilitate diagnostic and therapeutic endoscopy. Therapy is initiated with an IV bolus of 50 µg and is followed by a continuous infusion of 50 µg/hr for 2 to 5 days.[11,22] Patients should be monitored for bradycardia, hypertension, arrhythmia, and abdominal pain.[11,24] Endoscopy is recommended in any patient with suspected upper GI bleeding due to ruptured varices.[12,22] EVL is the recommended form of endoscopic therapy. An

additional endoscopic therapy option is injection of the tissue adhesive *N*-butyl cyanoacrylate for gastric varices.[12] Short-term antibiotic prophylaxis (maximum 7 days) is recommended.[12,22] Ceftriaxone 1 g IV daily is the preferred antibiotic selection for this indication.[22] Surgical procedures like TIPS are employed as salvage therapy in patients who have failed repeated endoscopy and vasoactive drug therapy.[12,22] In patients at highest risk for standard treatment failure, a preemptive decision to utilize early TIPS may occur.

Secondary Prophylaxis

Because rebleeding after initial control of variceal hemorrhage occurs in a median of 60% of patients, and because rebleeding carries a mortality rate of 33%, it is inappropriate to simply observe patients for evidence of further bleeding.[11,22] Only patients who undergo shunt surgery or TIPS to control their initial acute bleeding require no further intervention as secondary prophylaxis. Patients who undergo one of these procedures to treat their initial bleeding should be referred for transplantation if they are a candidate. For all others, combination therapy with a β-adrenergic blocker and chronic EVL to eradicate varices is the treatment of choice for secondary prophylaxis of variceal bleeding.[11,12,22] Nadolol and propranolol are the recommended β-adrenergic blockers for secondary prophylaxis because carvedilol has not been studied adequately for the prevention of rebleeding.[12,22] Secondary prophylaxis should be started once vasoactive drug therapy is discontinued and as soon as possible (as early as day 6) following the acute bleeding event.[11]

Treatment Recommendations: Variceal Bleeding—Secondary Prophylaxis

3 The combination of EVL and a nonselective β-adrenergic blocking agent is recommended since pharmacologic therapy provides protection against rebleeding until EVL can be repeated a sufficient number of times to obliterate all varices.[11,22] Pharmacologic therapy should be initiated with a nonselective β-adrenergic blocker such as propranolol 20 to 40 mg twice daily or nadolol at a dose of 20 to 40 mg once daily.[22] β-Adrenergic blocker therapy is titrated every 2 to 3 days to achieve a goal heart rate of 55 to 60 beats/min maintaining systolic blood pressure above 90 mm Hg. Maximum doses of propranolol 320 mg/day for patients without ascites and 160 mg/day for patients with ascites, and nadolol 160 mg/day for patients without ascites and 80 mg/day for patients with ascites are recommended. Patients should also 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.[11,23] EVL should be conducted every 1 to 4 weeks until variceal obliteration, then the patient should be followed by surveillance endoscopy in 3 to 6 months and every 6 to 12 months thereafter.[22]

The addition of isosorbide mononitrate to nonselective β-adrenergic blocker therapy reduces portal pressure more than a β-adrenergic blocker alone, but there is no difference in the overall rate of rebleeding with this combination and side effects are more likely than with β-adrenergic blocker monotherapy (namely, headache and light-headedness).[22] Pharmacologic therapy (either isosorbide mononitrate plus nonselective β-adrenergic blocker therapy or β-adrenergic blocker therapy alone) plus EVL is associated with lower rebleeding rates than EVL therapy alone, but is only moderately more effective than isosorbide mononitrate plus nonselective β-adrenergic blocker therapy.[28] Thus, drug therapy is considered the cornerstone for secondary prophylaxis against variceal bleeding and patients who cannot tolerate nonselective β-adrenergic blocker therapy should be considered for TIPS.[22]

The lowest rate of variceal rebleeding occurs in patients when pharmacologic therapy leads to a reduction in HVPG of greater than 20% of baseline or to a measurement less than 12 mm Hg (1.6 kPa).[22] Ideally, portal pressure monitoring would be used to assess the response to nonselective β-adrenergic blocker therapy and identify responders from nonresponders earlier in the treatment course.

There is ongoing debate regarding the use of β-adrenergic blockers for prophylaxis against variceal bleeding in patients with refractory ascites.[23] The Baveno VI Consensus statement recommends reduction or temporary discontinuation of β-adrenergic blockers in patients receiving secondary prophylaxis with systolic blood pressure <90 mm Hg, serum sodium <130 mEq/L (mmol/L), or acute kidney injury.[12] This recommendation assumes that other precipitating drug therapies have already been removed. Reinitiation of β-adrenergic blocker therapy can be considered if the patient's circulatory dysfunction improves. A summary of evidence-based treatment recommendations regarding portal hypertension and variceal bleeding is presented in Table 55-4.

