

COMPLICATIONS OF CHRONIC LIVER DISEASE



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LEARNING OBJECTIVES

1. Apply results from clinical studies and guidelines to the management of hepatic encephalopathy.
2. Design evidence-based treatment and prevention regimens for patients with ascites or complications of ascites such as spontaneous bacterial peritonitis and hepatorenal syndrome.
3. Given recent guidelines on the management of portal hypertension, justify the need for primary and secondary prophylaxis of variceal bleeding in patients with cirrhosis.
4. Assess and apply the role of the pharmacist in providing appropriate treatment recommendations to health care providers and drug education to patients regarding the management of complications caused by chronic liver disease.

INTRODUCTION

Cirrhosis results in around 29,000 deaths annually in the United States. Patients with cirrhosis who do not receive a liver transplant have a 5-year mortality rate of up to 85%. Cirrhosis is the result of chronic inflammation and development of fibrosis that leads to various complications of chronic liver disease. These complications are also markers for decompensated liver disease,

and most patients are given a diagnosis of cirrhosis in the presence of these complications. Decompensated (or unstable) liver disease occurs in 2% to 10% of patients with viral hepatitis and in about 25% of patients with alcoholic liver disease.

The severity of cirrhosis is important to assess because it serves as a predictor of patient survival, surgical outcomes, and the risk of complications such as variceal bleeding. Assessment tools commonly used in patients with cirrhosis include the model for end-stage liver disease (MELD), which has a score ranging from 0 to 40; and the Child-Pugh classification system, which has a score ranging from 0 to 15. Patients with a higher MELD score have a greater risk of dying within 3 months than patients with a lower score. The Child-Pugh score is used to group cases into three categories: (1) class A, score of less than 7 (mild disease); (2) class B, score of 7–9 (moderate disease); and (3) class C, score of 10–15 (severe disease).

This chapter discusses common complications such as portal hypertension, variceal bleeding, ascites and complications of ascites, and hepatic encephalopathy (HE). Portal hypertension, a complication of chronic liver disease, results from replacement of normal hepatic parenchyma with fibrotic tissue, leading to resistance to bloodflow through the liver. Portal hypertension

BASELINE REVIEW RESOURCES

The goal of PSAP is to provide only the most recent (past 3–5 years) information or topics. Chapters do not provide an overall review. Suggested resources for background information on this topic include:

- Phongsamran PV, Kim JW, Cupo Abbot J, Rosenblatt A. Pharmacotherapy for hepatic encephalopathy. *Drugs* 2010;70:1131–48.
- Runyon BA. Management of adult patients with ascites due to cirrhosis: an update. *Hepatology* 2009;49:2087–107.
- Kiser TH, MacLaren R, Fish DN. Treatment of hepatorenal syndrome. *Pharmacotherapy* 2009;29:1196–211.
- Garcia-Tsao G, Lim J; Members of Veterans Affairs Hepatitis C Resource Center Program. Management and treatment of patients with cirrhosis and portal hypertension: recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program. *Am J Gastroenterol* 2009;104:1802–29.

ABBREVIATIONS IN THIS CHAPTER

AAA	Aromatic amino acid
AASLD	American Association for the Study of Liver Diseases
BCAA	Branched chain amino acid
ESPEN	European Society for Parenteral and Enteral Nutrition
EVL	Endoscopic variceal ligation
HE	Hepatic encephalopathy
HRS	Hepatorenal syndrome
HVPG	Hepatic venous pressure gradient
IAC	International Ascites Club
MELD	Model for end-stage liver disease
SAAG	Serum-ascites albumin gradient
SBP	Spontaneous bacterial peritonitis

can lead to other complications of chronic liver disease, including the development of varices and variceal bleeding, ascites, and spontaneous bacterial peritonitis (SBP). In addition, the loss of hepatocytes and intrahepatic shunting of blood caused by portal hypertension diminishes the liver's metabolic and synthetic function; this may result in a reduction in ammonia metabolism, further leading to HE.

This chapter reviews and applies clinical study data and recent guidelines to explain the rationale for treatment of the complications of chronic liver disease.

HEPATIC ENCEPHALOPATHY

Hepatic encephalopathy, also sometimes referred to as portal-systemic encephalopathy, is a syndrome of neuropsychiatric abnormalities caused by acute or chronic hepatic insufficiency. The neuropsychiatric disturbances of HE are often at least partly reversible and may consist of a collage of changes in intellectual, cognitive, fine motor, emotional, affective, behavioral, and psychomotor functions. One-third to one-half of patients hospitalized for cirrhosis present with HE, and the average hospital length of stay is 5–7 days. The 1-year survival rate after the first episode of HE is 42%.

Clinically, HE is classified as three types: A, patients with acute liver failure; B, patients with large, noncirrhotic, portosystemic shunting without intrinsic liver disease; and C, patients with cirrhosis and portal hypertension or portal-systemic shunts. Type C is the most common form of HE and includes overt (or acute) HE, which is further divided into episodic or resistant HE. Overt HE is defined as the presence of symptoms (e.g., acute changes in mental status, asterixis) and elevated serum ammonia concentrations. However, chronic HE, also known as recurrent HE, is defined as patients with a previous episode of HE regardless of their presentation.

Patients with cirrhosis who present with neuropsychometric abnormalities of HE when tested, but who have no clinical or electroencephalographic manifestations, are given a diagnosis of minimal HE. Staging of HE consists of using the West Haven criteria (also known as the Conn score) to assess mental status changes. These criteria, which are used in several HE studies, define five stages (0–4) of altered mental status.

Factors involved in the pathogenesis of HE should be considered in its management and treatment. The main contributor to the development of HE is nitrogenous substances, usually ammonia, obtained from the gastrointestinal (GI) tract. Urease activity of bacteria (especially gram-negative anaerobes) in the colon and deamidation of glutamine (protein) in the small bowel lead to the production of portal ammonia, which is the main substrate for urea and glutamine synthesis in the liver. In patients with HE, there is an increased blood-brain barrier permeability to ammonia. The accumulation of serum ammonia leading to an increase in brain ammonia concentrations has direct neurotoxic effects and may sensitize neurons and astrocytes to injury by other factors and mechanisms. Although higher serum ammonia concentrations (i.e., greater than 200 mcg/dL) have been linked with increased risk of cerebral herniation in patients with fulminant hepatic failure, there is no direct relationship between serum ammonia concentrations and mental status.

Therapy Goals and Treatment Options

Most therapies used in the treatment and prevention of HE are aimed at correcting precipitating factors (e.g., GI bleeding, excessive protein intake) and decreasing the accumulation of neurotoxic, nitrogenous by-products (e.g., ammonia). The treatment approach in patients with overt HE includes providing supportive care, treating and removing precipitating factors, decreasing nitrogenous load from the GI tract, and evaluating the need for long-term therapy and liver transplantation. The approach in patients with recurrent HE focuses on preventing the future recurrence of HE, enhancing the patient's daily function, and evaluating the need for liver transplant.

Agents used in treating HE include nonabsorbable disaccharides (lactulose and lactitol) and antibiotics (rifaximin, neomycin, and metronidazole), with lactulose and rifaximin being the most common. Rifaximin, a semisynthetic derivative of rifamycin, received label approval by the U.S. Food and Drug Administration (FDA) for HE prevention in 2010; however, its use for HE predates this. Probiotics also used for the treatment and prevention of HE are lactic acid bacteria (e.g., lactobacilli, lactococci, bifidobacteria) and yeasts (e.g., *Saccharomyces* spp.). Zinc is increasingly being used for HE because it is thought that, as an element essential for several metabolic processes, it can serve as a cofactor for

enzymes of the urea cycle and further decrease ammonia concentrations. Zinc deficiency may also contribute to the pathogenesis of HE, especially in patients with cirrhosis. Combination therapy is an option for the treatment and prevention of HE when monotherapy does not produce sufficient results.

Dosing recommendations for treatment with lactulose and rifaximin depend on the indication. Specific recommendations are listed in Table 1-1. For patients presenting with acute HE, lactulose dosing should be initiated every hour until evacuation occurs, followed by maintenance doses titrated to achieve two or three soft bowel movements daily. However, for the treatment of chronic HE (or the prevention of HE), hourly administration of lactulose is not required. From previous studies of rifaximin used in the treatment of acute HE, rifaximin should be dosed at 400 mg by mouth three times/day.

For chronic HE, rifaximin is dosed on the basis of its prescribing information at 550 mg orally twice daily; however, given the study that resulted in the label approval for rifaximin, the drug should be administered in combination with lactulose therapy. Limited data are available on rifaximin use in patients with a MELD score greater than 25 and Child-Pugh class C. On the basis of the prescribing information, patients with severe liver disease (Child-Pugh class C) had increased systemic exposure of rifaximin. However, these systemic exposures did not reach the concentrations seen in animal toxicity studies. Overall, these data indicate caution should be used in patients with severe liver disease (Child-Pugh class C) and/or a MELD score greater than 25.

In 2001, the Practice Parameters Committee of the American College of Gastroenterology developed guidelines on the treatment and prevention of HE. The recommendation for treating acute HE is lactulose as first-line therapy, followed by neomycin. Similarly, for chronic HE, lactulose is first-line therapy, followed by neomycin or metronidazole. Few data exist to support the use of neomycin or metronidazole, and concerns about adverse drug effects with chronic use limit support of these agents for HE. Data regarding rifaximin were not yet available during development of the 2001 guidelines, and newer studies have clarified the therapeutic benefits of rifaximin in the treatment and prevention of HE. In addition, in 2009, the Veteran Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program recommended lactulose as first-line therapy for the treatment of acute and chronic HE and rifaximin for patients with persistent HE who are intolerant of or whose disease fails to respond to lactulose.

