Care of the Patient With Cirrhosis

Anitha Yadav, M.D., and Hugo E. Vargas, M.D.

Caring for patients with cirrhosis involves multidisciplinary and timely management of several complications while the patients are awaiting liver transplantation (LT). Prompt identification and treatment of complications can potentially improve survival and quality of life for this patient population. For practical purposes, in this review we focus on the complications of cirrhosis that are common to all causes of end-stage liver disease, underscoring issues that are important in some of those subpopulations.

Portal Hypertension

Portal hypertension (PTH) refers to the complex hemodynamic adjustment that occurs as the liver deals with increasing fibrosis and the subsequent increase in resistance to flow in the hepatic sinusoids. The pathophysiology of PTH includes splanchnic vasodilation, increase in the activation of the renin-angiotensin-aldosterone axis, and compensatory cardiovascular adjustments that help to increase hepatic sinusoid flow but lead to a constellation of complications that can threaten the survival of a patient with cirrhosis.¹

Ascites

Ascites is one of the most common complications of cirrhosis. Once ascites develops, the probability of survival at 5 years is only 44%.² All patients with new-onset ascites should undergo a diagnostic paracentesis. A serum-ascites-albumin gradient ≥ 1.1 g/dL is diagnostic of PTH-related ascites. Ascitic fluid cell count and differential, ascitic fluid protein, and, if infection is suspected, ascitic fluid cultures should also be obtained. All hospitalized patients with ascites should also undergo paracentesis to prevent mortality from spontaneous bacterial peritonitis.³

Management of ascites involves dietary education and medical therapy (Fig. 1). Diuretics are the mainstay of

therapy and should be discontinued in patients with renal dysfunction (serum creatinine >2.0 mg/dL), hyponatremia (serum sodium <120 mmol/L), and worsening hepatic encephalopathy.³ Less than 10% of patients with cirrhosis fail to respond to standard medical therapy and develop refractory ascites (Fig. 1). Patients who undergo large volume paracentesis for refractory ascites should receive albumin infusion (8 g/L of fluid removed) to reduce circulatory dysfunction and improve survival.⁴

Spontaneous Bacterial Peritonitis

Spontaneous bacterial peritonitis (SBP) is diagnosed when the ascitic fluid absolute polymorphonuclear leukocyte count is ≥ 250 cells/mm³. Diagnostic paracentesis should be performed in all patients with signs and symptoms (abdominal pain, fevers), encephalopathy, and renal failure and all hospitalized patients. The ideal approach is to drain a sample of ascites and inoculate the culture media at the bedside to maximize the yield of the cultures.³ Treatment and prophylaxis strategies for SBP are shown in Table 1.

Hepatorenal Syndrome

Hepatorenal syndrome is a serious functional renal dysfunction seen in patients with cirrhosis and ascites. The pathophysiology is complex and involves abnormal hemodynamics, splanchnic and systemic vasodilatation and renal vasoconstriction often triggered by a precipitating event.⁵ The diagnosis and management strategies are outlined in Table 2.

Gastroesophageal Varices

Gastroesophageal varices develop as a result of portal venous hypertension when the hepatic vein portal gradient is elevated (>6 mm Hg) but usually bleed when the pressure is elevated above 12 mm Hg.⁶ These collateral vessels

Abbreviations: CHE, covert hepatic encephalopathy; CT, computed tomography; EGD, esophago-gastroduodenoscopy; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; LT, liver transplantation; MHE, minimal hepatic encephalopathy; MRI, magnetic resonance imaging; NSBB, nonselective beta blockers; OHE, overt hepatic encephalopathy; PTH, portal hypertension.

From the Division of Gastroenterology and Hepatology, Mayo Clinic Arizona, Phoenix, AZ

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are present in almost 50% patients with cirrhosis. Approximately 30% of patients with varices will bleed within the first year of diagnosis. The presence of varices correlates with the severity of the liver disease. The main risk factors for variceal hemorrhage are variceal size, advanced liver

disease (Child-Pugh class B or C), and presence of red wale marks at endoscopy. Esophago-gastroduodenoscopy (EGD) is the gold standard for the diagnosis of varices and should be performed in all patients once a diagnosis of cirrhosis has been established.⁷

Primary prophylaxis with nonselective beta blockers (NSBB) or endoscopic variceal ligation for those who are not eligible for NSBBs does improve survival in patients with esophageal varices. There appears to be no impact if NSBBs are started before varices are seen or when they are very small.⁸ Current consensus recommends NSBBs (propranolol, nadolol or carvedilol) or endoscopic variceal ligation for the primary prevention of first variceal bleed.⁶ However, nitrates, shunt surgery, and endoscopic sclerotherapy are not recommended for primary prophylaxis.

If no varices are identified on initial screening endoscopy, no therapy is recommended. Repeat EGD should be obtained after 3 years, earlier if the patient decompensates.⁹ The current management strategies after results of screening endoscopy in patients with cirrhosis are shown in Figure 2.

