Complications of end-stage liver disease

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Case description

Mrs Z. was a 63-year-old woman with chronic hepatitis C infection and end-stage liver disease (ESLD). She had had 2 hospital admissions in the past 6 months for complications related to her ESLD, most recently for spontaneous bacterial peritonitis (SBP). Mrs Z. also had a history of refractory ascites requiring paracentesis every 2 weeks and large esophageal varices that had not previously bled. Her current list of medications included 120 mg of oral furosemide once daily, 300 mg of oral spironolactone once daily, 40 mg of bisoprolol once daily, 400 mg of oral norfloxacin once daily, 0.5 mg of oral hydromorphone twice daily and every hour as needed for pain, and 1 senna tablet orally at bedtime.

Mrs Z. lived at home with her daughter with support from her family physician and palliative home care nursing. Her Palliative Performance Scale (PPS) score was 40%, which meant she was mainly in bed, was unable to do most activities, and required much assistance with self-care.[1] She understood that her illness was incurable and progressive and that her estimated survival was on the order of weeks to months. She wanted the focus of her care to be on comfort at home with no further investigations or interventions. Within 2 weeks of being home, Mrs Z. became increasingly somnolent and confused. She was now inconsistent in taking her medications as prescribed and was having difficulty coping.

Cirrhosis is the final common end point in patients with progressive liver disease of various causes. It is now the 12th leading cause of death in North America and the 7th leading cause of death in people between the ages of 25 and 64 years.[2]

With the involvement of palliative care in managing more non-malignant disease such as ESLD, understanding of the various complications that are associated with the natural progression of cirrhosis is important. The most frequent complication of ESLD is ascites, as was discussed in a previous article.[3] This article will address the management of other common complications including hepatic encephalopathy (HE), SBP, and esophageal varices, with support from empiric evidence, systematic reviews, and expert consensus statements. Once developed, any of these complications herald a transition into the decompensated phase of cirrhosis, with increased morbidity, risk of sudden decline, and a shortened clinical course.

Hepatic encephalopathy

Hepatic encephalopathy is defined as a complex neuropsychiatric syndrome marked by personality changes, intellectual impairment, and an altered level of consciousness. Hepatic encephalopathy is associated with hepatocyte loss and dysfunction, and portosystemic shunting, which allow nitrogenous substances derived from the gut to adversely affect brain function. It is a common and distressing complication, developing in 30% to 45% of patients with decompensated cirrhosis.[4]

Hepatic encephalopathy resulting from cirrhosis is classified according to the severity of clinical manifestations, the time course, and the presence of precipitating factors.[5] The West Haven Criteria rank the clinical severity of HE from grade I to IV, as outlined in **Table 1**.[6] Grade I or minimal HE describes patients with no clinical symptoms but subtle findings on neurophysiologic and neuropsychometric testing, which might have implications for

EDITOR'S KEY POINTS

- Cirrhosis is the final common end point in patients with progressive liver disease of various causes. Other common complications of end-stage liver disease include ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, and esophageal varices.
- Management of hepatic encephalopathy includes addressing precipitating causes, reducing gut-derived nitrogenous products, and instituting concurrent supportive care.
- Up to 30% of patients with cirrhosis develop spontaneous bacterial peritonitis, with mortality ranging between 30% and 50%. Initiation of empiric therapy is often based on suspicion and is appropriate when 1 or more of the following are present: a temperature greater than 37.8°C, abdominal pain or tenderness, a change in mental status, or an ascitic fluid polymorphonuclear cell count of 250 cells/mm^3 or greater.
- The management of esophageal varices is aimed at patients who have never bled (primary prophylaxis), those who are actively bleeding, and prevention of a second hemorrhage in patients who have already bled (secondary prevention).