Overall, recent studies have shown that lactulose is as effective as neomycin and rifaximin in the treatment of HE. Lactitol is as effective as lactulose. For the treatment of stage 1 and 2 HE, studies have found probiotics

(bacterial) to be as effective as lactulose, with beneficial effects persisting weeks after treatment withdrawal and fewer adverse effects.

A meta-analysis of 22 randomized controlled studies compared nonabsorbable disaccharides with antibiotics, no intervention, or placebo in patients with acute and chronic HE. Compared with placebo or no intervention, the use of nonabsorbable disaccharides suggested improvement in HE but did not significantly affect mortality. When nonabsorbable disaccharides were compared with antibiotics, all-cause mortality rates and adverse events were similar between the two groups; however, rates of HE improvement were significantly lower with nonabsorbable disaccharides. Overall, high-quality data were lacking to support or refute the hypothesis that the use of nonabsorbable disaccharides results in significantly favorable outcomes in patients with HE.

A more recent meta-analysis showed that, compared with nonabsorbable disaccharides, rifaximin resulted in significantly less abdominal pain; however, similar effects on improvement in HE or reduction in portal-systemic encephalopathy index and diarrhea were noted. In addition, there was no significant improvement in HE or reduction in portal-systemic encephalopathy index, regardless of the type of HE (acute vs. chronic). Rifaximin did not show superior efficacy to nonabsorbable disaccharides.

Rifaximin was further evaluated for the prevention of HE in a prospective, double-blind, placebo-controlled, randomized, multicenter study. Of note, greater than 90% of patients received concomitant lactulose. Patients who received rifaximin had significant reductions in the first breakthrough HE episode and the first HE-related hospitalization compared with the placebo group. However, no benefit in the primary outcome was seen in patients with MELD scores of 19–24 or in patients who did not receive concomitant lactulose therapy. Adverse drug events and mortality were similar between groups. The study led to the approval of rifaximin for reducing the risk of overt HE recurrence in patients 18 years and older.

When making recommendations for the treatment and prevention of HE, it is important to consider not only the efficacy of these agents, but also their safety and tolerability. Although neomycin is a poorly absorbable antibiotic, a small amount may be systemically absorbed, potentially leading to ototoxic and nephrotoxic adverse effects. Thus, neomycin should be discontinued in patients with acute kidney insufficiency. Lactulose produces flatulence, diarrhea, and dyspepsia in up to 65% of patients. Lactitol was better tolerated because it lacks the strong, sweet taste of lactulose and produces less frequent adverse GI reactions. However, lactitol is currently unavailable in the United States. In addition, nonabsorbable disaccharides may have a variable dose response and should be administered with

Table 1-1. Dosing of Drugs Used in Patients with Complications of Chronic Liver Disease

Indication	Drug	Dosing Recommendation
HE treatment	Lactulose	30–45 mL orally every hour until evacuation; then 15–40 mL orally every 6–12 hours titrated to two or three soft bowel movements daily
		20–30 g (powder packet) orally every hour until evacuation, then 10–30 g (powder packet) orally every 6–12 hours titrated to two or three soft bowel movements daily
		200 g/300 mL in 700 mL of water or saline enema rectally every 4 hours as needed
	Metronidazole	250 mg orally every 6–12 hours
	Neomycin	1–2 g orally every 6 hours
	Rifaximin	400 mg orally three times/day
HE prevention	Lactulose	15–45 mL orally every 6–12 hours titrated to two to four soft bowel movements daily
		20–30 g (powder packet) orally every 6–12 hours titrated to two to four soft bowel movements daily
	Rifaximin	550 mg orally twice daily
Ascites	Furosemide	40 mg orally daily (maximum 160 mg/day)
	Spironolactone	100 mg orally daily (maximum 400 mg/day)
SBP treatment	Cefotaxime	1–2 g IV every 8 hours for 5 days
	Ceftriaxone	1–2 g IV daily for 5 days
	Ciprofloxacin	500 mg orally or 400 mg IV every 12 hours for 5 days
	Levofloxacin	500 mg IV/orally daily for 5 days
	Trimethoprim/sulfamethoxazole	3–5 mg/kg of TMP IV every 12 hours for 5 days
SBP prophylaxis without active GI bleed	Ciprofloxacin	750 mg orally once weekly
	Trimethoprim/sulfamethoxazole	1 double-strength tablet orally daily
	Norfloxacin	400 mg orally daily
SBP prophylaxis with active GI bleed	Ceftriaxone	1–2 g IV every 8 hours for 7 days
	Cefotaxime	1–2 g IV daily for 7 days
	Ciprofloxacin	500 mg orally or 400 mg IV every 12 hours for 7 days
	Trimethoprim/sulfamethoxazole	3–5 mg/kg of TMP IV every 12 hours for 7 days
HRS	Albumin	1 g/kg (up to 100 g) IV on day 1; then 20–60 g IV daily
	Midodrine	5–15 mg orally every 8 hours
	Octreotide	100–200 mg subcutaneously every 8 hours
Variceal bleeding prophylaxis	Nadolol	20–40 mg orally daily
	Propranolol	20 mg orally twice daily

GI = gastrointestinal; HE = hepatic encephalopathy; HRS = hepatorenal syndrome; IV = intravenously; SBP = spontaneous bacterial peritonitis; TMP = trimethoprim.

caution. Excessive dosing can result in severe diarrhea, further exacerbating electrolyte disturbances and hypovolemia. Prolonged use of metronidazole is limited by its potential risk of neurotoxicity and peripheral neuropathy. In addition, metronidazole metabolism is significantly decreased in patients with liver disease, and dosage adjustments may be warranted to prevent drug accumulation. Compared with lactulose and other antibiotics, rifaximin, probiotics, and zinc appear to be well tolerated. Although probiotics are considered safe, the ingestion of living bacteria can theoretically pose a risk in immunocompromised patients with HE. More studies are needed to evaluate the long-term safety of these agents.

Nutrition

Traditionally, protein restriction has been viewed as a standard approach to reducing both the nitrogenous load and theoretically decreasing ammonia plasma concentrations. However, data supporting this intervention are mainly anecdotal. Patients with cirrhosis present in a catabolic state, leading to an increase in protein breakdowns that actually requires increased protein intake. Restricting protein intake in patients with cirrhosis may have harmful consequences on nutritional status, which may further exacerbate the patient's clinical condition. In one study, restricting protein intake in patients with HE had no benefit (e.g., a further reduction in ammonia concentrations) compared with a normal protein diet. However, protein breakdown was worsened with a low-protein diet.

Protein breakdown can further lead to negative nitrogen balance and worsening of HE. Positive nitrogen balance can promote hepatic regeneration and increase the capacity of muscle to detoxify ammonia. To maintain positive nitrogen balance, the 2006 European Society for Parenteral and Enteral Nutrition (ESPEN) guidelines in patients with liver disease recommend a daily protein intake of 1–1.5 g/kg. Vegetable and dairy sources of protein are preferable to animal protein.

Branched chain amino acids (BCAAs) (e.g., leucine, isoleucine, valine) are favored over aromatic amino acids (AAAs) for several reasons: BCAAs interfere with AAAs ability to cross the blood-brain barrier (thus decreasing the accumulation of false neurotransmitters, which may contribute to HE). In addition, BCAAs increase hepatocyte growth factor synthesis, and BCAAs bypass liver metabolism. The ESPEN guidelines recommend the use of enteral BCAAs (grade A recommendation) instead of whole protein formulations (grade C recommendation) when a patient has decompensated liver cirrhosis and when HE arises after enteral nutrition. Currently, based on their availability, enteral BCAAs are added as a supplement to whole protein formulations to meet the protein intake requirements in patients with liver disease.

ROLE OF THE PHARMACIST

Recent studies show that nonabsorbable disaccharides are as effective in the treatment of HE as neomycin and rifaximin. For prevention of HE, lactulose monotherapy and combination therapy of rifaximin and lactulose reduced the risk of HE recurrence compared with placebo. Pharmacists should consider not only efficacy when making recommendations on HE therapy, but also the cost and safety of these agents. The approximate monthly cost of rifaximin (1100-mg/day dosing) is \$1100, which is significantly more than that of lactulose 60-g/day dosing at about \$100 per month. Several cost-effectiveness studies evaluating HE therapies and studies have shown that patients who received rifaximin had fewer hospitalizations compared with patients who received lactulose; however, these studies were limited by a lack of statistics reported and retrospective study design.

Resistance to antibiotics, which pharmacists should also consider, is especially notable when rifaximin is used in patients with an inflamed GI tract (e.g., *Clostridium difficile* infection); however, the risk of bacterial resistance to rifaximin is minimal because of its lack of systemic absorption and exposure to bacteria external to the GI tract. Although there are concerns with rifaximin use, rifaximin is better tolerated than lactulose.

