

Management of decompensated cirrhosis

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ABSTRACT

Decompensated cirrhosis is a common reason for admission to the acute medical unit, and such patients typically have complex medical needs and are at high risk of in-hospital death. It is therefore vital that these patients receive appropriate investigations and management as early as possible in their patient journey. Typical presenting clinical features include jaundice, ascites, hepatic encephalopathy, hepato-renal syndrome or variceal haemorrhage. A careful history, examination and investigations can help identify the precipitating cause (infections, gastrointestinal bleeding, high alcohol intake / alcohol-related hepatitis or drug-induced liver injury), so appropriate treatment can be given. A 'care bundle' that has been endorsed by the British Society of Gastroenterology is available to help guide the management of patients with decompensated cirrhosis for the first 24 hours and ensure all aspects are addressed. Specific management of complications, such as infections, gastrointestinal bleeding, hepatic encephalopathy and hepatorenal syndrome, are discussed.

KEYWORDS: Alcohol-related liver disease, ascites, cirrhosis, hepatic encephalopathy, hepatitis, hepato-renal syndrome, infections

Introduction

Decompensated cirrhosis is a frequent reason for admission to the acute medical unit, and such patients typically have complex medical needs that can lead to a prolonged hospital stay and a significant risk of an in-hospital death (10–20%). It is therefore vital that these patients receive the appropriate investigations and treatment as early as possible in their patient journey. The aim of this review is to provide an overview of the management of decompensated cirrhosis for non-specialists.

Decompensated cirrhosis is defined as an acute deterioration in liver function in a patient with cirrhosis and is characterised by jaundice, ascites, hepatic encephalopathy, hepatorenal syndrome or variceal haemorrhage. Common precipitants of hepatic decompensation include infections, gastrointestinal (GI) bleeding, high alcohol intake / alcohol-related hepatitis or drug-induced liver injury although no specific cause is found in approximately 50% of cases.¹ It is important to try to determine the underlying cause

of hepatic decompensation through a careful history, examination and investigations so appropriate treatment can be given.

Assessment of a patient with decompensated cirrhosis

Initial assessment of a patient with decompensated cirrhosis in the acute setting can be performed using the ABC (airway, breathing, circulation) approach.

Airway

The airway can be compromised in patients with severe hepatic encephalopathy where their conscious level is reduced (grade 3 or 4) or in those who present with large volume haematemesis. In these circumstances, early intubation and ventilation must be considered.

Breathing

Breathing is commonly compromised in patients with cirrhosis. Common causes of impaired breathing in cirrhotic patients include pneumonia (including aspiration pneumonia), pulmonary oedema (due to alcohol-related, ischaemic or cirrhotic cardiomyopathy), hepatic hydrothorax and gross ascites causing splinting of the diaphragm. Breathlessness can also be due to pulmonary complications of portal hypertension, namely portopulmonary hypertension (defined as pulmonary artery pressure >25 mmHg in a patient with portal hypertension and no other cause) and hepatopulmonary syndrome (HPS; triad of liver dysfunction, intrapulmonary vasodilation and arterial oxygenation defect). HPS is characterised by platypnoea and orthodeoxia (dyspnoea and hypoxia worse in the upright position and improved by lying flat) and can be diagnosed on bubble echocardiography. Both portopulmonary hypertension and HPS improve following liver transplant.

Breathing should be assessed by respiratory rate, oxygen saturations and auscultation of the chest. In the context of tense ascites, early paracentesis can improve respiratory function.

Circulation

Hypotension and tachycardia can occur as a result of sepsis, hypovolaemia/overdiuresis and GI bleeding. Tachycardia may not be present in subjects with significant hypovolaemia who are on beta-blockers. While it is important to identify and ameliorate the cause, the initial focus should be on adequate resuscitation. Hypovolaemic or shocked patients should be fluid resuscitated in

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the same manner as non-cirrhotic patients with an intravenous crystalloid, according to pulse and blood pressure, aiming for a mean arterial pressure >80 mmHg.^{2,3} Human albumin solution (5%) is an alternative volume expander, but is not always immediately available in an emergency situation. Those with evidence of GI haemorrhage should be managed as described below.