TABLE 55-3

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 2,000 mg/day should be instituted as well as oral diuretic therapy with an aldosterone antagonist or aldosterone antagonist plus loop diuretic	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 (0.25×10^9/L), empiric antibiotic therapy should be instituted	IA
If ascitic fluid PMN counts are <250 cells/mm^3 (0.25×10^9/L), but signs or symptoms of infection exist, empiric antibiotic therapy should be initiated while awaiting culture results	IB
If ascitic fluid polymorphonuclear leukocyte counts are >250 cells/mm^3 (0.25×10^9/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 ciprofloxacin	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 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.

Data from Reference 29.

TABLE 55-4

Evidence-Based Table of Selected 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

Data from Reference 12.

Management of Ascites and Spontaneous Bacterial Peritonitis

Ascites is the most common first sign of decompensation in patients with cirrhosis and represents a clinically important milestone in the natural progression of the disease.[10] The classic physical examination findings of ascites are a bulging abdomen with shifting flank dullness.[9,29] The development of ascites in patients with cirrhosis is an indication of advanced liver disease and is a poor prognostic sign.[10] Workup includes a history and physical examination, abdominal paracentesis and/or ultrasound, and ascitic fluid analysis.[9,29]

Spontaneous bacterial peritonitis is an infection of ascitic fluid that occurs in the absence of any evidence of an intraabdominal, surgically treatable source of infection. It is a common complication that develops in 1.5% to 3.5% of outpatients with cirrhosis and 10% of inpatients with cirrhosis.[9] The altered intestinal permeability and resultant bacterial translocation, in addition to changes in intestinal microbiota and immune system dysfunction place these patients at risk for developing SBP.[30] Most episodes of SBP have traditionally been caused by *Escherichia coli, Klebsiella pneumonia*, and pneumococci.[29] Concerns over quinolone-resistant bacteria and multidrug-resistant organisms have been recognized in clinical guidelines.[31] Symptoms and signs of SBP include abdominal pain, diarrhea, vomiting, and nonspecific symptoms, and patients may be asymptomatic.[32] Diagnostic paracentesis with analysis of ascitic fluid should be performed in all patients newly diagnosed with ascites.[9,29] SBP is diagnosed when there is positive ascitic fluid bacterial culture and ascitic fluid cell counts show an absolute polymorphonuclear (PMN) leukocyte count of greater than or equal to 250 cells/mm^3 (0.25×10^9/L).

Treatment guidelines for the management of adult patients with ascites and SBP were updated and approved by the Practice Guidelines Committee of the American Association for the Study of Liver Diseases (AASLD) in 2012 and 2021.[29,33] The European Association for the Study of the Liver (EASL) published ascites guidelines in 2018.[31] A synopsis of these guidelines follows.

Ascites

In adult patients with new-onset ascites as determined by physical examination or radiographic studies, abdominal paracentesis should be performed, and ascitic fluid analysis should include a cell count with differential, ascitic fluid total protein, and a serum-ascites albumin gradient (SAAG).[29,31,33] If infection is suspected, ascitic fluid cultures should be obtained at the time of the paracentesis. The SAAG can accurately determine whether ascites is a result of portal hypertension or another process. If the SAAG is greater than or equal to 1.1 g/dL (11 g/L), the patient almost certainly has portal hypertension. The treatment of ascites secondary to portal hypertension is relatively straightforward and includes abstinence from alcohol, sodium restriction, and diuretics.

1 Abstinence from alcohol is an essential element of the overall treatment strategy. Abstinence from alcohol can result in improvement of the reversible component of alcoholic liver disease, resolution of ascites, or improved responsiveness of ascites to medical therapy. Patients with cirrhosis not caused by alcohol have less reversible liver disease, and, by the time ascites is present, these patients may be best managed with liver transplantation rather than protracted medical therapy.

Beyond avoidance of alcohol, the primary treatment of ascites due to portal hypertension and cirrhosis is sodium restriction to 2,000 mg/day and oral diuretic therapy. 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 greater than 78 mmol/day. Evaluation of urinary sodium excretion, preferably utilizing a 24-hour urine collection, may be helpful, although

this collection can be difficult. A random spot urine sodium concentration that is greater than the potassium concentration correlates well with a 24-hour urinary sodium excretion over 78 mmol/day and is an easier test to complete. Severe hyponatremia, defined as serum sodium less than a threshold of 120 mEq/L (mmol/L), does warrant fluid restriction. However, hyponatremia of this severity is rare among patients with cirrhosis and ascites and, for this reason, rarely requires specific treatment.