Based on recent studies and considering the patient's financial ability and tolerance of HE therapy, several recommendations can be made. Because of the cost of rifaximin, lactulose is recommended as initial therapy for the treatment of HE. However, in patients intolerant of lactulose, consider changing to rifaximin. For the prevention of HE, lactulose monotherapy is recommended after the first episode of HE recurrence, and rifaximin may be an alternative in patients intolerant of lactulose. In addition, combination therapy with rifaximin and lactulose should be considered in cases refractory to monotherapy. There are potential risks of adverse effects with the use of neomycin and metronidazole, especially with prolonged use; however, in patients intolerant of lactulose who cannot afford rifaximin, these antibiotics can be considered with careful monitoring.

Other key things to consider for the management of HE include identifying and removing precipitating factors such as psychoactive drugs that can worsen and/or mimic HE (e.g., benzodiazepines) and providing medication education to patients, especially with dosing and titration of lactulose therapy based on bowel movements.

ASCITES AND COMPLICATIONS OF ASCITES

Ascites is a pathologic fluid accumulation within the peritoneal space that can lead to the development of SBP and hepatorenal syndrome (HRS). Ascites is a common consequence when portal hypertension leads to an increase in systemic and splanchnic vasodilation,

causing an increase in arterial pressure, sodium and water retention, and renal vasoconstriction. Spontaneous bacterial peritonitis is an infection of preexisting ascitic fluid that results from impaired GI contraction, intestinal mucosal damage, GI bacterial overgrowth, decreased ascitic protein, altered gut permeability, and impaired reticuloendothelial system function. The organisms most commonly causing SBP are gram-negative bacilli (up to 80%), especially *Escherichia coli* and *Klebsiella* spp., followed by gram-positive cocci (about 20%), mainly *Streptococcus* and *Staphylococcus* spp.

Ascites is the most common of the three major complications of cirrhosis (i.e., HE, varices, and ascites), and around 50% of patients with compensated cirrhosis develop ascites over 10 years. One-half of those patients die within 2 years of diagnosis. Spontaneous bacterial peritonitis occurs in 10% to 30% of patients with ascites, and patients with a concomitant GI hemorrhage, previous episode of SBP, or low protein concentration in ascitic fluid are at the highest risk of developing SBP. Unfortunately, recurrence rates are almost 70% within 1 year of an SBP episode without antibiotic prophylaxis.

Ascites is diagnosed by physical examination (e.g., abdominal distension, bulging flanks with dullness), abdominal ultrasonography, and diagnostic abdominal paracentesis with ascitic fluid analysis. A serum-ascites albumin gradient (SAAG) is calculated by subtracting ascitic fluid albumin from serum albumin. The SAAG is used in categorizing and assessing the cause of ascites: 1.1 g/dL or greater indicates the patient has portal hypertension; less than 1.1 g/dL indicates other causes of ascites (i.e., nephrotic syndrome, heart failure). The diagnosis of SBP is established with a polymorphonuclear leukocyte count of 250 cells/mm³ or greater in the ascitic fluid. Ascitic fluid culture should be obtained; however, up to 50% of these cultures are negative.

Around 20% of patients with ascites develop ascites again within 1 year and 40% within 5 years. Hepatorenal syndrome is a poor prognostic sign, especially in patients with end-stage liver disease and ascites. Mortality is high (95% within 30 days) in patients with untreated type 1 HRS, and spontaneous recovery is extremely unlikely. Patients with type 1 HRS have a median survival time of less than 2–4 weeks; however, median survival of patients with type 2 HRS is 6 months. This syndrome is a functional kidney failure that results when portal hypertension causes the release of vasodilatory mediators (e.g., nitric oxide), leading to changes in kidney perfusion and systemic arterial circulation.

Diagnosis of HRS is based on the exclusion of all other possible causes of kidney failure and evaluation using the updated 2007 International Ascites Club (IAC) criteria. Patients must meet all the IAC criteria to confirm the diagnosis (Box 1-1). A working group from the Acute Dialysis Quality Initiative and IAC is reevaluating and expanding the 2007 criteria to include

patients with acute and chronic kidney failure who do not meet the current criteria. However, before the new recommendations become the standard diagnostic criteria, they will need to be validated in clinical studies. There are two distinct types of HRS. Type 1 HRS is described as a rapidly progressive kidney failure defined by doubling of the baseline serum creatinine to a level greater than 2.5 mg/dL in less than 2 weeks. Type 2 HRS is described as moderate kidney failure defined by an increase in serum creatinine from 1.5 to 2.5 mg/dL with a steady or slowly progressive course.

Therapy Goals and Treatment Options

The treatment of ascites is based on results from the patient's physical examination, diagnostic abdominal paracentesis, and abdominal ultrasonography. The goals of therapy are to improve the patient's quality of life (e.g., improved respiratory function and abdominal discomfort), prevent complications of ascites, and avoid treatment-related adverse effects. The treatment approach in patients with ascites includes restricting dietary sodium intake (to 2 g/day), avoiding sodium-retaining drugs (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs]), avoiding rapid correction of asymptomatic hyponatremia, restricting fluid only in patients with symptomatic severe hyponatremia (serum sodium less than 120 mEq/L), providing natriuresis using diuretic therapy, and performing large-volume paracentesis or transvenous intrahepatic portosystemic shunts in patients with refractory ascites.

Box 1-1. International Ascites Club 2007 Criteria for Diagnosis of HRS

Patients must meet all the following to confirm the diagnosis:

1. Cirrhosis with ascites;
2. Serum creatinine greater than 1.5 mg/dL;
3. No improvement in serum creatinine after at least 2 days with diuretic withdrawal and volume expansion with albumin (recommended dose of albumin is 1 g/kg of body weight per day up to a maximum of 100 g/day);
4. Absence of shock;
5. No current or recent treatment with nephrotoxic drugs;
6. Absence of parenchymal kidney disease (defined by proteinuria [greater than 500 mg/day], microhematuria [greater than 50 red blood cells per high-powered field], and/or abnormal kidney

HRS = hepatorenal syndrome.

Information from Salerno F, Gerbes A, Gines P, Wong F, Arroyo V. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. *Gut* 2007;56:1310–8.

In 2009, the American Association for the Study of Liver Diseases (AASLD) updated guidelines on the management of adult patients with ascites caused by cirrhosis. In patients with cirrhosis and ascites, the first-line treatments include restricting sodium intake (to 2 g/day) and providing diuretic therapy (class IIa, level A recommendation). Agents used for the acute and chronic treatment of ascites include diuretics, with most of the data supporting furosemide and spironolactone use (see Table 1-1 for specific dosing recommendations). Therapeutic abdominal paracentesis is an option for the acute management of ascites; however, it should be reserved for patients with tense or refractory ascites, and diuretic therapy should be initiated immediately after the procedure.

Initially, most patients are started on a combination diuretic regimen with furosemide and spironolactone, titrated to achieve a maximal weight loss of 0.5 kg/day; however, the 40-mg to 100-mg dosing ratio of furosemide to spironolactone should be maintained, if possible. Data support the use of this combination because using spironolactone alone can result in hyperkalemia, especially in patients with fluid overload, and furosemide alone is less effective than spironolactone. However, patients intolerant of furosemide therapy may use spironolactone alone. Eplerenone, amiloride, and triamterene have been used in patients who develop gynecomastia on spironolactone; however, data on the effectiveness of treating ascites with these agents are unavailable. The efficacy of diuretic therapy can be assessed by evaluating a 24-hour urinary sodium measurement or a random urine sodium/potassium ratio. To achieve mobilization of ascites, results should be greater than 78 mmol of urine sodium per day or a urine sodium/potassium ratio greater than 1.

Tolvaptan, a vasopressin receptor antagonist, increases serum sodium concentrations and has been studied in patients with cirrhosis for the treatment of euvolemic and hypervolemic hyponatremia. However, the limited outcome data available in patients with cirrhosis show the benefit versus risks (e.g., increased risk of GI bleeding) do not support the use of this agent. All patients with cirrhosis and ascites should be considered for liver transplantation.

The treatment and prevention of SBP is based on results from diagnostic abdominal paracentesis and history of SBP. Once the diagnosis of SBP is made on the basis of the results from ascitic fluid analysis, patients should immediately receive empiric antibiotics to target common organisms that can cause SBP. Delay in antibiotic therapy can result in worsening infection and even death. Antibiotics can be narrowed or changed on the basis of cultures and antibiotic sensitivities if available. Antibiotic choice and dosing recommendations depend on indication (i.e., SBP treatment or prophylaxis, presence of active GI bleeding) (see Table 1-1).

The AASLD guidelines recommend that the empiric treatment of SBP includes antibiotic therapy with a third-generation cephalosporin (class I, level A recommendation). The preferred agent is cefotaxime; however, ceftriaxone may be used as an alternative option. Cefotaxime is the antibiotic of choice because it was shown superior to ampicillin plus tobramycin. In patients without previous quinolone exposure who are not vomiting, in shock, presenting with a grade II or higher HE, or with a serum creatinine greater than 3 mg/dL, the guidelines suggest that oral ofloxacin can be used instead of intravenous third-generation cephalosporin (class IIa, level B recommendation); however, ofloxacin is not used in practice because of its adverse effects. Alternative fluoroquinolones such as ciprofloxacin or levofloxacin should be limited to use in patients with severe allergy to penicillins (e.g., anaphylaxis) because extensive use of these agents has resulted in an increase in gram-positive and quinolone-resistant organisms causing SBP. Five days of treatment for SBP was found to be as effective as 10 days, especially with respect to infection-related mortality, in-hospital mortality, bacteriologic cure, and ascitic fluid infection recurrence. Based on these results, it is recommended to treat SBP for 5 days. Adding intravenous albumin, 1.5 g/kg on day 1 and 1 g/kg on day 3, has been shown to decrease SBP mortality from 29% to 10%.

