Management of patients with decompensated cirrhosis

Author: Phillip M Harrison[A]

ABSTRACT

During the assessment of a patient with liver disease, finding the patient has decompensated cirrhosis, as defined by the presence of jaundice, ascites, variceal haemorrhage or hepatic encephalopathy, has major implications regarding management and prevention of cirrhosis-related complications, as well as consideration for a referral for liver transplantation evaluation. Prognosis is markedly worse in patients with decompensated compared with compensated cirrhosis. In general, any patient with decompensated cirrhosis should receive evaluation and medical care by a hepatologist. Since patients frequently present with more than one facet of liver decompensation, such cases pose a complex management challenge requiring input from a multidisciplinary team and close liaison with a liver transplant centre.

Introduction

In a patient with cirrhosis, the presence of jaundice, ascites, variceal haemorrhage or hepatic encephalopathy defines the onset of liver decompensation. The transition to decompensated cirrhosis may be due to progression of the underlying liver disease or a superimposed acute insult; it occurs in 11% of patients per year and is associated with a high mortality (one-year mortality in compensated cirrhosis is 7% compared with 20% following liver decompensation).[1]

Orthotopic liver transplantation is the treatment of choice for patients with decompensated cirrhosis and such patients must be discussed with or referred for assessment to a transplant centre. However, there are more potential recipients on transplant waiting lists than available organs and the long waiting times of some patients listed for liver transplantation reinforces the need for assertive management in this population in order to ensure survival until liver grafting.[2] This article will discuss the factors precipitating liver decompensation and the management of complications not only in patients awaiting transplantation, but also in those for whom liver grafting is not appropriate.

Ascites

Renal sodium retention is present in around 60% of patients with cirrhosis; consequently, these individuals retain fluid and develop ascites or peripheral oedema. Ascites is frequently

the first manifestation of liver decompensation, arising in 50% of patients with cirrhosis over 10 years of follow up. It is an important development in the natural history of cirrhosis as it is associated with 50% mortality over the two years after its detection. Patients with ascites should restrict their sodium intake (80–120 mmol/day) by not adding salt to food and avoiding pre-prepared meals. If dietary measures fail to resolve the fluid retention, diuresis can be achieved using the aldosterone antagonist spironolactone, starting at a dose of 100 mg once per day. Patients not achieving control of ascites require furosemide in combination with spironolactone in order to enhance natriuresis. Doses of spironolactone and furosemide are increased simultaneously in increments of 100 mg and 40 mg up to maximum doses of 400 mg and 160 mg, respectively. However, dose adjustments should only be undertaken at intervals of 10–14 days because the active metabolites of spironolactone have long half-lives and it takes this time period to achieve new steady state levels.

Ascites is refractory when it cannot be mobilised by medical therapy.[3] Clinically, two forms are recognised: diuretic-resistant ascites, which is unresponsive to maximal doses of diuretics, and diuretic intractable ascites, which occurs when diuretic use is limited due to development of side effects, such as hyponatraemia, hyperkalaemia, hepatic encephalopathy and renal dysfunction. Although the aim of diuretic therapy is to control ascites, these drugs are associated with a high risk of complications mandating regular clinical and biochemical monitoring of patients while on treatment. In this population, hyponatraemia is an independent predictor of death.[4]

Patients with refractory ascites have a poor prognosis with median survival of 6 months. The mainstay of treatment is large volume paracentesis (LVP), which generally needs to be repeated every 4–8 weeks. However, since LVP can precipitate a circulatory disturbance resulting in dilutional hyponatraemia and renal dysfunction, intravenous human albumin is administered to minimise the risk of these complications.[5] Placement of a transjugular intrahepatic portosystemic shunt (TIPS) is more effective than LVP in clearing ascites but increases the incidence of hepatic encephalopathy. TIPS may improve survival in patients with refractory ascites requiring frequent LVP[6] but patients must be carefully selected, ie have well preserved liver synthetic and cardiac functions, and no previous encephalopathy.