Diuretic Therapy

5 The AASLD practice guidelines traditionally recommend that diuretic therapy be initiated with the combination of spironolactone 100 mg and furosemide 40 mg by mouth daily in the morning, titrated every 3 to 5 days utilizing a ratio of 100:40 to attain adequate natriuresis and weight loss (reasonable daily weight loss goal is 0.5 kg).[29] Maximum daily doses are 400 mg spironolactone and 160 mg furosemide. Currently, both AASLD and EASL guidelines recommend consideration of initiation of diuretic therapy with spironolactone alone for the first occurrence of ascites with titration every 3 days to a maximum of 400 mg daily.[31,33] Subsequent addition of furosemide is recommended in those with insufficient weight loss, hyperkalemia, or longstanding or recurring ascites. Due to the likelihood for development of drug-induced hyperkalemia with spironolactone when used as monotherapy at doses sufficient to illicit a sufficient diuresis, combination therapy is often required except in patients with minimal fluid overload.[29] Furosemide as lone diuretic therapy is inferior to spironolactone in the treatment of ascites and is not recommended. Serum potassium and renal function should be monitored frequently and rapid correction of asymptomatic hyponatremia in patients with cirrhosis should be avoided. 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. For patients who respond to diuretic therapy, this approach is preferred over the use of serial paracenteses. In patients with refractory ascites, serial paracenteses may be employed. Albumin infusion of 6 to 8 g for each liter of ascitic fluid removed can be considered post-paracentesis when more than 5 L of ascitic fluid is removed from the patient.[29,33,34] Referral for liver transplantation should be made in patients with refractory ascites. TIPS is a therapeutic modality for the treatment of refractory ascites that may be considered in appropriately selected patients. Peritoneovenous shunting may be considered in treatment-refractory patients who are not candidates for paracenteses, transplant, or TIPS.

Patients with cirrhosis and ascites should avoid nonsteroidal anti-inflammatory drugs, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers except under special circumstances. Angiotensin converting enzyme inhibitors and angiotensin receptor blockers should not be used in patients with refractory ascites. While these therapies are not part of the standard therapies of the complications of cirrhosis, nonselective β-adrenergic blocker therapy is indicated for primary and secondary prophylaxis against variceal bleeding in portal hypertension. Unfortunately, nonselective β-adrenergic blocker therapy can cause hypotension in patients with refractory ascites making the condition worse. For this reason, the risks versus benefits of nonselective β-adrenergic blocker therapy in refractory ascites must be carefully weighed, and nonselective β-adrenergic blockers avoided or not started in this population unless the benefit of bleeding prophylaxis outweighs the risk of worsening ascites. Systolic blood pressure should be maintained above 90 mm Hg.

Spontaneous Bacterial Peritonitis

Relatively broad-spectrum antibiotic therapy that adequately covers the most commonly encountered pathogens (*E. coli, K. pneumoniae*, *S. aureus, E. faecalis, and E. faecium*) has been recommended in patients with documented or suspected SBP.[33] Patients with ascitic fluid PMN counts greater than or equal to 250 cells/mm^3 (0.25 × 10^9/L) should receive empiric antibiotic therapy.[29,31,33] Current AASLD guidelines recommend a third-generation cephalosporin (eg, cefotaxime or ceftriaxone) as first line therapy for community-acquired SBP (ie, when diagnosed at time of admission or within 48 hours of admission) in patients without risk factors for infection with multi-drug resistant organisms (MDRO).[33] Piperacillin/tazobactam is recommended in patients with risk factors for MDRO infection. Vancomycin should be added in patients with prior infection with, or a positive swab for, methicillin resistant *S. aureus.* Daptomycin should be added in patients with prior infection with, or positive swab, for vancomycin-resistant enterococcus. Patients with prior history of treatment with piperacillin/tazobactam should be treated with meropenem with or without vancomycin.

AASLD and EASL also recommend albumin infusion in patients with SBP who, in addition to PMN counts of 250 cells/mm^3 (0.25 × 10^9/L) or greater, also have at least one of the following: SCr over 1 mg/dL (88 µmol/L), BUN over 30 mg/dL (10.7 mmol/L), or total bilirubin over 4 mg/dL (68.4 µmol/L).[29,31,33] Albumin IV 1.5 g/kg body weight within 6 hours of SBP detection followed by 1 g/kg on day 3 (maximum dose 100 g) is recommended. This is then

followed by an additional albumin IV infusion of 1 g/kg on day 3 (maximum dose 100 g). 6 All patients who have survived an episode of SBP should receive long-term antibiotic prophylaxis with daily ciprofloxacin 500 mg daily (since norfloxacin is no longer available).[27,29,31,33] Long-term prophylaxis should also be considered for the prevention of SBP in patients with low-protein ascites (<1.5 g/dL [15 g/L]) who also have one of the following: serum creatinine greater than or equal to 1.2 mg/dL (106 µmol/L), blood urea nitrogen greater than or equal to 25 mg/dL (8.9 mmol/L), serum sodium less than or equal to 130 mEq/L (mmol/L), or Child-Pugh score of greater than or equal to 9 with bilirubin greater than or equal to 3 mg/dL (51.3 µmol/L).[29,31] Short-term prophylaxis (7 days) is indicated in patients with cirrhosis and GI hemorrhage.[12,22] Rifaximin, a synthetic antibiotic which is not systemically absorbed and acts locally within the gastrointestinal tract, is superior to no antibiotic therapy for primary and secondary prophylaxis against SBP.[34] However, it remains undetermined if rifaximin is superior to systemically absorbed antibiotics for SBP prophylaxis. A summary of evidence-based treatment recommendations regarding ascites and SBP is given in Table 55-3.