Antibiotic prophylaxis for SBP is differentiated as either primary prophylaxis or secondary prophylaxis (see Table 1-1). Patients with a history of SBP should receive secondary SBP prophylaxis. Patients who have low ascitic protein or active GI bleeding should receive primary SBP prophylaxis. One recent study showed that patients who received norfloxacin for SBP primary prophylaxis had improved survival compared with placebo. However, because of its low systemic concentrations, norfloxacin should be limited to SBP prophylaxis and not treatment. Moreover, patients who presented with a low ascitic protein measurement (less than 1.5 g/dL) and at least one of the following criteria—blood urea nitrogen of 25 mg/dL or greater, serum creatinine of 1.2 mg/dL or greater, serum sodium of 130 mEq/L or less, or Child-Pugh score of 9 or more with a bilirubin of 3 mg/dL or greater—had improved survival compared with placebo. Based on these results, the criteria for SBP prophylaxis defined in this study are currently recommended in the AASLD guidelines.

Patients who do not have active GI bleeding but who have an indication for SBP prophylaxis (e.g., previous episode of SBP) should receive long-term oral prophylaxis with norfloxacin or trimethoprim/sulfamethoxazole. Oral once-weekly dosing of ciprofloxacin was evaluated in one prospective controlled study and shown to be effective in preventing SBP. The guidelines recommend against intermittent dosing because it may rapidly select for resistant flora; however, only limited data support

this. One study evaluated the use of daily oral ciprofloxacin versus placebo in patients with cirrhosis and low ascitic fluid protein concentrations (less than 1.5 g/dL) for the prevention of SBP. Patients who received daily ciprofloxacin had SBP about 4 times less often than placebo; however, the results were not statistically significant. The probability of 12-month survival was significantly increased in the ciprofloxacin group. Overall, once-daily dosing of ciprofloxacin for SBP prophylaxis is preferred by the AASLD because of concerns about an increased risk of resistance. Once-weekly dosing of ciprofloxacin for SBP prophylaxis could be an option; however, further studies are needed to evaluate its safety and efficacy.

Patients with cirrhosis and active GI bleeding are also at risk of SBP. In these patients, the recommendation for SBP prophylaxis is to initiate an intravenous third-generation cephalosporin (e.g., ceftriaxone) (class I, level A recommendation). Alternative options (e.g., ciprofloxacin, trimethoprim/sulfamethoxazole) should be limited to patients with a severe allergy to penicillins. A meta-analysis showed a 9% increase in survival in patients with cirrhosis and variceal bleeding who received SBP prophylaxis with antibiotics. However, another meta-analysis of patients with cirrhosis who received antibiotic SBP prophylaxis and presented with upper GI bleeding showed statistically significant reductions in bacterial infections. The analysis showed decreases in all-cause mortality, rebleeding, and hospital length of stay, although the differences did not meet statistical significance.

Liver transplantation is the only definitive treatment of HRS. The primary goal of pharmacologic agents is to provide a bridge to transplantation by reversing splanchnic vasodilation, improving kidney function, and prolonging survival time. Pharmacologic agents such as octreotide plus midodrine, norepinephrine, vasopressin, or terlipressin have been used to bridge patients to transplantation. None of these agents has FDA label approval for use in patients with HRS.

The recommendation for the treatment of type 1 HRS is the administration of combination vasoactive drugs (e.g., octreotide), midodrine, and albumin therapy (class IIa, level B classification); however, the guidelines do not address the treatment of type 2 HRS. (For dosing recommendations, see Table 1-1.) The safety and efficacy data on these treatment regimens are limited to small, nonrandomized trials; retrospective analyses; and a few randomized controlled trials. Most of the studies evaluated the efficacy of available agents in patients with type 1 HRS and showed improvement in kidney function and HRS reversal. Terlipressin (a vasopressin analog), when administered with albumin, showed a significantly higher complete reversal of HRS compared with terlipressin monotherapy. However, terlipressin is currently unavailable in the United States and is

undergoing a phase III study (REVERSE [REsynchronization reVERses Remodeling in Systolic left vEntricular dysfunction] trial) to evaluate its efficacy and safety for HRS. Other agents such as octreotide monotherapy and dopamine have been evaluated for the treatment of HRS and have not been shown to be more effective than placebo. None of the available studies evaluated the diagnosis of HRS on the basis of the updated 2007 IAC criteria. The IAC criteria currently recommend albumin because of better and more sustained volume expansion compared with isotonic saline. In addition, kidney failure in the setting of infection (excluding septic shock) is considered HRS, and treatment may be started despite clearance of the infection.

Recent studies have evaluated the combination of vasoactive drugs, midodrine, and albumin therapy in patients with type 2 HRS. The use of midodrine, albumin, and terlipressin or noradrenalin was evaluated in patients with type 1 and type 2 HRS. There was no significant difference for complete treatment response in the noradrenalin group versus the terlipressin group. There were significant decreases in serum creatinine from baseline in the terlipressin group compared with the noradrenalin group; however, there was no significant difference in the recurrence rate during follow-up. In addition, the survival rate was not significantly different between the groups. Overall, the authors concluded that noradrenalin was as effective as terlipressin in treating patients with type 1 and type 2 HRS.

Another study retrospectively evaluated the effect of octreotide with midodrine in addition to albumin compared with control for the treatment of type 1 and type 2 HRS. Overall, the authors concluded that administration of the combination of midodrine, octreotide, and albumin significantly improved kidney function (glomerular filtration rate [GFR]) and transplant-free survival in patients with type 1 and type 2 HRS. Both of these studies have several limitations (e.g., lack of treatment allocation concealment and blinding); however, they provide some evidence to support using a combination of vasoactive drugs (e.g., octreotide and terlipressin), midodrine, and albumin therapy in patients with type 2 HRS. Based on current guidelines and clinical studies, combination therapy with octreotide, midodrine, and albumin, or intravenous norepinephrine and albumin should be used for the treatment of type 1 and type 2 HRS. However, because of the additional resources (e.g., nursing time) needed to administer intravenous norepinephrine, it should be limited to patients intolerant of oral therapy.

Role of the Pharmacist

Nonadherence to diuretic therapy and sodium restriction are major areas where pharmacists can affect ascites treatment in patients with cirrhosis. Many of these patients are nonadherent to diuretic

therapy because of their intolerance of diuretics secondary to adverse effects (e.g., muscle cramping, dehydration). In addition, diuretic therapy can become less effective over time. The efficacy of and adherence to diuretic therapy can be assessed by a 24-hour urinary sodium measurement or a random spot urine sodium concentration/spot urine potassium ratio. Pharmacists are valuable resources in making recommendations regarding diuretic dosing and suggesting alternative therapy in patients intolerant of their diuretic regimen. Recommendations should be based on patient's adherence to diuretic therapy, adverse effects (e.g., hyperkalemia, gynecomastia), and lack of symptom response to treatment (if adherent).

In patients with indications for SBP therapy or prophylaxis, pharmacists can make antibiotic therapy recommendations on the basis of previous antibiotic use (i.e., patient developing SBP while taking norfloxacin for SBP prophylaxis), bacterial resistance patterns, patient allergies, and patient adherence to therapy. In patients presenting with possible HRS, it is important for pharmacists to ensure that drugs that can cause or worsen kidney failure (e.g., aminoglycosides or NSAIDs) are discontinued and avoided. Although NSAIDs are often used in patients with cirrhosis as an alternative to acetaminophen for the treatment of pain, they can also affect kidney function, decrease the effectiveness of diuretic therapy, and increase the risk of upper GI bleeding, all of which are concerns in patients with cirrhosis. Pharmacists should educate prescribers and patients on the risks versus benefits of NSAID therapy.

PORTAL HYPERTENSION AND VARICEAL BLEEDING PREVENTION

Portal hypertension that results from chronic liver disease can cause further complications including the development and bleeding of varices. Around 50% of patients with cirrhosis develop gastroesophageal varices, and the presence of varices correlates with the severity of liver disease. Varices occur in 40% of patients with mild liver disease (Child-Pugh class A) and in 85% of patients with severe liver disease (Child-Pugh class C). The strongest predictor of the occurrence of varices in patients with cirrhosis without a history of variceal bleeding is a hepatic venous pressure gradient (HVPG) of greater than 10 mm Hg. Risk factors associated with the progression of varices (e.g., small to large varices) include decompensated cirrhosis (Child-Pugh class B and C), alcoholic cirrhosis, and the presence of red wale marks on baseline endoscopy.

Gastroesophageal varices can progress to variceal bleeding, the incidence of which varies from 5% to 15% per year. Strong predictors of variceal bleeding include varix size, with the highest risk of bleeding with large

varices (greater than 5 mm), severe liver disease (Child-Pugh class C cirrhosis, presence of ascites or tense ascites), and previous variceal bleeding. Unfortunately, mortality is at least 20% after 6 weeks of the variceal hemorrhage. Varices are more prevalent in the esophageal area; however, 5% to 33% of patients present with gastric varices. The incidence of gastric variceal bleeding in 2 years is 25%.