Spontaneous bacterial peritonitis

Patients with ascites are at risk of spontaneous bacterial peritonitis (SBP) with studies reporting an incidence of SBP

Author: [A]consultant hepatologist, Institute of Liver Studies, King's College Hospital, London, UK

ranging from 10% to 27% at the time of hospital admission. SBP may be asymptomatic but usually presents with abdominal pain or a manifestation of liver decompensation. All patients with ascites requiring hospital admission must undergo a diagnostic paracentesis. The diagnosis of SBP is established by finding a neutrophil count >250/mm³ in ascitic fluid; blood and ascitic fluid cultures should be performed but negative cultures do not refute the diagnosis of SBP and should not prevent or delay treatment with intravenous antibiotics.[7] Even with optimal management, mortality from SBP is around 10–20%.

Following a first episode of SBP, around 70% of patients suffer recurrent infection within one year. Transmural gut bacterial translocation is believed to be the predominant source of infection and oral antibiotic prophylaxis reduces the recurrence of SBP to 20%.[8] Primary antibiotic prophylaxis not only reduces the risk of a first episode of SBP but also improves survival and should be started in all patients with ascites and a low ascitic fluid protein (<10 g/l).[3] The optimal class of antibiotic and duration of primary and secondary prophylaxis remain unclear but at present it is recommended that either an oral quinolone or oral co-trimoxazole is continued until resolution of ascites or liver transplantation is performed.

Hepatorenal syndrome

Common precipitants of renal failure in cirrhosis include hypovolemia, nephrotoxic drugs, including radiological contrast agents, and coexistent intrinsic renal disease. Hepatorenal syndrome refers to renal failure in decompensated cirrhosis after exclusion of these causes.[9] It is classed as either type 1, which is rapidly progressive in less than two weeks, or type 2, which is more indolent.[9] Type 1 is commonly triggered by a bacterial infection, such as SBP, whereas type 2 is associated with refractory ascites. Type 2 has a better prognosis

than type 1, with median survival around six months compared with two weeks, respectively.

Although liver transplantation is the only definitive treatment for hepatorenal syndrome, other therapies are used to support the patient until liver grafting. Terlipressin following intravenous human albumin increases urine volume and sodium excretion, and importantly enhances survival[10] but it is not effective in all cases. Midodrine improves renal parameters but it has not been convincingly shown to enhance survival[11] and so its role is not established. Renal replacement therapy has also not been shown to improve long-term survival but it has a role in the management of patients with severe acidosis, hyperkalaemia or severe volume overload.

Gastrointestinal bleeding

Oesophageal varices develop in approximately 5–10% of patients with cirrhosis per year. The risk of variceal haemorrhage is related not only to variceal size but also to the severity of the liver disease and whether a patient with alcohol-related liver disease continues to drink.

Since 30–50% of patients with oesophageal varices due to portal hypertension will bleed from varices, prophylactic regimens to prevent bleeding have been developed. Both non-selective β-blocker therapy and endoscopic variceal band ligation reduce the risk of variceal haemorrhage and improve survival.[12] Band ligation is the preferred option for primary prophylaxis in those with medium or large varices, since it lowers the occurrence of variceal bleeding more than non-selective β-blocker therapy. Patients with cirrhosis should undergo screening upper gastrointestinal endoscopy,[13] firstly after initial diagnosis and then either at three-year intervals if no varices are detected or earlier if the patient develops liver decompensation.

Variceal haemorrhage is a serious complication of portal hypertension due to cirrhosis and is associated with a mortality of 25–50%. Mortality within six weeks of the initial bleed is related closely to the severity of liver disease. Blood transfusion for volume support is required to maintain the haemoglobin around 80 g/l and reversal of coagulopathy, if present, must be achieved by administration of fresh frozen plasma, cryoprecipitate and platelets, as required.[13] Activated recombinant factor VIIa should not be used routinely in patients with variceal bleeding because it is mostly ineffective and may cause serious adverse thrombotic events.[14] During resuscitation following a variceal haemorrhage, patients require endotracheal intubation for airway protection before endoscopic assessment; this is especially important in those with liver decompensation and severe hepatic encephalopathy (grades III and IV). Infections occur in patients with gastrointestinal haemorrhage and presence of infection escalates rebleeding and mortality. Intravenous antibiotics must be given on admission to all patients with cirrhosis and upper gastrointestinal bleeding.[15]