Management of Hepatic Encephalopathy

Hepatic encephalopathy will occur in 30% to 40% of patients with cirrhosis at some point during the course of their disease.[13] The clinical manifestations of HE vary widely from subclinical alterations to coma. In addition to classification based on underlying disease, HE is also classified based on severity, time course, and the presence of precipitating factors. To determine the severity of HE, a grading system that relates neurologic and neuromuscular signs can be used (Table 55-6). The time course of HE is classified as episodic, persistent, or recurrent. Recurrent HE refers to HE episodes that occur in time intervals less than 6 months apart. Persistent HE refers to behavioral symptoms that are always present and periodically interspersed with episodes of overt HE relapses. A precipitating factor or factors such as constipation, infection, diuretic overuse, GI bleeding, or electrolyte abnormalities can be identified in most episodic cases of HE related to cirrhosis, but spontaneous episodic HE can occur as well. 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 empiric HE treatment. Treatment for HE is primarily focused on reducing ammonia blood concentrations through drug therapy aimed at inhibiting ammonia production or enhancing its removal. Treatment for HE should include avoidance and prevention of precipitating factors in an effort to avoid acute decompensation. In cases where a precipitant of episodic HE has been identified and adequately treated or removed, long-term prophylaxis against another acute HE episode may not be required. Otherwise, chronic therapy to prevent acute decompensation is often required.

TABLE 55-5

Drug Monitoring Guidelines

Drug	Adverse Drug Reaction	Monitoring Parameter	Comments
Nonselective β-adrenergic blocker	Heart failure, bronchospasm, glucose intolerance	BP, HR Goal BP: Sytolic >90 mm Hg Goal HR: 55-60 beats/min or maximal tolerated dose	Nadolol, propranolol
Nonselective β-adrenergic blocker; alpha-blocker	Similar to nonselective β-adrenergic blocker, but potentially better tolerated	Goal BP: Sytolic > 90 mm Hg	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 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 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; HR, heart rate; beats/min, beats per minute; EKG, electrocardiogram; SCr, serum creatinine; mmol, millimole.

Data from Reference 11–13,22–24,29, and 35.

TABLE 55-6

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

Data from Reference 13.

Hyperammonemia

7 Treatment interventions to reduce ammonia blood concentrations are recommended in patients with HE. Decreasing ammonia blood concentrations by reducing the nitrogenous load from the gut remains a mainstay of therapy for patients with HE. Treatment options most commonly used to decrease ammonia load from the gut include nutritional management, nonabsorbable disaccharides, and antibiotics.

Guidelines for nutritional support of patients with liver disease have been published by the International Society for Hepatic Encephalopathy and Nitrogen Metabolism.[36] Protein withdrawal is a cornerstone of treatment for patients during acute episodes of HE.[13] However, prolonged restriction can lead to malnutrition and poorer prognosis among HE patients. Once successful reversal of HE symptoms is achieved, protein is added back to the diet in combination with other therapies until a target of 1.2 to 1.5 g/kg/day of protein is reached. Vegetable-source and dairy-source protein may be preferable to meat-source protein because the latter contains a higher calorie-to-nitrogen ratio. Also, the higher fiber content of vegetable protein lowers colonic pH, increasing catharsis. Oral branched-chain amino acid formulations improve symptoms in episodic HE and may be considered as alternative or add-on therapy in patients who do not respond to conventional measures.

The use of lactulose, a nonabsorbable disaccharide, is the standard therapy for both acute and chronic HE. Lactulose removes nitrogenous waste from the gastrointestinal tract through its laxative effect.[37] In addition, when it reaches the colon, it is metabolized by the microbiota in the lower gastrointestinal tract producing short-chain organic acids. These acids inhibit the growth of ammonia-producing bacteria further reducing the overall ammonia load in the gut. Another laxative, polyethylene glycol 3350, has been compared with lactulose for the treatment of acute HE.[38] Patients receiving polyethylene glycol 3350 had higher rates of HE symptom improvement after 24 hours and their acute HE resolved 1 day sooner than those who received lactulose. Polyethylene glycol may be considered for patients suffering an acute HE episode.

Neomycin has activity against most gram-negative bacteria and inhibits intestinal glutaminase thereby reducing bacterial production of glutamate and ammonia.[35] For this reason, oral neomycin can be used for the treatment of HE. However, this agent is rarely used due to the severity of its potential adverse effects including ototoxicity and nephrotoxicity. Anaerobic bacteria produce urease that hydrolyzes urea to ammonia in the gut. Metronidazole targets these gram-negative anaerobic gut bacteria and, as a result, can be utilized in the management of HE as well. However,

neurotoxicity may be problematic so metronidazole is only considered as an alternative agent for HE.