Therapy Goals and Treatment Options

The prevention of variceal bleeding is categorized into primary and secondary prophylaxis. The goals for primary prophylaxis are to detect the presence and size of varices and to treat patients to prevent the first variceal hemorrhage. The goal for secondary prophylaxis is to prevent the recurrence of variceal bleeding. For primary prophylaxis, patients are classified as having the highest risk of variceal bleeding when they present with medium/large varix, red wale marks on varix, and Child-Pugh class C. Patients at lowest risk of variceal bleeding include those with no varices; it is not recommended to treat these patients. Specific recommendations for primary and secondary prophylaxis are discussed in the following paragraphs. The treatment of acute variceal bleeding is discussed in the acute GI bleeding chapter of this book.

Therapies used for preventing variceal bleeding include nonselective β -blockers and endoscopic variceal ligation (EVL). Nonselective β -blockers are more effective at preventing variceal bleeding than selective β -blockers because of their β -1 and β -2 antagonist properties. The nonselective β -blocker reduces portal pressure by decreasing cardiac output and causing splanchnic vasoconstriction. Guidelines from the AASLD (2007), as well as the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program (2009), recommend primary and secondary prevention of variceal bleeding based on patient risks and varix size.

For primary prevention in patients with the highest risk of variceal bleeding, the recommended first-line treatment is either nonselective β -blockers or EVL. However, in patients with medium to large varix who are not at high risk of bleeding (Child-Pugh class A patients and no red signs), nonselective β -blocker therapy is recommended unless patients have contraindications to or are intolerant of β -blockers. Patients with a small varix and higher risk factors for variceal bleeding (red wale marks on varix and/or Child-Pugh class B/C) should receive primary prevention with nonselective β -blockers. Randomized controlled studies have shown that patients at risk of variceal bleeding who received nonselective β -blockers had a significant reduction in the incidence of variceal bleeding compared with placebo (25% vs. 15%, respectively).

In patients with small varices who are not at a high risk of bleeding or in patients with no varices, the guidelines recommend primary prevention with nonselective β -blockers; however, the long-term benefit of therapy has not been determined. Patients with small varices without a high risk of variceal bleeding who received nonselective β -blockers had a small, nonsignificant reduction in the incidence of variceal bleeding; however, nonselective blockers were effective in delaying variceal growth. The use of the nonselective β -blocker timolol was studied in patients with no varices and baseline portal hypertension (defined as an HVPG greater than 5 mm Hg) and showed no benefit in preventing varices. All patients with gastric fundal varices or previous variceal bleeding should receive nonselective β -blockers. The duration of nonselective β -blockers is indefinite regardless of risk factors and varix size.

The guidelines recommend against using nitrates alone or in combination with nonselective β -blockers or EVL because of the lack of efficacy with these therapies or conflicting results. Nitrates (e.g., isosorbide mononitrate) were commonly used for this indication; however, several studies have shown that nitrates are ineffective at preventing the first episode of variceal bleeding. In addition, nitrates are associated with higher mortality in patients 50 years and older. Combination therapy with nonselective β -blockers and nitrates has been studied for the prevention of variceal bleeding. In randomized controlled studies, this combination was not effective in preventing variceal bleeding and resulted in an increase in adverse events compared with control (propranolol or nadolol plus placebo).

The combination of nonselective β -blockers and EVL was evaluated for the primary prevention of variceal bleeding in a randomized study of patients with high-risk varices. Results showed no differences in the incidence of bleeding or mortality compared with EVL alone. However, one randomized controlled study of patients with high-risk varices showed that combination therapy with nonselective β -blockers and EVL resulted in significantly lower first variceal bleeding rates than nonselective β -blockers alone. Given the conflicting results, combination nonselective β -blockers and EVL cannot be recommended at this time.

Most of the studies evaluating primary and secondary prophylaxis with nonselective β -blockers used nadolol and propranolol. In a recent controlled study, carvedilol was evaluated for use in the primary prevention of variceal bleeding. Carvedilol demonstrated a significant reduction in the incidence of first variceal bleeding compared with EVL; however, no difference in mortality was noted. Compared with nadolol and propranolol, the vasodilating activity of carvedilol may result in higher rates of arterial hypotension, sodium retention, and edema, which are concerns in patients with advanced, decompensated cirrhosis. Currently,

until more data are available, carvedilol is not recommended first line for the primary prophylaxis of variceal bleeding. Carvedilol may be an option in patients not responding to nadolol or propranolol or in patients with other comorbidities, necessitating the use of carvedilol (e.g., chronic heart failure, arterial hypertension).

It is important not only to consider the efficacy of these agents in the prevention of variceal bleeding, but also their safety and tolerability. Nonselective β -blockers should be titrated to a maximal tolerated dose and target heart rates of 55–60 beats/minute. Dosing recommendations are listed in Table 1-1. Common adverse effects associated with nonselective β -blockers, especially nadolol and propranolol, include light-headedness, fatigue, and shortness of breath. Direct comparisons between nadolol and propranolol have not been made; however, nadolol seems to have fewer adverse effects than propranolol (around 10% vs. 17%, respectively). Contraindications to nonselective β -blockers must be considered before therapy initiation; these include patients with reactive airway disease (e.g., asthma), insulin-requiring diabetes, decompensated or acute congestive heart failure, heart block, bradycardia, and peripheral vascular disease.

Role of the Pharmacist

The pharmacist is in a unique position to work with various members of the team caring for patients with chronic liver disease and portal hypertension. These patients are cared for by hepatologists, gastroenterologists, and, many times when admitted to the hospital, general medicine practitioners. Pharmacists should be aware of the guidelines in the primary and secondary prevention of variceal bleeding, educate practitioners about the importance of treatment, and ensure the initiation of therapy when indicated. At times, when patients are moving from one health care setting to another (e.g., from hospital to home), nonselective β -blockers are discontinued; however, it is essential for the pharmacist to ensure therapy continuation if indicated. Pharmacists can also play a valuable role in assessing adherence to and intolerance of nonselective β -blockers, removing or adjusting other drugs that may increase the risk of upper GI bleeding (e.g., NSAIDs), and educating patients on maintaining a low-sodium diet.

CONCLUSION

When making recommendations on appropriate treatment of patients with complications related to chronic liver disease, pharmacists and other clinicians must consider the recent guidelines evaluating the efficacy and safety of new and existing medications and their role in therapy. It is also important to evaluate recent studies in determining the validity of current treatment guidelines. One example is with the recent

guidelines on the treatment of HE. Data with rifaximin were available after these guidelines were developed, and no recommendations were made regarding rifaximin. Although data are limited in some areas of chronic liver disease, such as with the treatment of HRS, most complications of chronic liver disease have solid evidence to support recommendations on treatment and prevention. When making recommendations, it is important to consider not only evidence supporting the efficacy and safety of drugs to treat complications of chronic liver disease, but also patient factors, such as nonadherence, therapy intolerance, and cost.

ANNOTATED BIBLIOGRAPHY

1. Jiang Q, Jiang XH, Zheng MH, Jiang LM, Chen YP, Wang L. Rifaximin versus nonabsorbable disaccharides in the management of hepatic encephalopathy: a meta-analysis. *Eur J Gastroenterol Hepatol* 2008;20:1064–70.

In this recent meta-analysis, the investigators evaluated five randomized controlled trials (n=264) comparing rifaximin with nonabsorbable disaccharides for the treatment of HE. Results showed no difference between rifaximin and nonabsorbable disaccharides in the clinical improvement of HE (relative risk [RR] 1.08; 95% confidence interval [CI], 0.85–1.38; p=0.53). When evaluating acute and chronic HE, there was no difference in the clinical improvement of HE between both groups (acute HE: RR 0.98; 95% CI, 0.85–1.13; p=0.74; and chronic HE: RR 0.87; 95% CI, 0.40–1.88; p=0.72). Rifaximin resulted in significantly less abdominal pain than nonabsorbable disaccharides (RR 0.28; 95% CI, 0.08–0.95; p=0.04), but there was no significant difference in diarrhea (RR 0.90; 95% CI, 0.17–4.70; p=0.9). Overall, rifaximin did not show superior efficacy compared with nonabsorbable disaccharides.

2. Bass NM, Mullen KD, Sanyal A, Poordad F, Neff G, Leevy CB, et al. Rifaximin treatment in hepatic encephalopathy. *N Engl J Med* 2010;362:1071–81.

This study was a prospective, double-blind, placebo-controlled, randomized, multicenter study that compared rifaximin 550 mg twice daily (n=140) with placebo (n=159) for the prevention of HE. Of note, greater than 90% of patients received concomitant lactulose. Patients who received rifaximin had a significant reduction in the first breakthrough HE episode (22.1% vs. 45.9%, respectively; hazard ratio [HR] 0.42; 95% CI, 0.28–0.64; p<0.001) and first HE-related hospitalization (13.6% vs. 22.6%, respectively; HR 0.5; 95% CI, 0.29–0.87; p=0.01) compared with the placebo group. However, no benefit in the primary outcome was seen in patients with MELD scores of 19–24 (p=0.21) or in patients who did not receive concomitant lactulose therapy (p=0.33). Adverse drug events (80% in the rifaximin group vs. 79.9% in the placebo group; p>0.05) and mortality (9% vs. 11%; p>0.05) were similar in both groups. This study led to the approval of rifaximin for

the reduction in risk of overt HE recurrence in patients 18 years and older. Important points to consider with this study are that no patients were enrolled with a MELD score greater than 25, and only 9% of patients were Child-Pugh class C. These study limitations may decrease the applicability of these results in this patient population.