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Table 1. West Haven Criteria for altered mental state in hepatic encephalopathy

STAGE	DESCRIPTION
Grade I	• Trivial lack of awareness • Euphoria or anxiety • Shortened attention span • Impairment of addition or subtraction • Altered sleep rhythm
Grade II	• Lethargy or apathy • Disorientation for time • Obvious personality change • Inappropriate behaviour • Dyspraxia • Asterixis
Grade III	• Somnolence or semistupor • Responsive to stimuli • Confused • Gross disorientation • Bizarre behaviour
Grade IV	• Coma

Data from Vilstrup et al.[6]

fitness to drive.[7] Overt HE (grades II and III) is used to describe patients who demonstrate gross disorientation or asterixis, and overt HE can progress to grade IV, which is coma. Hepatic encephalopathy can be further subcategorized as episodic, recurrent, or persistent.[5]

Ammonia continues to be the toxin most often implicated in the pathogenesis of HE. However, an elevated serum ammonia level is not required to make a diagnosis of HE and does not aid in staging or prognosticating.[6] If a patient with HE has an elevated ammonia level, it does not rule out coexistent medical conditions that might explain abnormal mental status, rendering HE a diagnosis of exclusion.

The cornerstone of HE management includes addressing precipitating causes, reducing gut-derived nitrogenous products, and instituting concurrent supportive care. The most common precipitants of HE include infections, gastrointestinal bleeding, electrolyte disorders, hypovolemia, constipation, and psychotropic medications.[6] Although the symptoms of HE are thought to be mostly reversible, it can be challenging to identify and manage possible precipitants if certain investigations and interventions are not within a patient's goals of care. Even if a possible precipitant is identified, care to further avoid precipitants might not be possible, especially in the context of interventions contributing to comfort. With or without the search for and management of precipitating factors, measures to reduce the nitrogenous load from the gut are implemented simultaneously.

First-line treatment includes nonabsorbable disaccharides such as lactulose, which work by reducing gut pH and interfering with the uptake of glutamine, thus reducing both the synthesis and the absorption of ammonia. A 30-mL dose of lactulose can be given orally once or twice daily and this can be titrated up with the aim of having 2 to 3 soft stools per day.[6] Lactulose can also be administered via nasogastric tube or as a rectal enema (300 mL in 1 L of water retained for 1 hour with the patient in the Trendelenburg position). Common side effects include diarrhea, bloating, and abdominal cramps, which can lead to poor compliance. Attention must also be paid to avoiding diarrhea, dehydration, hyponatremia, and worsening of HE while titrating lactulose.

Various antibiotics have been used in managing HE by decreasing the intestinal load of ammonia-producing gut bacteria. They are mainly second-line treatment for patients who cannot tolerate or who respond poorly to disaccharide monotherapy.[8] Rifaximin, a semisynthetic, nonabsorbable oral antibiotic (550 mg twice daily), has minimal systemic absorption with few side effects. When added to lactulose, rifaximin has been shown to reduce the risk of recurrence of HE from 46% to 21%[9] and it can be obtained in Canada through the Special Access Programme. The alternative antibiotics neomycin and metronidazole are no longer widely used owing to limited evidence of efficacy and to risks associated with their use; neomycin carries the risk of nephrotoxicity and ototoxicity, and metronidazole carries the risk of peripheral neurotoxicity.[6]

In the past, a diet high in animal protein was implicated in worsening serum ammonia levels and the symptoms of HE. However, many patients with ESLD have protein-calorie malnutrition, and protein restriction is generally not recommended.[6]

If present, agitation in patients with HE might resolve with the above-mentioned approaches. Medications that depress central nervous system function, especially benzodiazepines, should be avoided or used with caution, as they can worsen symptoms of HE.[10]

Spontaneous bacterial peritonitis

Spontaneous bacterial peritonitis is defined as an ascitic fluid infection with a polymorphonuclear cell count of 250 cell/mm^3 or greater and an ascitic fluid culture positive for bacteria, in the absence of a surgically treatable source. Spontaneous bacterial peritonitis is the most common and severe infection in patients with cirrhosis: up to 30% of patients with cirrhosis develop SBP,[11] with a mortality rate ranging between 30% and 50%.[12]

Management of SBP is aimed at patients who have never had SBP but who are considered to be at high risk of its development (primary prophylaxis), those who develop SBP, and prevention of a second episode in those with previous SBP (secondary prevention). Because of the high incidence and the high mortality rate if left untreated, it is prudent to have specific

discussions about if and when antibiotics are within the patient's goals of care.