Pharmacological treatments, such as octreotide and terlipressin are effective and should be used if endoscopic intervention is not immediately available.[16] Variceal band ligation is superior to sclerotherapy in control of haemorrhage and prevention of rebleeding, and is associated with fewer complications.[17] In the event of a failure to control bleeding, TIPS is the preferred rescue option.[18] Balloon tamponade may be employed temporarily until the patient is ready for TIPS but

---

Key points

All patients with decompensated cirrhosis must be considered for suitability for liver transplantation

All patients with ascites requiring hospital admission must undergo a diagnostic paracentesis to exclude spontaneous bacterial peritonitis

Antibiotic prophylaxis using an oral quinolone or oral co-trimoxazole should be started in all patients with ascites and a low ascitic fluid protein (<10 g/l) to reduce the risk of a first episode of spontaneous bacterial peritonitis

Patients with cirrhosis and medium or large oesophageal varices should be offered a course of endoscopic band ligation to lower the occurrence of variceal bleeding

In a patient with hepatic encephalopathy, elective intubation is recommended for all gastrointestinal endoscopies, other procedures requiring sedation, and prior to transportation from a smaller hospital to a tertiary liver centre, in order to prevent aspiration

KEYWORDS: Jaundice, ascites, variceal haemorrhage, hepatic encephalopathy, liver transplant, nutrition, hepatorenal syndrome, spontaneous bacterial peritonitis ■

it may cause aspiration or oesophageal perforation in as many as 20% of cases, which limits its use.

Hepatic encephalopathy

Hepatic encephalopathy is a brain dysfunction caused by liver impairment or portosystemic shunting; it manifests as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma.[19] It is a debilitating complication of cirrhosis, severely affecting the lives of patients and their carers, but can respond to treatment. The risk for the first bout of hepatic encephalopathy is 5–25% within five years after the diagnosis of cirrhosis and is greatest in those with decompensated liver disease.[19] The development of hepatic encephalopathy is associated with a high mortality (50–65% at five years). A precipitating event can usually be identified in an acute bout, commonly a gastrointestinal bleed, infection, electrolyte disturbance or the use of sedatives, especially opiates and benzodiazepines.

A low protein diet is no longer recommended as it is ineffective and contributes to protein malnutrition in a patient with cirrhosis. Lactulose is administered orally, at a dose sufficient to achieve two loose stools per day, and enemas should be used in severe acute encephalopathy. The non-absorbable antibiotic rifaximin is efficacious and has no significant side effects but is expensive. Oral neomycin, vancomycin and metronidazole are no longer given due to significant systemic side effects following prolonged usage.

Aspiration is common in patients with hepatic encephalopathy as a consequence of weak airway reflexes and reduced muscle mass; therefore, elective intubation is recommended for all routine gastrointestinal endoscopies and other procedures requiring patient sedation, particularly in those with a model for end-stage liver disease (MELD) score >30. It may also be prudent to consider electively intubating a patient with encephalopathy and decompensated cirrhosis prior to transportation from a smaller hospital to a tertiary liver centre.

Nutritional support

Patients with cirrhosis have high resting energy expenditure but frequently have protein malnutrition resulting in muscle wasting, which can be severe. Those with protein malnutrition have a greater risk of hepatorenal syndrome, longer hospital stay (8.7 vs 5.7 days) and higher in-hospital mortality (relative risk 1.76; 95% confidence interval 1.59–1.94) compared with those with better nutritional status. Accordingly, nutritional support with oral protein calorie supplements is a vital component of the management of patients with decompensated cirrhosis. If oral intake is poor, then enteral feeding should be established using a post-pyloric feeding tube.