Other complications of cirrhosis are also of significant impact to the well-being of the patient with cirrhosis and will be listed below. These complications have more to do with preventive measures that are unique complications of cirrhosis and warrant careful attention.

Figure 1 Management of ascites and therapeutic options for refractory ascites. Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; NSAIDs, nonsteroidal anti-inflammatory drugs; TIPS, transjugular intrahepatic portosystemic shunt.

Figure 2 Management strategies after results of screening endoscopy in patients with cirrhosis. Abbreviations: EGD, esophago-gastroduodenoscopy; EVL, endoscopic variceal ligation; NSSB, nonselective beta blocker.

TABLE 1 Diagnosis, Management, and Prophylaxis of Spontaneous Bacterial Peritonitis

Diagnosis	Ascitic fluid absolute polymorphonuclear leukocyte count is ≥ 250 cells/mm ³ in the absence of surgically treatable intra-abdominal source of infection
Risk factors	Prior episode of SBP, ascitic fluid total protein concentration < 1.0 g/dL, and variceal hemorrhage
General measures	Albumin infusion (1.5 g/kg on day 1 and 1 g/kg on day 3) if blood urea nitrogen > 30 mg/dL, creatinine > 1 mg/dL, bilirubin > 4 mg/dL
Specific treatment	Intravenous third-generation cephalosporin (cefotaxime 2 g every 8 hours or ceftriaxone 2 g every 24 hours) Oral ofloxacin (400 mg twice per day) can be an alternative in hospitalized patients with no evidence of shock, vomiting, hepatic encephalopathy (grade II), renal dysfunction (creatinine > 3 mg/dL) or previous exposure to quinolone
Secondary prophylaxis	Continue antibiotic therapy for 7 days
Primary prophylaxis	Long-term oral norfloxacin or trimethoprim/sulfamethasoxazole In patients with cirrhosis and gastrointestinal hemorrhage, intravenous ceftriaxone or oral norfloxacin twice daily should be given to prevent infections Oral norfloxacin or trimethoprim/sulfamethasoxazole should be considered in cirrhosis patients with 1) ascitic fluid total protein count < 1.5 g/dL along with renal dysfunction (creatinine ≥ 1.2 mg/dL, blood urea nitrogen ≥ 25 mg/dL or serum sodium ≤ 130) or 2) liver failure (Child-Pugh score ≥ 9) and serum bilirubin ≥ 3 mg/dL

TABLE 2 Diagnosis and Management Strategy for Hepatorenal Syndrome

International Ascites Club definition	Cirrhosis with ascites Serum creatinine > 133 μ mol/L (1.5 mg/dL) No improvement of serum creatinine after at least 2 days with diuretic withdrawal and volume expansion with albumin Absence of shock No current or recent treatment with nephrotoxic drugs Absence of parenchymal kidney disease
Types of HRS	
Type 1	Rapid progressive renal failure with doubling of the initial serum creatinine concentrations to a level > 226 mmol/L (2.5 mg/dL) in < 2 weeks
Type 2	Moderate to slowly progressive renal failure with serum creatinine between 1.5 and 2.5 mg/dL (133-226 μ mol/L)
Precipitant factors	Infection, bleeding, large volume paracentesis without albumin administration over diuresis, and acute hepatitis secondary to alcohol or virus
General management	Early identification and treatment of the precipitating event
Specific management	
Type 1 HRS	Vasoconstrictors (terlipressin or norepinephrine) with albumin or midodrine (a selective α -1 adrenergic agonist), octreotide (a somatostatin analog), and albumin
Type 2 HRS	Treatment options are typically directed toward the management of the refractory ascites
Other options	TIPS may be an alternative option in selected cases when medical therapy fails; renal replacement therapy may be used as a bridging therapy until LT
Definitive treatment	LT is the definitive treatment for patients with type 1 and 2 HRS

Abbreviations: HRS, hepatorenal syndrome; LT, liver transplantation; TIPS, transjugular intrahepatic portosystemic shunt.

Hepatic Encephalopathy

Hepatic encephalopathy (HE) is a debilitating complex neuropsychiatric complication characterized by motor-sensory derangements ranging from subclinical cognitive impairment to overt coma, with many varied intervening mental status and neuromuscular changes in between. The prevalence of overt HE at the time of diagnosis of cirrhosis is around 11%.¹⁰ HE is classified into various subtypes based on type of underlying disease (type A, B, and C), severity of manifestations (minimal, grade I-IV), time course (episodic, recurrent and persistent), and precipitating factors. Patients with minimal HE (MHE) have mild cognitive and psychomotor impairment without overt clinical evidence of those changes. Covert HE (CHE) includes minimal and grade 1 HE.