Primary prophylaxis of SBP has been associated with a decreased risk of bacterial infection and decreased mortality in patients considered to be at high risk of SBP, which includes patients with a history of variceal bleeding or ascites fluid protein levels below 1.0 g/dL.[13] Primary prophylaxis is achieved with long-term use of quinolones, such as 400 mg of norfloxacin daily or, as an alternative, 1 double-strength tablet of trimethoprim-sulfamethoxazole daily.[13]

With acute SBP, early recognition is important because there is a very short window of opportunity to intervene with antibiotics before septic shock develops. However, the clinical manifestations of SBP are nonspecific, and approximately 10% of patients with SBP are asymptomatic.[14] Considering this, initiation of empiric therapy is often based on suspicion and is appropriate when 1 or more of the following findings are present: a temperature greater than 37.8°C (100°F), abdominal pain or tenderness, a change in mental status, or an ascitic fluid polymorphonuclear cell count of 250 cells/mm^3 or greater.[15]

The most common organisms are the Gram-negative, single-species *Escherichia coli* bacteria or *Klebsiella* species, and treatment includes a 5-day course of a third-generation cephalosporin: 2 g of cefotaxime intravenously every 8 hours is the criterion standard, and 1 g of ceftriaxone intravenously or intramuscularly twice daily is an alternative. This broad-spectrum therapy is started until, ideally, the results of susceptibility testing are available.[15] Use of non-selective β-blockers in patients who develop SBP is associated with worse outcomes, including increased mortality, and these should be permanently discontinued.[16]

After the first episode of SBP, the rate of recurrence is up to 70%,[17] and secondary prophylaxis is indicated in all patients. Quinolones (400 mg of norfloxacin daily and alternatively 1 double-strength tablet of trimethoprim-sulfamethoxazole daily) decrease the risk of SBP recurrence from 70% to 20%.[18]

A patient's ability to swallow antibiotics, especially in the context of primary and secondary prophylaxis of SBP, should be discussed in advance, as a progressive decline in function with the risk of acute decompensation can limit the oral route of antibiotic administration.

Esophageal varices

Esophageal varices, a direct consequence of increased portal pressure, are a common complication of cirrhosis, and their presence correlates with the severity of liver disease. Approximately 50% of patients with cirrhosis develop esophageal varices, and of these one-third will develop a variceal bleed.[19] With any episode of active bleeding, there is a 30% chance of mortality and a 70% risk of hemorrhage recurrence within 1 year.[20]

Management of esophageal varices is aimed at patients who have never bled (primary prophylaxis), those who are actively bleeding, and prevention of a second hemorrhage in patients who have already bled (secondary prevention).

Primary prophylaxis of patients with cirrhosis begins with screening endoscopy, findings of which describe the size and characteristics of the varices. Medical therapy for primary prevention focuses on decreasing portal hypertension and is offered to patients considered to be at increased risk of a variceal hemorrhage—these patients include those with Child B or C cirrhosis (**Table 2**),[19] patients with larger varices, and those with red signs on the varices.

Primary prophylaxis includes indefinite use of non-selective β-blockers such as nadolol or propranolol, with the goal of reducing the baseline resting heart rate by 25%, with a heart rate no lower than 55 beats/min.[20] Nadolol has the advantage of being administered only once daily, typically starting at 40 mg once a day; however, it is renally excreted and its starting dose might require modification if the patient has any renal insufficiency. Propranolol is usually started at 20 mg twice daily. If a patient cannot tolerate β-blockers or there are contraindications to their use, such as a previous episode of SBP or in cases of noncompliance, prophylactic esophageal variceal ligation can be offered.