Rifaximin 550 mg twice daily is effective in the treatment of HE.[13] It maintains remission better than lactulose alone and reduces the number of hospitalizations for HE as well; however, 90% of patients in this study received concomitant lactulose.[39] Rifaximin has also been shown in one study to decrease the incidence of overt HE in patients who underwent TIPS for intractable ascites or variceal bleeding prevention.[40]

Zinc is a cofactor for the urea cycle enzymes and is important for ammonia detoxification.[36] Zinc supplementation may be considered in patients with HE.[13] Zinc levels are frequently deficient in patients with cirrhosis. However, supplementation cannot be recommended in the absence of deficiency. Since zinc can inhibit copper absorption leading to anemia, care should be taken in recommending zinc unless truly indicated.

Drugs Affecting Neurotransmission

Flumazenil, a benzodiazepine receptor antagonist, may be considered for short-term therapy in refractory encephalopathy with suspected or confirmed benzodiazepine intake.

Treatment Recommendations: Hepatic Encephalopathy

7 The mainstay of therapy of HE involves measures to lower blood ammonia concentrations and includes diet therapy, lactulose, and antibiotics alone or in combination with lactulose. Other adjunctive therapies include zinc replacement in patients with zinc deficiency and flumazenil in cases of refractory HE with the possibility of benzodiazepine use.

The target daily protein intake for patients with HE is recommended to be within 1.2 to 1.5 g/kg/day. Consideration may be made to substitute meat-source protein with vegetable or dairy protein. Supplementation with elemental zinc may be considered in patients with cirrhosis who are zinc deficient. A typical dose of elemental zinc is 50 mg/day.

In episodic HE, lactulose is initiated at a dose of 30 mL (20 g) orally every 1 to 2 hours until catharsis begins and the patient experiences one to two bowel movements. The dose is then adjusted to produce two to three soft stools per day for chronic therapy. Patients are monitored for changes to their electrolytes periodically as well as for changes in mental status.

Rifaximin 550 mg twice daily plus lactulose is superior to lactulose alone in patients with a history of recurrent HE.[39] Rifaximin is usually well tolerated. Because of its more favorable adverse effect profile, rifaximin is now considered the next line of therapy for recurrent HE over either metronidazole or neomycin.[13]

Systemic Complications

In addition to the more common complications of chronic liver disease discussed earlier, other complications can occur, including hepatorenal syndrome, hepatopulmonary syndrome, coagulation disorders, and endocrine dysfunction.

Hepatorenal syndrome, a functional renal failure in the setting of cirrhosis, occurs in the absence of structural kidney damage.[41] Portal hypertension leads to the release of vasodilators that results in blood pooling in the splanchnic vasculature reducing renal blood flow causing renal hypoperfusion. This causes activation of the renin-angiotensin-aldosterone system that results in severe renal vasoconstriction and fluid retention leading to ascites. As liver disease progresses, systemic vasodilation worsens and, subsequently, increased renal vasoconstriction occurs and renal blood flow is further decreased. The result is hepatorenal syndrome that can be separated into two main types. Type 1 occurs rapidly and has a precipitating cause such as SBP. Type 2 occurs more slowly and does not have a precipitating event.

Management of hepatorenal syndrome begins with discontinuing diuretics and any other medication that could potentially decrease effective blood volume and to expanding the intravascular volume with IV albumin at a dose of 1 g/kg on day one followed by 40 to 50 g/day for the duration of therapy.[33] Precipitating factors, such as infection, fluid loss, and blood loss, should be investigated and treated if found.[41] Liver transplantation is the only definitive treatment for hepatorenal syndrome and the only therapy that will prolong survival. Arteriolar vasoconstrictor-based treatments such as norepinephrine or, when necessary, the less effective midodrine plus octreotide, are used in combination with IV albumin to bridge patients until transplantation.[33]

Hepatopulmonary syndrome affects up to 50% of patients with cirrhosis.[42] This abnormality is characterized by a defect in arterial oxygenation, which is caused by the pulmonary vascular dilatation that occurs in the presence of liver disease. These patients present with insidious onset of dyspnea, dyspnea upon standing, clubbing, and cyanosis. Patients with cirrhosis with these findings should be evaluated for hepatopulmonary syndrome, which is diagnosed based on the presence of arterial hypoxemia. Arterial hypoxemia is defined by measurements of the partial pressure of oxygen, testing for an increased alveolar–arterial oxygen gradient, and contrast-enhanced echocardiography. There is no effective medical management for hepatopulmonary syndrome. Liver transplantation offers the best chance for long-term recovery.

Patients with cirrhosis who are actively bleeding receive resuscitation with packed red blood cells targeting a hemoglobin of 7 to 9 g/dL (70-90 g/L; 4.34 to 5.59 mmol/L).[15,22] Platelet transfusion is used to maintain platelets over 50,000/mm^3 (50×10^9/L) during the period of active bleeding.[15] Cryoprecipitate to maintain fibrinogen levels over 100 mg/dL (1 g/L) is also usually recommended.

The presence of cirrhosis can produce abnormal circulating levels of various hormones.[43] Hypogonadism, diabetes mellitus, osteoporosis, and thyroid disorders are among the endocrine disorders that may develop related to advanced liver disease.