The diagnosis of HE involves exclusion of other causes of brain dysfunction and identification of the precipitating

causes (infections, gastrointestinal bleeding, diuretic overuse, electrolyte abnormalities, sedatives, and constipation).¹¹ Overt HE (OHE) is diagnosed by clinical criteria, and testing for MHE and CHE encompass neurophysiological and psychometric tests. Diagnosing MHE and CHE has prognostic significance because it is associated with progression to OHE, poor quality of life, and high risk of accidents.

Treatment of OHE involves excluding nonhepatic causes of encephalopathy, identifying and treating the precipitating factors, supportive care, and initiating appropriate treatment. A summary of the available pharmacological therapies is given in Table 3. Educating patients and relatives regarding medication compliance, potential side effects, recognition of early signs of HE, and measures to prevent recurrence is imperative. Treatment of MHE/CHE is not routinely recommended but can be considered in a selected patient population.

TABLE 3 Summary of Therapies Used in the Management of Hepatic Encephalopathy

Therapy	Uses	Dose	Adverse Effects
Lactulose (nonabsorbable disaccharide)	Treatment of episodic OHE and prevention of recurrent episodes after the initial episode	30–45 mL two to four times daily	Aspiration, dehydration, hypernatremia, and ileus
Rifaximin (antibiotic)	Add-on therapy to lactulose for treatment and prevention of HE recurrence after the second episode	550 mg twice daily	Peripheral edema, nausea
Metronidazole (antibiotic)	Alternative choice for treatment of OHE	250 mg–500 mg three times daily	Metallic taste, peripheral neuropathy, ototoxicity
Neomycin (antibiotic)	Alternative choice for treatment of OHE	250 mg two to four times daily	Ototoxicity Nephrotoxicity
Oral BCAAs (leucine, isoleucine, and valine)	Alternative or additional agent to treat patients unresponsive to conventional therapy		No known adverse effects
LOLA	Alternative or additional agent to treat patients nonresponsive to conventional therapy	20 g/day LOLA intravenous	Nausea/vomiting

Abbreviations: BCAAs, branched chain amino acids; LOLA, L-ornithine L-aspartate

Hepatocellular Carcinoma Screening

Screening for hepatocellular carcinoma (HCC) is recommended for all patients at high risk for developing HCC, including all patients with cirrhosis and patients who do not have cirrhosis but are hepatitis B carriers (Asian males >40 years of age, Asian females >50 years of age, Africans >20 years of age, and patients with a family history of HCC).¹² Studies have shown a survival benefit with surveillance when HCC was diagnosed early and curative treatments were performed.¹³ Hence, surveillance for HCC is recommended with ultrasound (60% sensitivity, 90% specificity) every 6 months based on tumor growth rates. Alpha-fetoprotein is not a reliable measure for surveillance or diagnosis of HCC due to its lack of adequate sensitivity and specificity. With respect to candidates listed for LT, vigilant surveillance is necessary because tumor development will provide increased priority for LT. Furthermore, surveillance will help identify wait-list candidates who develop HCC that exceeds the guidelines for LT.

The diagnosis of HCC involves radiological examination, including four-phase multidetector computed tomography (CT), dynamic contrast-enhanced magnetic resonance imaging (MRI), or liver biopsy. The presence of arterial enhancement followed by washout in the portal and/or delayed phases on the CT or MR is diagnostic of HCC (sensitivity and specificity of 90% and 95%, respectively). Liver biopsy is limited to lesions with no typical imaging characteristics or for those detected in noncirrhotic liver.

Nodules found on surveillance ultrasound should be managed further depending on the size of the lesion:

- Nodule <1 cm found during surveillance should be followed by ultrasound examination every 3–6 months.

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- Nodule >1 cm: four-phase multidetector CT or dynamic MRI should be performed. If the appearances are typical of HCC, the lesion should be managed as HCC. If the findings are not diagnostic for HCC, a second imaging study should be performed, or the lesion should be biopsied.

Immunization

The Advisory Committee on Immunization Practices in the United States recommends hepatitis A, hepatitis B, 23-valent pneumococcal polysaccharide vaccine (PPSV23), and inactivated influenza immunization for all patients with chronic liver disease. The immunogenicity for hepatitis A and B vaccination is reduced in patients with decompensated cirrhosis.¹⁴ Hence, vaccination is recommended early in the natural history of their liver disease. Patients should also receive standard immunizations such as diphtheria and tetanus booster immunizations every 10 years. Because cirrhosis patients are immunocompromised, inactivated/killed vaccines are preferred over live/attenuated vaccines.

Malnutrition

Daily protein intake (1.2–1.5 g/kg/day) is recommended to avoid malnutrition, and oral branched chain amino acids can be considered for individuals intolerant of all protein.¹⁵ In severe malnutrition, initiation of enteral feeding improves nutritional status, reduces complications, and prolongs survival. ■

CORRESPONDENCE

Hugo E. Vargas, M.D., Division of Gastroenterology and Hepatology, Mayo Clinic Arizona, 5777 East Mayo Boulevard, Phoenix, AZ 85054. E-mail: vargas.hugo@mayo.edu

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