Half of patients with an active variceal bleed will have it spontaneously stop without any intervention. Rebleeding will occur in approximately one-third of patients within 6 weeks.[20] If the gastrointestinal bleed is massive and rapid, patients will lapse into hypoxic coma followed by cardiac arrest. If the gastrointestinal bleed is ongoing and prolonged, the patient might be conscious

Table 2. Child-Pugh classification of severity of cirrhosis: *A total score of 5 to 6 is considered class A (well compensated disease); 7 to 9 is class B (substantial functional compromise); and 10 to 15 is class C (decompensated disease).*

	POINTS ASSIGNED		
PARAMETER	1	2	3
Ascites	None	Mild or moderate	Tense
Bilirubin level, μmol/L	< 34.2	34.2 to 51.3	> 51.3
Albumin level, g/L	> 35	28 to 35	< 28
Prolonged prothrombin time, s	< 4	4 to 6	> 6
INR	< 1.7	1.7 to 2.3	> 2.3
Hepatic encephalopathy	None	Grade I to II	Grade III to IV

Data from Garcia-Tsao et al.[19]
INR—international normalized ratio.

for a longer period and require management of symptoms including dyspnea, confusion, congestion, and restlessness. In the context of ESLD, a variceal bleed also introduces a cascade of possible sequelae including the risk of developing SBP, HE, and renal impairment, any or all of which can alter the anticipated clinical course. It is important to have discussions about the anticipated clinical course in advance.

If a patient survives a variceal bleed, secondary prophylaxis focuses on supportive care and optimizing nonselective β-blockers. Ongoing endoscopic interventions, and the last-resort use of a transjugular intrahepatic portosystemic shunt or shunt surgery, are less often used with patients receiving palliative care.

Case resolution

Upon follow-up with Mrs Z., further pertinent history revealed complaints of abdominal pain requiring the use of 3 breakthrough doses of hydromorphone a day, decreased oral intake, and constipation. Mrs Z.'s vital signs included a temperature of 37.9°C, a heart rate of 110 beats/min, blood pressure of 105/70 mm Hg, and an oxygen saturation of 88% on room air. Mrs Z. was disoriented, was speaking incoherently, and was noted to have asterixis.

Mrs Z.'s PPS score was now 20%, indicating she was totally bed-bound and required complete care, and she was thought to have developed overt HE secondary to multiple coexisting precipitants, some of which posed management challenges. Further discussions were held with Mrs Z.'s daughter regarding recognizing the symptoms of HE, understanding its fluctuating course and poor prognosis, and minimizing the risk of falls, skin breakdown, and aspiration.

Mrs Z.'s constipation was addressed first as a correctable precipitant of her HE. Lactulose enemas were attempted, as Mrs Z. could not safely swallow oral medication. The role of subcutaneous hydration and antibiotics, including the option of intramuscular antibiotics for treatment of a second possible episode of SBP, were discussed and were determined to not be in line with Mrs Z.'s goals of care. Although hydromorphone is a possible contributing precipitant, it was continued to maintain Mrs Z.'s comfort and switched from the oral to the subcutaneous route of administration and carefully monitored. Antipsychotic medications were discussed to manage any agitation, despite their potential effect on HE, because comfort was Mrs Z.'s main goal of care. Haloperidol was prescribed at 0.5 mg subcutaneously every 4 hours as needed. Within 2 days, Mrs Z.'s lactulose enemas were discontinued secondary to the increased burden of administration with no clear symptomatic benefit. Stimulant laxative suppositories were scheduled for every 3 days as needed.

Over the ensuing week, Mrs Z. became unrousable and entered the actively dying phase in the comforts of her home.

Conclusion

The complications of ESLD are common and they can either develop in isolation or simultaneously. When considering management of any complication, the potential effects of the treatments should be considered against the risk of developing or worsening other complications. It is prudent to have careful discussions in advance of any crisis, considering each complication and the potential for rapid decline and taking into account a patient's goals of care, PPS score, prognosis, total symptom burden, and the burden-to-benefit ratio of available treatment options.