Hydration status can be difficult to assess in cirrhotic patients.³ Some patients appear peripherally overloaded because of hypoalbuminaemia, but are intravascularly deplete. Patients also tend to be vasodilated, which makes them chronically hypotensive – chasing a ‘normal’ blood pressure can push them into fluid overload. A careful assessment of pulse, blood pressure, jugular venous pulse and mucous membranes is needed, in addition to hourly fluid balance (aiming for urine output of >0.5 mL/kg) and daily body weight measurement.

Disability

Documentation of the patient’s Glasgow Coma Scale score, grade of encephalopathy (Table 1) and signs of alcohol withdrawal is mandatory. In addition, the temperature (sepsis can cause hyper- or hypothermia) and blood glucose (liver failure can cause hypoglycaemia) should be recorded. Asterixis is an important sign, identifying patients with ≥grade 2 encephalopathy.⁴

Exposure

A complete physical examination of the patient should be undertaken to look for the underlying cause of hepatic decompensation. Abdominal examination may reveal ascites, and any abdominal tenderness could suggest spontaneous bacterial peritonitis (SBP). Rectal examination is important to exclude melaena. Important things not to miss are possible foci of infection, such as cellulitis or septic arthritis. A neurological examination should be performed, as subdural haematoma or a cerebral vascular accident with dysphasia can be misdiagnosed as encephalopathy. There may also be signs of chronic liver disease (muscle atrophy, spider naevi, palmer erythema, caput medusa and gynaecomastia).

A full medical history and investigations should be conducted as shown in Box 1.

Table 1. West-Haven criteria for grading hepatic encephalopathy

Grade of encephalopathy	Symptoms/signs
Grade 1	Trivial lack of awareness, euphoria or anxiety, shortened attention span, impaired performance of addition or subtraction
Grade 2	Lethargy or apathy, minimal disorientation for time or place, subtle personality change, inappropriate behaviour, asterixis
Grade 3	Somnolence to semi-stupor, but responsive to verbal stimuli, confusion, gross disorientation
Grade 4	Coma

Box 1. History and investigations

History

- Symptoms leading to current presentation
- History of known liver disease
- Previous decompensations/complications of liver disease
- Previous endoscopies – any known varices?
- Infective symptoms – fever, dysuria, shortness of breath, cough, painful or swollen joints, rashes
- Bowel habit? Constipation? Meleana/haematemesis
- Recent foreign travel
- Abdominal pain or swelling
- Alcohol consumption (units/day) – currently and in the past
- Medications and compliance
- Recreational drug use / over the counter medication

Initial baseline investigations

- Blood tests: full blood count, C-reactive protein, urea and electrolytes, liver enzymes, coagulation, lactate, bone profile, magnesium, blood glucose, venous/arterial blood gas, alpha fetoprotein, alcohol level
- Chest X-ray
- Urinalysis, microscopy, culture and sensitivity
- Blood cultures
- Ascitic tap in those with ascites – white cell count and differential, culture and fluid albumin
- Doppler ultrasound abdomen

Management of decompensated cirrhosis

Decompensated cirrhosis is a complex disorder affecting multiple systems and therefore requires a systematic approach to its management. A ‘care bundle’, endorsed by the British Society of Gastroenterology, is available to help guide the management of patients with decompensated cirrhosis for the first 24 hours.^{5,6} A multicentre review in three English hospitals found that use of this care bundle improved all aspects of care and can help ensure patients with decompensated cirrhosis receive optimum management early in their hospital admission.⁷

Infections

As patients with cirrhosis are effectively immunosuppressed, infections are one of them most common reasons for hepatic decompensation. The most common infections in patients with cirrhosis are SBP, urinary tract infections, pneumonia and cellulitis. Gram-negative bacteria (particularly *Escherichia coli*) and Gram-positive cocci are the most common pathogens.⁸ SBP is infection in the ascitic fluid in the absence of a surgical cause. Symptoms include fever, abdominal pain, hypotension and encephalopathy, but one-third of patients are asymptomatic.⁸ Therefore, any patient admitted with clinically detectable ascites and decompensated liver disease should have a diagnostic ascitic tap performed on admission. SBP is confirmed by finding an ascitic fluid polymorphonuclear count of >250/mm³ (0.25×10⁹/L)

or positive fluid culture. If SBP is suspected, broad-spectrum antibiotics (cephalosporins/co-amoxiclav or quinolones) should be started after the sample has been taken and prior to the results becoming available if there will be a delay in sample processing. Antibiotic choice can then be rationalised according to sensitivities, once available. Acute kidney injury (AKI) develops in up to 40% of patients with SBP, and administration of intravenous albumin 1.5 g/kg on day 1 and 1 g/kg on day 3 (given as 20% human albumin solution) can significantly reduce the risk of developing hepatorenal syndrome, and may reduce short-term mortality.⁹