Liver Transplantation

The complications seen in patients with chronic liver disease are essentially secondary effects of the circulatory and metabolic changes that accompany liver failure. Unless the underlying etiology of a patient's fibrosis can be cured, cirrhosis generally progresses. Consequently, liver transplantation is often the only treatment that can offer a cure for the most severe complications of end-stage cirrhosis.

ALTERED DRUG PHARMACOKINETICS AND PHARMACODYNAMICS

Cirrhosis modulates the behavior of drugs in the body by inducing kinetic alterations in drug absorption, distribution, and clearance.[44] Patients with cirrhosis may exhibit pharmacodynamic changes with increased sensitivity to the effects of certain drugs including opiates, benzodiazepines, and nonsteroidal anti-inflammatory drugs (NSAIDs). These pharmacodynamic changes are separate and distinct from the enhancement of drug effects seen in patients with cirrhosis as a result of pharmacokinetic changes. The pathophysiologic changes that have particular impact on drug handling within the body include reduced liver blood flow, decreased first-pass extraction, systemic shunting, hypoalbuminemia, ascites, portal gastropathy, loss of cytochrome P450 enzymatic metabolic activity, reduced glutathione stores, impaired biliary excretion, and impaired renal excretion. Reduced hepatic blood flow, lower first-pass extraction, and portosystemic shunting result in higher bioavailability and serum levels of drugs. Hypoalbuminemia results in higher concentrations of free drug due to less protein binding. Ascites increases the volume of distribution of hydrophilic drugs. Serum levels of various drugs can be higher after normal dosing secondary to impaired biliary and renal excretion that is possible in cirrhosis. Reduced enzymatic clearance by hepatocytes can also lead to reduced first-pass metabolism and reduced hepatic clearance.

Drugs with a high extraction ratio (high-extraction drugs) are dependent on blood flow for metabolism, and the rate of metabolism will be sensitive to changes in blood flow. Drugs with a low extraction ratio (low-extraction drugs) are dependent on intrinsic metabolic activity for metabolism, and the rate of metabolism will reflect changes in intrinsic clearance and protein binding. Furthermore, hepatic biotransformation involves two types of metabolic processes: phase I and phase II reactions. Phase I reactions involve the cytochrome P450 system and include hydrolysis, oxidation, dealkylation, and reduction reactions. Phase II reactions involve conjugation of the drug with an endogenous molecule, such as sulfate or amino acid, rendering it more water soluble and enhancing its elimination. Drug metabolism by phase I reactions, especially oxidation, tend to be significantly impaired in patients with cirrhosis, whereas drugs eliminated by conjugation are relatively unaffected.

The variability and complexity of the interaction between the extent and severity of liver disease and individual characteristics of the drug make it difficult to predict the degree of pharmacokinetic perturbation in an individual patient. There are no sensitive and specific clinical or biochemical markers that allow us to quantify the extent of liver insufficiency or degree of metabolic activity. In addition, renal insufficiency and alterations that commonly accompany cirrhosis further complicate empiric dosing recommendations in these patients. Dosing recommendations are most commonly nonspecific, with recommendations labeled for patients with mild-to-moderate liver impairment. Dosing information for patients with more severe liver impairment is not available. As a result, when patients with cirrhosis require therapy with drugs that undergo hepatic metabolism (eg, benzodiazepines), monitoring response to therapy and anticipating drug accumulation and enhanced effects is essential. In the case of benzodiazepines, selection of an agent such as lorazepam, an intermediate-acting agent that is metabolized via conjugation and has no active metabolites, is easier to monitor than a drug such as diazepam, a long-acting benzodiazepine that is oxidized in the liver and has an active metabolite

with a long half-life of its own.

EVALUATION OF THERAPEUTIC OUTCOMES

Table 55-5 summarizes the management approach for patients with cirrhosis and includes possible adverse drug effects. Cirrhosis is generally a chronic progressive disease that requires aggressive medical management to prevent or delay common complications. Table 55-5 also lists monitoring criteria that need to be carefully followed in order to achieve the maximum benefit from the medical therapies employed and prevent adverse effects. A therapeutic plan including therapeutic end points for each medical and diet therapy needs to be developed and discussed with patients who have cirrhosis.

ABBREVIATIONS

AASLD	American Association for the Study of Liver Diseases
ALT	alanine transaminase
AST	aspartate transaminase
EASL	European Association for the Study of the Liver
EVL	endoscopic variceal ligation
GABA	γ-aminobutyric acid
GGT	γ-glutamyl transpeptidase
HE	hepatic encephalopathy
HSC	hepatic stellate cell
HVPG	hepatic venous pressure gradient
INR	international normalized ratio
MDRO	multi-drug resistant organism
MELD	model for end-stage liver disease
PMN	polymorphonuclear
PT	prothrombin time
SAAG	serum-ascites albumin gradient
SBP	spontaneous bacterial peritonitis
TIPS	transjugular intrahepatic portosystemic shunt

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SELF-ASSESSMENT QUESTIONS

1. A patient has the following information: albumin 4.1 g/dL (41 g/L), serum bilirubin 3.3 mg/dL (56.4 µmol/L), prothrombin time that is 5 seconds prolonged, no ascites, and no encephalopathy. In terms of Child-Pugh score, what is the patient's severity?