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Competing interests
None declared

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References

1. Palliative Performance Scale (PPSv2) version 2. In: Victoria Hospice Society. *Medical care of the dying*. 4th ed. Victoria, BC: Victoria Hospice Society; 2006. p. 121.
2. Kung HC, Hoyert DL, Xu J, Murphy SL. Deaths: final data for 2005. *Natl Vital Stat Rep* 2008;56(10):1-120.
3. Perri GA. Ascites in patients with cirrhosis. *Can Fam Physician* 2013;59:1297-9 (Eng), e538-40 (Fr).
4. Poordad FF. Review article: the burden of hepatic encephalopathy. *Aliment Pharmacol Ther* 2007;25(Suppl 1):3-9.
5. Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT. Hepatic encephalopathy—definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. *Hepatology* 2002;35(3):716-21.
6. Vilstrup H, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, et al. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. *Hepatology* 2014;60(2):715-35.
7. Kircheis G, Knoche A, Hilger N, Manhart F, Schnitzler A, Schulze H, et al. Hepatic encephalopathy and fitness to drive. *Gastroenterology* 2009;137(5):1706-15.e1-9.
8. Als-Nielsen B, Gluud LL, Gluud C. Nonabsorbable disaccharides for hepatic encephalopathy. *Cochrane Database Syst Rev* 2004;(2):CD003044.
9. Kimer N, Krag A, Moller S, Bendtsen F, Gluud LL. Systematic review with meta-analysis: the effects of rifaximin in hepatic encephalopathy. *Aliment Pharmacol Ther* 2014;40(2):123-32.
10. Prabhakar S, Bhatia R. Management of agitation and convulsions in hepatic encephalopathy. *Indian J Gastroenterol* 2003;22(Suppl 2):S54-8.
11. Rimola A, Garcia-Tsao G, Navasa M, Piddock LJ, Planas R, Bernard B, et al. Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: a consensus document. International Ascites Club. *J Hepatol* 2000;32(1):142-53.
12. Gines P, Rimola A, Planas R, Vargas V, Marco F, Almela M, et al. Norfloxacin prevents spontaneous bacterial peritonitis recurrence in cirrhosis: results of a double-blind, placebo-controlled trial. *Hepatology* 1990;12(4 Pt 1):716-24.
13. Soares-Weiser K, Brezis M, Tur-Kaspa R, Paul M, Yahav J, Leibovici L. Antibiotic prophylaxis of bacterial infections in cirrhotic inpatients: a meta-analysis of randomized controlled trials. *Scandinavian J Gastroenterol* 2003;38(2):193-200.
14. Caruntu FA, Benea L. Spontaneous bacterial peritonitis: pathogenesis, diagnosis, treatment. *J Gastrointestin Liver Dis* 2006;15(1):51-6.
15. Runyon BA. Management of adult patients with ascites due to cirrhosis: an update. *Hepatology* 2009;49(6):2087-107.
16. Mandorfer M, Bota S, Schwabl P, Bucsics T, Pfisterer N, Kruzik M, et al. Nonselective beta blockers increase risk for hepatorenal syndrome and death in patients with cirrhosis and spontaneous bacterial peritonitis. *Gastroenterology* 2014;146(7):1680-90.e1.
17. Gines P, Cardenas A, Arroyo V, Rodes J. Management of cirrhosis and ascites. *New Engl J Med* 2004;350(16):1646-54.
18. Saab S, Hernandez JC, Chi AC, Tong MJ. Oral antibiotic prophylaxis reduces spontaneous bacterial peritonitis occurrence and improves short-term survival in cirrhosis: a meta-analysis. *Am J Gastroenterol* 2009;104(4):993-1001.
19. Garcia-Tsao G, Sanyal AJ, Grace ND, Carey WD. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. *Am J Gastroenterol* 2007;102(9):2086-102.
20. O'Brien J, Triantos C, Burroughs AK. Management of varices in patients with cirrhosis. *Nat Rev Gastroenterol Hepatol* 2013;10(7):402-12.