Ascites

Ascites, accumulation of fluid in the abdomen due to portal hypertension, is the most common complication of cirrhosis. Approximately 60% of cirrhotic patients develop ascites within 10 years of diagnosis.¹⁰ A no added salt diet and diuretic therapy are the first-line treatments for patients with mild to moderate ascites. In patients with normal renal function, the combination of spironolactone (50–100 mg/day) and furosemide (20–40 mg/day) is an appropriate starting regimen and can be titrated up every 5 days as tolerated, and according to response.¹⁰ A more cautious introduction of diuretics is needed in those with renal dysfunction. Close monitoring of electrolytes is mandatory as electrolyte abnormalities and renal dysfunction are common. Patients with tense ascites should have large volume paracentesis and then be established on diuretics.¹⁰ Intravenous albumin replacement (100 mL 20% albumin for every 2.5 L drained) should be given at the time of paracentesis to reduce the risk of precipitating hepatorenal syndrome.⁹

Gastrointestinal bleeding

Bleeding from gastroesophageal varices account for 50% of GI bleeds in cirrhotic patients¹¹ and carries a high mortality (15% 30-day mortality in a recent UK-wide audit¹²). Establishing intravenous access rapidly and commencing fluid resuscitation and blood product transfusion is key in the initial management of a large variceal bleed. Coagulopathy and thrombocytopenia are common in patients with cirrhosis, so correction of coagulopathy is recommended in patients with active bleeding with an INR >1.5 seconds (fresh-frozen plasma), platelets <50×10⁹/L and fibrinogen <1 g/L (cryoprecipitate).¹³ For patients who have non-massive GI bleeding, a restrictive blood transfusion strategy is recommended, transfusing blood when the haemoglobin (Hb) concentration falls below 7.0 g/L, with a target Hb of 8.0 g/L.¹⁴ More liberal transfusion strategies (transfusion when Hb <9.0 g/L) increase rebleeding and mortality rates, probably in part by increasing the portal pressure.

GI bleeding in a cirrhotic patient should be assumed to be from varices until proven otherwise, and treated with terlipressin (2 mg four times per day) and intravenous antibiotics (according to local policy).^{13,15} Treatment with terlipressin and intravenous antibiotics controls bleeding in 80% of patients with variceal haemorrhage and has been shown to reduce mortality and risk of infection post-bleed.

Endoscopy should be performed within 12 hours, or more urgently if the patient has been haemodynamically unstable and is actively bleeding.¹⁶ Patients with large volume haematemesis or encephalopathy should be intubated for the procedure to reduce the risk of aspiration.¹⁶ Variceal band ligation is the preferred treatment for oesophageal varices. Endoscopic injection

of *N*-butyl-2-cyanoacrylate ('glue') may be appropriate for the treatment of gastric varices.¹⁶ If haemostasis cannot be achieved then balloon tamponade with a Sengstaken-Blackmore tube, or equivalent, should be used.¹³ Transjugular intrahepatic portosystemic shunt should be considered if haemostasis cannot be achieved endoscopically or the patient rebleeds.¹³ UK guidelines advise a combination of non-selective beta-blocker (such as carvedilol 6.25–12.5 mg daily) in addition to variceal band ligation for secondary prophylaxis of variceal bleeds following discharge.¹³

Hepatic encephalopathy

Hepatic encephalopathy refers to the range of neurological abnormalities seen in patients with cirrhosis. The exact mechanism is not known, but is thought to be due to excess circulating toxins crossing the blood-brain barrier, including ammonia and glutamine. Hepatic encephalopathy is graded from 1 to 4 (Table 1).¹⁷ A diagnosis of hepatic encephalopathy is made on the basis of history and examination. The presence of asterix is diagnostic of hepatic encephalopathy. Other causes of mental state changes should be excluded, and consider a computerised tomography head to rule out pathology, such as subdural haematoma.¹⁷ Serum ammonia levels do not aid the diagnosis of hepatic encephalopathy in cirrhotic patients presenting acutely.¹⁸