   A. Grade A

   B. Grade B

   C. Grade C

   D. Grade D

2. Your 64-year-old patient presents with abdominal distention and bulging flanks with dullness due to cirrhotic ascites which has been a recurring problem for this patient over the last six months. Which of the following diuretic options is most appropriate for this patient?

   A. Amiloride

   B. Furosemide

   C. Hydrochlorothiazide

   D. Spironolactone plus furosemide

3. A 42-year-old patient takes lactulose for hepatic encephalopathy which has been titrated to result in two to three loose bowel movements per day. They continue to experience symptoms of encephalopathy including drowsiness and obtundation. Which agent should be added next for this patient based on the information above?

   A. Ceftriaxone

   B. Neomycin

   C. Norfloxacin

   D. Rifaximin

4. Your patient has been evaluated and it has been determined that medication management to prevent the first occurrence of variceal bleeding is indicated. Which of the following represents an appropriate recommendation for this patient?

   A. Atenolol

   B. Bisoprolol

   C. Metoprolol

   D. Nadolol

5. Which of the following represents an appropriate goal for a patient started on propranolol for variceal bleeding prophylaxis?

   A. Heart rate of 55 to 60 beats/min; diastolic blood pressure > 90 mm Hg

   B. Heart rate of 55 to 60 beats/min; systolic blood pressure > 90 mm Hg

   C. Heart rate of 60 to 65 beats/min; diastolic blood pressure > 90 mm Hg

   D. Heart rate of 60 to 65 beats/min; systolic blood pressure > 90 mm Hg

6. A patient who develops type 2 hepatorenal syndrome may be managed with which of the below combinations as bridge to transplant?

   A. Albumin + cefotaxime + rifaximin

   B. Albumin + norepinephrine

   C. Carvedilol + furosemide + spironolactone

   D. Lactulose + rifaximin + midodrine

7. A patient was successfully treated for an episode of spontaneous bacterial peritonitis (SBP). Which option is the most appropriate antibiotic as indefinite therapy for secondary prophylaxis of SBP?

   A. Metronidazole

   B. Neomycin

   C. Ceftriaxone

   D. Ciprofloxacin

8. A 47-year-old patient with a history of alcoholic cirrhosis is admitted to the hospital with their first episode of community acquired spontaneous bacterial peritonitis. Which one of the following options represents reasonable empiric antibiotic selection for this patient?

   A. Albumin

   B. Cefotaxime

   C. Vancomycin plus tobramycin

   D. Trimethoprim/sulfamethoxazole

9. A patient presents to the emergency department with moderate hepatic encephalopathy. In addition to supportive care, which medication would be first-line therapy to reduce nitrogenous load?

   A. Lactulose

B. Metronidazole

C. Neomycin

D. Rifaximin

10. Which medication should be discontinued in a patient with cirrhosis and ascites?

A. Furosemide

B. Nadolol

C. Naproxen

D. Spironolactone

11. A patient is admitted to the hospital, requiring management of acute variceal hemorrhage. The patient has a history of myocardial infarction (6 months ago). Which medication is the best intervention to decrease portal blood flow and pressure?

A. Nitroglycerin

B. Octreotide

C. Carvedilol

D. Vasopressin

12. A 42-year-old patient presented to the emergency department with large bleeding varices, based on an esophagogastroduodenoscopy. Which goal would be the most appropriate based on the patient's condition?

A. Achieve a systolic blood pressure of 80 mm Hg with fluid resuscitation

B. Intake a target of 1.2 to 1.5 g/kg/day of protein

C. Maintain a hemoglobin concentration of 7 to 9 g/dL (70-90 g/L; 4.34-5.59 mmol/L)

D. Restrict sodium intake to 2,000 mg/day

13. A patient is prescribed and adherent with spironolactone plus furosemide for ascites. Concentration of which of the following will be greater than the concentration of potassium on a spot urine collection if the patient is meeting goal for their diuretic therapy?

A. Chloride

B. Creatinine

C. Glucose

D. Sodium

14. Which of the following is a laboratory abnormality possibly indicative of cirrhosis?

A. Hyperalbuminemia

B. Low alkaline phosphatase

C. Low prothrombin time

D. Thrombocytopenia

15. Drugs metabolized through which of the following processes are most likely to be affected by cirrhosis?

    A. Conjugation

    B. Hydrolysis

    C. Oxidation

    D. Sulfation

SELF-ASSESSMENT QUESTION-ANSWERS

1. **B.** The patient will receive 3 points for bilirubin over 3 mg/dL (51.3 µmol/L), 1 point for albumin>3.5 g/dL (35 g/L), 1 point for no ascites, 1 point for no encephalopathy, and 2 points for prothrombin time prolonged between 4 and 6 seconds. This makes their total score 8 points which corresponds to a Grade of B.