3. Terg R, Fassio E, Guevara M, Cartier M, Longo C, Lucero R, et al. Ciprofloxacin in primary prophylaxis of spontaneous bacterial peritonitis: a randomized, placebo-controlled study. *J Hepatol* 2008;48:774–9.

This study was a prospective, randomized, double-blind, placebo-controlled trial that compared oral ciprofloxacin 500 mg/day (n=50) with placebo (n=50) for the primary prevention of SBP. Patients included were 19–79 years old with cirrhosis, ascites, and low ascitic total protein concentration (i.e., less than 1.5 g/dL). Baseline characteristics were similar in both groups. Results showed that the ciprofloxacin group had SBP occur about 4 times less often than placebo (4% vs. 14%, respectively); however, the results were not statistically significant. In addition, the probability of patients remaining SBP free was not significantly different between groups (p=0.07). However, the probability of 12-month survival was significantly increased in the ciprofloxacin group (86% vs. 66% in the placebo group; p<0.04) with an absolute risk reduction of 17%, a relative risk reduction of 59%, and a number of patients needed to treat of six. Forty-eight percent of patients in the placebo group and 36% of patients in the ciprofloxacin group developed complications during follow-up (p = nonsignificant), with kidney failure, encephalopathy, and GI bleeding as the most common. Overall, the authors concluded that primary SBP prevention with ciprofloxacin reduces SBP occurrence and improves survival in patients with cirrhosis and low ascitic protein concentration. On the basis of these results, ciprofloxacin may be used as an option for primary SBP prevention; however, resistance was briefly addressed in this study. Two infections with *Escherichia coli* (both in the treatment group) were resistant to ciprofloxacin, and one patient in each group developed methicillin-sensitive *Staphylococcus aureus* (MSSA) infection. Although further details were not provided, the potential increased resistance with daily use of ciprofloxacin should be considered.

4. Chavez-Tapia NC, Barrientos-Gutierrez T, Tellez-Avila FI, Soares-Weiser K, Uribe M. Antibiotic prophylaxis for cirrhotic patients with upper gastrointestinal bleeding. *Cochrane Database Syst Rev* 2010;9:CD002907.

In this recent meta-analysis, the investigators evaluated 12 randomized controlled studies (n=1241) comparing antibiotics with placebo or no antibiotics for the prevention of SBP in patients with cirrhosis and upper GI bleeding. Antibiotics used in the studies included ofloxacin or ciprofloxacin plus amoxicillin/clavulanic acid, ceftriaxone, ciprofloxacin, ofloxacin, cefotaxime, ampicillin/sulbactam, cefazolin/cephalexin, gentamicin plus vancomycin plus nystatin,

neomycin plus colistin plus nystatin, imipenem/cilastin, and norfloxacin. Results showed that antibiotic use for SBP prophylaxis resulted in a significant reduction in mortality (RR 0.79; 95% CI, 0.63–0.98), mortality related to bacterial infections (RR 0.43; 95% CI, 0.19–0.97), bacterial infections (RR 0.36; 95% CI, 0.27–0.49), and overall rebleeding (RR 0.53; 95% CI 0.38–0.74). Mortality benefits were diminished with stratification of antibiotics by group; however, there was still a significant reduction in bacterial infections with all antibiotic groups. Cephalosporins were associated with the highest effect on bacterial infections, followed by quinolones, quinolones with β -lactams, and other antibiotic groups. Overall, patients with cirrhosis who received antibiotics for SBP prophylaxis after an upper GI bleed had significant reductions in mortality, bacterial infections, and rebleeding rates.

5. Fernandez J, Navasa M, Planas R, Montoliu S, Monfort D, Soriano G, et al. Primary prophylaxis of spontaneous bacterial peritonitis delays hepatorenal syndrome and improves survival in cirrhosis. *Gastroenterology* 2007;133:818–24.

This was a prospective, randomized, placebo-controlled study that compared norfloxacin (n=35) and placebo (n=33) for primary SBP prevention in patients who presented with low ascitic protein measurement (less than 1.5 g/dL) and at least one of the following criteria: blood urea nitrogen of 25 mg/dL or more, serum creatinine of 1.2 mg/dL or more, serum sodium of 130 mEq/L or less, and Child-Pugh score of 9 or more with a bilirubin of 3 mg/dL or more. Patients in the norfloxacin group received norfloxacin 400 mg by mouth daily. The primary outcomes measured were 3-month and 1-year probabilities of survival. Results showed that patients who received norfloxacin had significant improvement in 3-month survival (94% vs. 62%; p=0.003) and improvement in 1-year survival (60% vs. 48%; p=0.05) compared with placebo. The incidence of kidney failure (7 patients vs. 16 patients; p=0.03) and SBP (2 patients vs. 10 patients; p=0.02) was significantly lower with norfloxacin than with placebo. Overall, the authors concluded that primary SBP prevention with norfloxacin reduces mortality as well as the development of SBP and kidney failure.

6. Alessandria C, Ottobrelli A, Venon-Debernardi W, Todros L, Cerenzia MT, Martini S, et al. Noradrenalin vs. terlipressin in patients with hepatorenal syndrome: a prospective, randomized, unblinded, pilot study. *J Hepatol* 2007;47:499–505.

This study prospectively compared noradrenalin (n=10) with terlipressin (n=12) for the treatment of type 1 and type 2 HRS. Patients were eligible for inclusion if they had HRS and were excluded if they had heart or respiratory failure, coronary disease, or peripheral artery disease. Patients were randomized to receive continuous infusion of noradrenalin or terlipressin. Noradrenalin was administered at an initial rate of 0.1 mcg/kg/minute titrated to a maximal dose of 0.7 mcg/kg/minute. Terlipressin was given as an intravenous

bolus of 1 mg every 4 hours and increased to 2 mg every 4 hours after 3 days of treatment if serum creatinine was not decreased by at least 25%. Albumin was administered during the treatment period. Treatment was administered until complete reversal of HRS or for a maximum of 2 weeks. The primary outcome was clinical response (defined as complete, partial, or recurrence) to treatment. Twenty-two patients were included in the analysis. Baseline characteristics were similar between the two treatment groups (p>0.05). There was no significant difference for complete treatment response between the noradrenalin group (70%) and terlipressin group (83%). Five patients (22.7%) did not respond to any treatment. Significant decreases in serum creatinine occurred from baseline in the terlipressin group compared with the noradrenalin group (2.5 \pm 0.3 mg/dL to 1.2 \pm 0.1 mg/dL vs. 2.3 \pm 0.2 mg/dL to 1.2 \pm 0.1 mg/dL, respectively; p<0.05). There was no significant difference in the recurrence rate during follow-up between noradrenalin (29%) and terlipressin (60%). In addition, the survival rate was not significantly different between the groups. The authors concluded that noradrenalin was as effective as terlipressin in treating patients with type 1 and type 2 HRS. The AASLD guidelines recommend the use of combination vasoactive drugs (specifically octreotide), midodrine, and albumin for the treatment of type 1 HRS; however, norepinephrine could be an option in patients intolerant to oral therapy.

7. Skagen C, Einstein M, Lucey MR, Said A. Combination treatment with octreotide, midodrine, and albumin improves survival in patients with type 1 and type 2 hepatorenal syndrome. *J Clin Gastroenterol* 2009;43:680–5.

This study was a retrospective evaluation of the effect of octreotide with midodrine in addition to albumin for the treatment of type 1 and type 2 HRS. Patient inclusion was on the basis of the following criteria: documented liver disease with evidence for portal hypertension determined by ultrasonography or clinical parameters (e.g., varices, ascites, and splenomegaly) and diagnosis of HRS. Patients in the treatment group (n=75) received the combination of octreotide and midodrine with albumin. Octreotide was administered 100–200 mcg subcutaneously three times/day with midodrine 7.5–15 mg orally three times/day in addition to albumin (50–100 g intravenously daily). Patients in the control group (n=87) received no therapy. The primary outcomes measured were transplant-free survival and GFR. Baseline characteristics were similar among groups, except for a significantly higher presence of ascites in the treatment group (98.7%) than in the control group (89.7%, p=0.02). There was a significantly higher rate of transplant-free survival in the treatment group at 1 month (74%) and at 3 months (53%) compared with the control group at 1 month (39%) and at 3 months (27%, p<0.0001). At the 1-month follow-up, GFR was significantly higher in the treatment group (47.67 \pm 33.98 mL/minute) than in the control group (34.39 \pm 18.79 mL/minute; p=0.03). Liver transplant rates were significantly higher in patients with HRS

type 2 in the treatment cohort (58%) than in the control group (25%, $p=0.04$). No differences were observed in the need for dialysis, rate of transvenous intrahepatic portosystemic shunts, or use of vasoconstrictors other than midodrine ($p>0.05$). The authors concluded that the combination of midodrine, octreotide, and albumin improved kidney function and transplant-free survival in patients with type 1 and type 2 HRS. Current guidelines recommend this combination for the treatment of type 1 HRS; however, this study also supports its use in treating type 2 HRS.

8. Tripathi D, Ferguson JW, Kochar N, Leithead JA, Therapondos G, McAvoy NC, et al. Randomized controlled trial of carvedilol versus variceal band ligation for the prevention of the first variceal bleed. *Hepatology* 2009;50:825–33.