Precipitants of hepatic encephalopathy include infection, constipation, electrolyte disturbance (particularly hypokalaemia), sedative drugs and GI bleeding. The mainstay of treatment of acute hepatic encephalopathy involves correcting the precipitant and encouraging elimination of toxins using lactulose (orally or via nasogastric tube, titrated to bowel frequency, aiming for 2–3 soft stools per day) and enemas, if required. The non-absorbable antibiotic, rifaximin (550 mg twice per day), can be added if the patient fails to respond to laxatives.¹⁷

Alcohol-related hepatitis

Alcohol-related hepatitis is a syndrome of rapid onset jaundice (<3 months), liver failure and systemic inflammation associated with prolonged heavy alcohol consumption. Typical clinical findings in patients with alcohol-related hepatitis are tender hepatomegaly, fever, ascites or encephalopathy. Blood tests show hyperbilirubinaemia, coagulopathy, neutrophilia and a modest transaminitis (2–6 times the upper limit of normal) with an aspartate aminotransferase / alanine aminotransferase ratio >2. It can be difficult to differentiate alcohol-related hepatitis from other causes of hepatic decompensation, so other causes, such as sepsis, need to be excluded.¹⁹

Long-term abstinence from alcohol is the most important prognostic factor in patients with alcohol-related hepatitis and every effort should be made to help patients achieve this. Specific treatment of alcohol-related hepatitis should be considered if the patient's Maddrey discriminant function, a widely used prognostic score for alcohol-related hepatitis, is >32, as this predicts an increased risk of early mortality.

Although the treatment for alcohol-related hepatitis remains contentious, prednisolone 40 mg for 28 days has the best evidence.^{20,21} The STOPAH (Steroids or Pentoxifylline for Alcoholic Hepatitis) trial, which was published in 2015, tried to definitively determine whether prednisolone was effective in severe alcohol-related hepatitis.²⁰ This trial enrolled more than 1,000 patients

with a clinical diagnosis of severe alcohol-related hepatitis at multiple sites across the UK and randomised them to 28 days treatment with placebo, prednisolone 40 mg, pentoxifylline 400 mg or prednisolone and pentoxifylline. Overall, there was a trend towards a reduction in 28-day mortality in those treated with prednisolone compared with placebo (odds ratio [OR] 0.72, CI 0.52–1.01, $p=0.06$), but pentoxifylline had no effect. Statistical analysis revealed subtle differences in the clinical characteristics between treatment groups in this study. Following multivariate analysis, correcting for baseline factors associated with survival, treatment with prednisolone was associated with improved 28-day survival compared with placebo (OR 0.61, CI 0.41–0.91, $p=0.02$). Unfortunately, there was no significant difference between the groups at 3 months or 1 year follow-up (overall: 54% survival at 1 year). There was a worryingly high rate of alcohol relapse (60%), which may have contributed to the poor 1-year survival rates.

When the results of the STOPAH trial were included in a meta-analysis, treatment with corticosteroids for alcohol-related hepatitis was associated with a significant reduction in short-term mortality.²¹ Prednisolone may therefore have a modest impact

on short-term mortality in severe alcohol-related hepatitis, but pentoxifylline is ineffective.

The main risk from using steroids in patients with alcohol-related hepatitis is sepsis, so it is important to exclude or treat sepsis before commencing steroids. For patients who start prednisolone, consider assessing their response at 7 days using the Lille score as 40% have no significant improvement in liver function (Lille score of ≥ 0.45) and have an increased risk of sepsis if steroids are continued beyond 7 days.²² Given the lack of highly effective treatments for alcohol-related hepatitis, a number of compounds are now undergoing clinical trials (Table 2).²³

AKI, hepatorenal syndrome and hyponatraemia

AKI is common in patients with decompensated cirrhosis, with approximately 20% of patients affected.²⁴ It can occur secondary to pre-renal AKI (45%), acute tubular necrosis / primary renal disease (including nephrotoxic drugs) (32%), or hepatorenal syndrome (23%) and is often multifactorial.²⁴ AKI in cirrhotic patients is defined as the increase in creatinine of $>26 \mu\text{mol/L}$ within 48 hours and/or $\geq 50\%$ from baseline over 7 days.²