2. **D.** Diuretic therapy with aldosterone antagonist and loop diuretic is the mainstay of ascites management. Aldosterone antagonist monotherapy may be attempted in those with a first occurrence of ascites whereas the combination is preferred in those with longstanding ascites. Loop diuretic as monotherapy is not recommended nor are other diuretic options. Spironolactone plus furosemide is likely the most appropriate selection for diuretic therapy in a patient with ascites due to cirrhosis. The combination promotes effective sodium excretion and diuresis while maintaining eukalemia.

3. **D.** Patients with intolerance to or insufficient resolution of encephalopathy symptoms should have rifaximin added to continuing lactulose therapy. Rifaximin has replaced neomycin and metronidazole for add-on owing to its superior tolerability and more favorable side effect profile.

4. **D.** Nadolol, propranolol, and carvedilol are recommended options for primary prophylaxis against gastroesophageal bleeding. Nonselective β-adrenergic blockers are recommended for this indication as they reduce portal pressure by reducing cardiac output and, most importantly, through their β_2 action leading to splanchnic vasoconstriction reducing portal blood flow.

5. **B.** A suggested target for β-adrenergic blocker therapy, when used as prophylaxis against variceal bleeding, is a heart rate of 55 to 60 beats/minute. Systolic blood pressure should be maintained above 90 mm Hg as the risk for inadequate perfusion leading to complications like hepatorenal syndrome is a concern with hypotension.

6. **B.** Once severe complications of cirrhosis occur, such as hepatorenal syndrome, patients should be evaluated for transplantation as other therapeutic options, including norepinephrine plus albumin or midodrine plus octreotide and albumin, are only temporary measures that may be instituted to “bridge” a patient until transplantation can occur.

7. **D.** Patients who have survived an episode of spontaneous bacterial peritonitis should receive indefinite secondary prophylaxis against another episode. An appropriate antibiotic choice would be ciprofloxacin for this indication.

8. **B.** Appropriate empiric treatment for suspected acute spontaneous bacterial peritonitis requires IV antibiotic therapy. Current guidelines recommend and, for empiric therapy with a third-generation cephalosporin in patients with cirrhosis at low risk for multi-drug resistant organism infection. This would include those with community acquired spontaneous bacterial peritonitis and no prior history of antibiotic exposure. Thus, cefotaxime represents an appropriate option in this patient. Piperacillin/tazobactam is recommended in patients with risk factors for muti-drug resistant organism infection. Vancomycin should be added in patients with prior infection with, or a positive swab for, methicillin resistant *S. aureus.* Daptomycin should be added in patients with prior infection with, or positive swab, for vancomycin-resistant enterococcus. Patients with prior history of treatment with piperacillin/tazobactam should be treated with meropenem with or without vancomycin. Trimethoprim/sulfamethoxazole is not recommended for empiric treatment for acute peritonitis.

9. **A.** Lactulose is the first-line drug therapy option used to reduce circulating systemic nitrogenous waste. Rifaximin may be added to lactulose or used in patients unable to tolerate lactulose. Metronidazole and neomycin are no longer preferred options for add-on and are not recommended as initial therapy.

10. **C.** Patients with ascites should avoid use of nonsteroidal anti-inflammatory drugs such as naproxen. Furosemide and spironolactone will be fundamental therapies in the management of ascites. β-Adrenergic blocker therapy can be used in patients with ascites, but reductions in dose for both propranolol and nadolol are recommended when ascites is present. Appropriate blood pressure maintenance, ensuring that systolic blood pressure remains above 90 mm Hg, is important.

11. **B.** Octreotide is the recommended splanchnic vasoconstrictor for patients with acute variceal bleeding. Vasopressin is not preferred and nitroglycerin is not an appropriate choice for this indication. Carvedilol represents an option for primary prophylaxis against variceal bleeding but is not an appropriate choice for the treatment of acute bleeding.

12. **C.** An appropriate goal of therapy for acute variceal bleeding is hemoglobin of 7 to 9 g/dL (70-90 g/L; 4.34-5.59 mmol/L). While maintaining an appropriate blood pressure will also be important, fluid resuscitation alone may be insufficient if blood loss is severe. Maintenance of an appropriate daily protein intake is a target for encephalopathy rather than acute variceal bleeding. Restriction of sodium intake is an appropriate goal relative to the management of ascites.

13. **D.** A random spot urine sodium concentration that is greater than the potassium concentration correlates well with a 24-hour urinary sodium excretion over 78 mmol/day and is an easier test to complete.

14. **D.** Thrombocytopenia typically accompanies cirrhosis. Hypoalbuminia, elevated alkaline phosphatase, and elevated prothrombin time would be anticipated.

15. **C.** Enzymatic metabolism by hepatocytes is most likely to be impacted by cirrhosis. This represents an impairment in oxidation. Other metabolic processes, including conjugation, hydrolysis, and sulfation, are impacted to a lesser extent than oxidation.