This study was a prospective, randomized, controlled, multicenter trial comparing carvedilol ($n=77$) and EVL ($n=75$) for primary prevention of variceal bleeding. Adult patients with cirrhosis and grade 2 or larger esophageal varices without previous variceal hemorrhage were included in the study. Patients in the carvedilol group were initiated on carvedilol 6.25 mg/day titrated to a target dose of 12.5 mg/day (based on systolic blood pressure). Baseline characteristics were similar between groups. Results showed that carvedilol demonstrated a significant reduction in the incidence of first variceal bleeding compared with EVL (10% vs. 23%, respectively; $p=0.04$); however, no difference in mortality (35% vs. 37%, respectively; $p=0.71$) or bleeding-related mortality (3% vs. 1%, respectively; $p=0.26$) was noted. Overall, the authors concluded that carvedilol is effective for the primary prevention of variceal bleeding in patients with cirrhosis and high-risk varices. Although data are limited on the use of carvedilol for primary prevention of variceal bleeding, these results support the use of carvedilol as an alternative to nadolol or propranolol in specific patient populations (e.g., patients with congestive heart failure requiring β -blocker therapy).

9. Groszmann RJ, Garcia-Tsao G, Bosch J, Grace ND, Burroughs AK, Planas R, et al. Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. *N Engl J Med* 2005;353:2254–61.

This is the most recent study evaluating the use of β -blockers in low-risk patients without varices. Most recent studies focused in high- or moderate-risk patients. This prospective, randomized, placebo-controlled study compared timolol ($n=108$) and placebo ($n=105$) for the prevention of gastroesophageal varices in patients with cirrhosis and portal hypertension (an HVPG of 6 or greater). Patients (19–74 years of age) were eligible if they did not have gastroesophageal varices. Patients in the timolol group were initiated on timolol 5 mg by mouth daily (titrated on the basis of heart rate). The primary outcome measured was the development of varices or variceal hemorrhage. Most patients were Child-Pugh class A (91% in the timolol group and 87% in the placebo group), and no patients in either

group were Child-Pugh class C. Results showed no significant difference in the primary outcome between the timolol group and placebo (39% vs. 40%, respectively; $p=0.89$). However, moderate or severe adverse events were significantly higher in the timolol group than in placebo (48% vs. 32%, respectively; $p=0.02$). Overall, the authors concluded that nonselective β -blockers are ineffective for the primary prevention of gastroesophageal varices and variceal hemorrhage in patients with cirrhosis and portal hypertension without the presence of varices at baseline (no or lowest risk of variceal bleeding).

10. Sarin SK, Wadhawan M, Agarwal SR, Tyagi P, Sharma BC. Endoscopic variceal ligation plus propranolol versus endoscopic variceal ligation alone in primary prophylaxis of variceal bleeding. *Am J Gastroenterol* 2005;100:797–804.

This was a prospective randomized controlled study comparing the combination of propranolol and EVL ($n=72$) with EVL alone ($n=72$) for the primary prevention of variceal bleeding. Patients with portal hypertension and high-risk varices (defined as grade 3 or 4 varices) with red signs and without a history of bleeding were included in the study. Results at 20 months showed no differences between combination propranolol and EVL and EVL alone in the actuarial probability of bleeding (7% vs. 11%, respectively; $p=0.72$) or mortality (8% vs. 15%, respectively; $p=0.37$). However, the recurrence of varices was significantly lower in the combination propranolol and EVL group than with EVL alone (19% vs. 33%, respectively; $p=0.03$), but no patient had recurrence of variceal bleeding. The incidence of adverse effects in patients who received propranolol was 22% (p value was not reported). Overall, the investigators concluded that both combination therapy with propranolol and EVL and EVL alone were effective in the prevention of variceal bleeding in patients with high-risk varices. On the basis of these results, adding propranolol to EVL may not be necessary because the risk of variceal bleeding or death is not significantly different from EVL alone.

SELF-ASSESSMENT QUESTIONS

Questions 1–4 pertain to the following case.

T.R. is a 64-year-old woman (weight 60 kg) who presents to the emergency department with abdominal distension, nausea/vomiting, and fever. She reports chronic hepatitis C cirrhosis (diagnosed 1 year ago) that was treated with peginterferon alfa-2b plus ribavirin. Currently, she is taking no medications. She is allergic to sulfa drugs with a reaction of hives. Physical examination shows that T.R. is jaundiced with marked abdominal distension, bulging flanks with dullness, and a temperature of 101.9°F, heart rate 99 beats/minute, respiratory rate 18 breaths/minute, blood pressure 135/63 mm Hg, and oxygen saturation 100% on room air. Abdominal ultrasonography shows that T.R. has large ascites. Her laboratory and radiologic results show a serum creatinine of 0.9 mg/dL, potassium of 4.2 mEq/L, and white blood cell (count) (WBC) of 20.2×10^3 cells/mm³; her toxicology screen is negative, esophagogastroduodenoscopy (EGD) shows no varices, and ascitic fluid shows a protein of 1.1 g/dL, albumin of 1 g/dL, and WBC of 406/mm³ with 76% neutrophils. Cultures are pending.

1. Which one of the following would be best to initiate in the acute treatment of ascites in T.R.?
 - A. Norfloxacin 400 mg by mouth twice daily.
 - B. Trimethoprim/sulfamethoxazole 180 mg intravenously every 12 hours for 5 days and intravenous albumin 90 g on day 1 and 60 g on day 3.
 - C. Cefotaxime 1 g intravenously every 8 hours for 5 days and intravenous albumin 90 g on day 1 and 60 g on day 3.
 - D. Ciprofloxacin 750 mg by mouth once weekly.
2. T.R. is treated and is now stable enough to go home. Her ascites fluid culture was negative. Which one of the following, taken orally daily, would be best to recommend for chronic drug treatment of T.R.'s ascites?
 - A. Spironolactone 100 mg and furosemide 40 mg.
 - B. Spironolactone 100 mg.
 - C. Furosemide 40 mg.
 - D. Eplerenone 25 mg.
3. Which one of the following is best to recommend for spontaneous bacterial peritonitis (SBP) prophylaxis in T.R.?
 - A. Norfloxacin 400 mg by mouth once daily.
 - B. Trimethoprim/sulfamethoxazole double strength 1 tablet by mouth once daily.
 - C. No treatment indicated.
 - D. Ciprofloxacin 500 mg by mouth every 12 hours.
4. Four weeks after her recent hospitalization, T.R. presents to the clinic for follow-up on her ascites treatment. She is currently treated with diuretic therapy. Random spot urine sodium and potassium concentrations are obtained, and the results are 81 mmol/L and 30 mmol/L, respectively. Which one of the following is the best assessment of the effectiveness of T.R.'s diuretic therapy?
 - A. Her ascites is responding appropriately.
 - B. Her ascites has an inadequate response.
 - C. Not enough information is given to assess response.
 - D. A 24-hour urine collection should be performed.

Questions 5–7 pertain to the following case.

R.S. is a 42-year-old man who presents to the emergency department with significant mental status changes and asterixis. He has chronic alcoholic cirrhosis (diagnosed 5 years ago), Child-Pugh class B; refractory hepatic encephalopathy (HE) (diagnosed 5 years ago with two recurrent episodes of HE in the past year); and portal hypertension. He is taking lactulose 30 mL by mouth four times/day and reports two to four semisoft stools daily. He reports no known drug allergies. The toxicology screen is only positive only for benzodiazepines, abdominal ultrasonography shows no ascites, and EGD shows many varices in the esophagus, which are large and not bleeding. Sclerotherapy is conducted.

5. Which one of the following is best to recommend for treatment of HE in R.S.?
 - A. Discontinue lactulose and start rifaximin 550 mg by mouth twice daily.
 - B. Increase lactulose dose to result in six to eight semisoft stools daily.
 - C. Discontinue lactulose and start rifaximin 400 mg by mouth three times/day.
 - D. Continue current lactulose regimen and start rifaximin 400 mg by mouth three times/day.
6. Which one of the following would best help treat HE in R.S.?
 - A. Discontinue benzodiazepines.
 - B. Initiate branched chain amino acids (BCAAs).
 - C. Restrict protein intake.
 - D. Treat GI bleeding with intravenous proton pump inhibitor.

7. Which one of the following is best to recommend for the management of portal hypertension in R.S.?
- Endoscopic variceal ligation (EVL).
 - Carvedilol 12.5 mg by mouth twice daily.
 - Nadolol 20 mg by mouth daily.
 - Propranolol 20 mg by mouth twice daily and EVL.

Questions 8–10 pertain to the following case.

W.P. is a 58-year-old man who presents to the emergency department with abdominal distension and decreased urine output. He has alcoholic cirrhosis and HE. W.P. is currently taking neomycin 2 g by mouth every 6 hours and has no known drug allergies. His physical examination shows marked abdominal distension, temperature 98.5°F, heart rate 96 beats/minute, respiratory rate 20 breaths/minute, blood pressure 125/68 mm Hg, and oxygen saturation 100% on room air. The rest of the examination is unremarkable. Laboratory and radiologic results show a serum creatinine of 3.5 mg/dL (baseline serum creatinine 1 week ago was 0.9 mg/dL) and serum potassium of 5.7 mg/dL; toxicology screen is negative, abdominal ultrasonography shows many large ascites, and EGD shows no varices. All other laboratory and radiologic results are normal. W.P. is currently taking nothing by mouth except for medications.