Conclusion

Patients with decompensated cirrhosis who are listed for or who are suitable for liver transplantation require attentive management in order to ensure survival until surgery. Patients frequently present with more than one facet of liver decompensation and such cases pose a complex management challenge requiring input from a multidisciplinary team and close liaison with a liver transplant centre. ■

References

1   Fleming KM, Aithal GP, Card TR, West J. The rate of decompensation and clinical progression of disease in people with cirrhosis: a cohort study. *Aliment Pharmacol Ther* 2010;32:1343–50.
2   Mukerji AN, Patel V, Jain A. Improving survival in decompensated cirrhosis. *Int J Hepatol* 2012;2012:318627.
3   European Association for the Study of the L. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. *J Hepatol* 2010;53:397–417.
4   Serste T, Gustot T, Rautou PE *et al*. Severe hyponatremia is a better predictor of mortality than MELDNa in patients with cirrhosis and refractory ascites. *J Hepatol* 2012;57:274–80.
5   Gines A, Fernandez-Esparrach G, Monescillo A *et al*. Randomized trial comparing albumin, dextran 70, and polygeline in cirrhotic patients with ascites treated by paracentesis. *Gastroenterology* 1996;111:1002–10.
6   Rossle M, Ochs A, Gulberg V *et al*. A comparison of paracentesis and transjugular intrahepatic portosystemic shunting in patients with ascites. *N Engl J Med* 2000;342:1701–7.
7   Rimola A, Garcia-Tsao G, Navasa M *et al*. Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: a consensus document. International Ascites Club. *J Hepatol* 2000;32:142–53.
8   Gines P, Rimola A, Planas R *et al*. Norfloxacin prevents spontaneous bacterial peritonitis recurrence in cirrhosis: results of a double-blind, placebo-controlled trial. *Hepatology* 1990;12:716–24.
9   Arroyo V, Gines P, Gerbes AL *et al*. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. International Ascites Club. *Hepatology* 1996;23:164–76.
10 Martin-Llahi M, Pepin MN, Guevara M *et al*. Terlipressin and albumin vs albumin in patients with cirrhosis and hepatorenal syndrome: a randomized study. *Gastroenterology* 2008;134:1352–9.
11 Singh V, Dhungana SP, Singh B *et al*. Midodrine in patients with cirrhosis and refractory or recurrent ascites: a randomized pilot study. *J Hepatol* 2012;56:348–54.
12 Gluud LL, Klingenberg S, Nikolova D, Gluud C. Banding ligation versus beta-blockers as primary prophylaxis in esophageal varices: systematic review of randomized trials. *Am J Gastroenterol* 2007;102:2842–8; quiz 2841, 2849.
13 Garcia-Tsao G, Sanyal AJ, Grace ND *et al*. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. *Hepatology* 2007;46:922–38.
14 Sozio MS, Chalasani N. Activated recombinant factor VIIa should not be used in patients with refractory variceal bleeding: it is mostly ineffective, is expensive, and may rarely cause serious adverse events. *Hepatology* 2014;60:1786–8.
15 Bernard B, Grange JD, Khac EN *et al*. Antibiotic prophylaxis for the prevention of bacterial infections in cirrhotic patients with gastrointestinal bleeding: a meta-analysis. *Hepatology* 1999;29:1655–61.
16 Patch D, Burroughs AK. Pharmacological treatment of portal hypertension. *Prog Liver Dis* 1995;13:269–92.
17 Garcia-Pagan JC, Bosch J. Endoscopic band ligation in the treatment of portal hypertension. *Nat Clin Pract Gastroenterol Hepatol* 2005;2:526–35.
18 Sanyal AJ, Freedman AM, Luketic VA *et al*. Transjugular intrahepatic portosystemic shunts for patients with active variceal hemorrhage unresponsive to sclerotherapy. *Gastroenterology* 1996;111:138–46.
19 Vilstrup H, Amodio P, Bajaj J *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;60:715–35.

Address for correspondence: Dr P Harrison, Institute of Liver Studies, King's College Hospital, Denmark Hill, London SE5 9PJ, UK.
Email: phillip.harrison@kcl.ac.uk