8. Which one of the following treatments is best to initiate in W.P.?
- Octreotide, midodrine, and intravenous albumin.
 - Midodrine and intravenous albumin.
 - Octreotide and continuous-infusion normal saline.
 - Continuous-infusion norepinephrine and intravenous albumin.
9. A few hours after his admission to the general medicine floor, W.P. has profuse vomiting and difficulty breathing. He is intubated and transferred to the intensive care unit. All previous treatments are discontinued. Which one of the following treatments is best to recommend for W.P.?
- Continuous-infusion norepinephrine and intravenous albumin.
 - Octreotide, midodrine, and intravenous albumin.
 - Continuous-infusion vasopressin.
 - Continuous-infusion octreotide and intravenous albumin.

10. One week later, W.P. is stable enough to go home. Recent laboratory results show a serum creatinine of 0.9 mg/dL, serum potassium of 5.6 mEq/L, and serum sodium of 138 mEq/L. Which one of the following is best to initiate in W.P.?
- Restrict dietary sodium intake to 2 g/day; initiate spironolactone 100 mg by mouth daily and furosemide 40 mg by mouth daily.
 - Perform large-volume paracentesis and initiate tolvaptan.
 - Restrict dietary sodium intake to 2 g/day; initiate eplerenone 50 mg by mouth daily and furosemide 40 mg by mouth daily.
 - Restrict dietary sodium intake to 2 g/day; initiate furosemide 40 mg by mouth daily.

Questions 11 and 12 pertain to the following case.

I.R. is a 66-year-old woman (weight 72 kg) who has an episode of variceal bleeding while hospitalized. She is treated appropriately for the variceal bleeding but develops significant mental changes and asterixis a day later. I.R. has ascites and chronic hepatitis C cirrhosis (Child-Pugh class B). She is taking spironolactone 50 mg by mouth twice daily and furosemide 40 mg by mouth once daily and reports no known drug allergies. Laboratory serum results show a WBC of 9.6×10^3 cells/mm³, creatinine of 0.9 mg/dL, potassium of 4.5 mEq/L, chloride of 101 mEq/L, bicarbonate of 23 mEq/L, aspartate aminotransferase of 57 IU/L, alanine aminotransferase of 69 IU/L, and alkaline phosphatase of 154 IU/L. Toxicology screen is negative, abdominal ultrasonography shows mild ascites, and EGD shows recent variceal bleeding. The rest of the physical examination as well as the laboratory and radiologic tests are normal.

11. Which one of the following is best to recommend for I.R.?
- Discontinue spironolactone and furosemide; initiate lactulose titrated to two to four bowel movements per day.
 - Initiate lactulose titrated to two to four bowel movements per day.
 - Discontinue spironolactone and furosemide; initiate rifaximin 400 mg by mouth three times/day.
 - Initiate rifaximin 400 mg by mouth three times/day.
12. I.R. has been in the hospital for 5 days and is not tolerating a regular diet. The primary team asks for recommendations. Which one of the following dietary recommendations is most appropriate for I.R.?

- A. Enteral BCAAs, restricting daily protein intake to 58 g.
 - B. Enteral BCAAs, maintaining daily protein intake at 86 g.
 - C. Whole protein enteral nutrition, maintaining daily protein intake at 86 g.
 - D. Whole protein enteral nutrition, restricting daily protein intake to 58 g.
13. As a clinical pharmacist providing care for patients with complications of chronic liver disease, you are asked to provide several components to the service to have an impact on patient care. **Which one of the following would be most appropriate and provide the greatest impact on care in this patient population?**
- A. Develop HE treatment protocols on the basis of current guidelines.
 - B. Counsel patients with chronic liver disease on maintaining a daily protein intake of 1 g/kg.
 - C. Counsel patients with chronic liver disease on restricting dietary sodium to 2 g/day.
 - D. Assess patients' adherence to and tolerance of drugs to make therapy adjustments.
14. A 53-year-old man presents to the clinic with severe diarrhea (five or six watery bowel movements daily) and worsening mental status. He has chronic alcoholic cirrhosis (Child-Pugh class B), chronic kidney disease, and HE (which is stable). He stopped drinking alcohol 5 years ago. He is taking a multivitamin daily and lactulose 30 mL by mouth once daily (the dose was reduced 2 days ago from the previous dose of 30 mL by mouth twice daily). He continues to have diarrhea despite several dose reductions during the past few weeks. He has no known drug allergies. He recently lost his job and has no prescription coverage. His laboratory results today show a serum creatinine of 2.2 mg/dL, potassium of 4.5 mEq/L, and serum sodium of 137 mEq/L. **Which one of the following is the best therapy for this patient?**
- A. Administer metronidazole as monotherapy.
 - B. Administer neomycin as monotherapy.
 - C. Decrease lactulose dose to 15 mL by mouth once daily, titrated to two to four soft bowel movements a day.
 - D. Administer rifaximin as monotherapy.
15. One week ago, a 65-year-old woman with heart failure (ejection fraction of 30%), chronic alcoholic cirrhosis (Child-Pugh class C), seasonal allergies, and portal hypertension was hospitalized for heart failure. She was sent home on metoprolol 25 mg by mouth twice daily. She is also taking loratidine 10

mg and a multivitamin by mouth once daily. She has no known drug allergies. Today she presents to the clinic to review the results of her recent EGD, which shows several medium nonbleeding varices in her esophagus. Her blood pressure is 115/60 mm Hg, and her heart rate is 60 beats/minute. **Which one of the following is the best recommendation for this patient?**

- A. Discontinue metoprolol and initiate nadolol.
- B. Continue metoprolol.
- C. Discontinue metoprolol and initiate carvedilol.
- D. Continue metoprolol and initiate isosorbide dinitrate.

Questions 16–18 pertain to the following case.

R.R. is a 45-year-old man (weight 100 kg, height 6'2") with chronic hepatitis C cirrhosis (Child-Pugh class C) who presents to the emergency department with abdominal distension. He reports no known drug allergies. Abdominal ultrasonography shows large ascites, and diagnostic abdominal paracentesis shows ascitic protein of 1 g/dL, albumin of 1.4 g/dL, and WBC of 170/mm³ with 75% neutrophils. Serum creatinine is 1.4 mg/dL, and serum albumin is 2.2 g/dL. The rest of the examination is normal.

16. **Which one of the following is best to initiate in R.R.?**
- A. Ciprofloxacin 500 mg by mouth twice daily for 5 days, followed by oral trimethoprim/sulfamethoxazole.
 - B. Intravenous cefotaxime 1 g every 8 hours for 5 days.
 - C. Intravenous cefotaxime 2 g every 8 hours for 7 days, followed by oral ciprofloxacin 500 mg/week.
 - D. Trimethoprim/sulfamethoxazole 1 double-strength tablet by mouth once daily.
17. Ten months later, R.R. returns to the hospital with fever and abdominal distension. He was taking oral norfloxacin for SBP prophylaxis and was adherent to therapy. He is given a diagnosis of SBP and treated appropriately. His ascitic fluid culture shows no growth. Ascitic fluid shows a protein of 0.8 g/dL, albumin of 1 g/dL, and WBC of 302/mm³ with 98% neutrophils. He is stable and ready to go home. **Which one of the following recommendations is most appropriate for R.R.?**
- A. Discontinue norfloxacin and initiate trimethoprim/sulfamethoxazole.
 - B. Discontinue norfloxacin and initiate ciprofloxacin.

- C. Continue norfloxacin for SBP prophylaxis.
 - D. Continue norfloxacin and initiate trimethoprim/sulfamethoxazole.
18. Which one of the following is the best therapy for R.R.?
- A. Obtain an EGD to assess for varices.
 - B. Initiate nadolol.
 - C. Initiate octreotide and midodrine.
 - D. No additional therapy is recommended.
19. A 40-year-old man with a history of chronic hepatitis C cirrhosis and hypertension presents to the clinic with abdominal distension. He is currently taking hydrochlorothiazide 25 mg by mouth once daily and milk thistle 1 capsule by mouth once daily. He denies any drug allergies. Abdominal ultrasonography shows moderate ascites, and laboratory serum results show a creatinine 1 mg/dL, potassium 4 mEq/L, sodium 136 mEq/L, and albumin 4 g/dL. His blood pressure is 125/65 mm Hg, and his heart rate is 65 beats/minute. **After discontinuing hydrochlorothiazide, which one of the following would be best to manage this patient's ascites?**
- A. Spironolactone 50 mg by mouth daily and furosemide 40 mg by mouth daily.
 - B. Spironolactone 100 mg by mouth daily.
 - C. Spironolactone 50 mg by mouth twice daily and furosemide 40 mg by mouth daily.
 - D. Furosemide 40 mg by mouth daily.
20. A 38-year-old man presents to the clinic with the following laboratory serum results: creatinine 1.5 mg/dL, potassium 4.2 mEq/L, sodium 115 mEq/L, and albumin 4 g/dL. His medical history includes chronic alcoholic cirrhosis (Child-Pugh class C), hypertension, and a previous episode of variceal bleeding (resolved). He stopped drinking alcohol 3 years ago. He currently takes spironolactone 100 mg by mouth daily, furosemide 40 mg by mouth daily, propranolol 20 mg by mouth twice daily, and amlodipine 5 mg by mouth daily. He has no known drug allergies. His blood pressure is 120/66 mm Hg, and his heart rate is 60 beats/minute. He denies fluid overload (lower extremity edema or pulmonary edema), mental status changes, or asterixis. **Which one of the following would be best to recommend for this patient?**
- A. Discontinue propranolol.
 - B. Discontinue spironolactone and furosemide.
 - C. Initiate sodium chloride tablets.
 - D. Discontinue spironolactone.