Table 2. New and future treatments for alcohol-related hepatitis

Mechanism of action	Method	Evidence	Current trials ^a
Inhibition of oxidative stress	N-acetyl cysteine (NAC) +corticosteroids	NAC (IV 5 days) + corticosteroids significantly reduced mortality at 1 month vs steroids alone	Current trial of intravenous NAC + corticosteroids vs corticosteroids alone NCT02971306
	S-adenosylmethionine	Promising in small studies only, trials required	
Blockade of apoptosis	ASK-1 (apoptosis signal-regulating kinase-1) inhibitor GS-4997/selonsertib		Current trial ASK-1 inhibitor +corticosteroids NCT02854631
Reducing inflammation	Anti-tumour necrosis factor alpha	Increased mortality in clinical trials	
Bile acids	Obeticholic acid (Farnesoid R receptor [FXR] analogue)	In mice models cholic acid stimulates liver growth, response lost in FXR-/- mice	
Regeneration	Granulocyte colony stimulating factor (GCSF)	Improved survival vs placebo in pilot trial	Current trials of GCSF alone, in combination with NAC, or in null/partial responders to corticosteroid
	Recombinant human IL-22, F-652)	Cytokine IL-22 induces liver regeneration	Current trial (TREAT 008), NCT02655510
	Stem cell transplant	No survival benefit / improvement in liver function in randomised controlled trial	
Modulation of gut microbiota	Probiotics		Current trial NCT02335632
	Rifaximin		NCT02485106
	Faecal transplant		NCT02458079
Transplant	Early salvage liver transplant	Initial trial improved survival in patients with alcohol-related hepatitis not responding to steroids (77% vs 25% matched controls)	Current trial NCT01756794
Prophylactic antibiotics	Amoxicillin/co-amoxiclav		Current trial NCT02281929

^aTrial details can be found at ClinicalTrials.gov

Initial treatment of AKI in cirrhotic patients is correction of hypovolaemia with intravenous fluid. Human albumin solution (1 g/kg for 2 days; 5% albumin if hypovolaemic or 20% if euvoalaemic) is recommended by international guidelines.² Large volumes of 0.9% saline or 5% dextrose should be avoided as this can promote accumulation of ascites (saline) or hyponatraemia (dextrose).²⁴ Diuretics, nephrotoxins and vasodilators should be suspended. Other intrinsic causes of renal dysfunction should be excluded. If there is no significant improvement in renal function after 48 hours, hepatorenal syndrome is likely, so consider adding terlipressin 0.5–1 mg four times per day (titrating up to 12 mg/day maximum), in combination with 20–40 g albumin per day.^{2,24}

Hyponatraemia is also common in decompensated cirrhosis and is frequently multifactorial (diuretics, alcohol consumption, portal hypertension, proton pump inhibitors, intravenous dextrose etc). Suspend any potential precipitating drugs. Treatment depends on fluid status, with hypovolaemic hyponatraemia being more common than hypervolaemia. For patients with persistent hyponatraemia despite cessation of diuretics, intravenous albumin can improve the serum sodium levels.²⁵ Fluid restriction should be reserved for patients with severe hyponatraemia (<120–5 mmol/L) who are euvoalaemic or hypervolaemic with normal renal function.²⁶ Vaptans (vasopressin receptor agonists such as tolvaptan) have been shown to improve hyponatraemia and ascites in patients with cirrhosis, but do not effect survival and carry a risk of hepatotoxicity, and so currently they are not recommended.²⁷ Small studies have suggested a role for midodrine (a vasopressor) and octreotide in treatment of cirrhotic patients with hyponatraemia and ascites; however, these findings need to be confirmed.²⁸ Whichever method is used, it is important to correct the sodium slowly (<10 mmol/24 hours) to avoid the risk of precipitating central pontine myelinolysis.

Nutrition

Addressing the patient's nutritional needs is very important in decompensated liver disease, as sarcopenia is highly prevalent. All patients should have a nutritional assessment, food chart and, if required, oral/nasogastric nutritional supplements aiming to provide a total energy intake of about 35–40 kcal/kg daily.¹⁰ Refeeding syndrome is a common complication, so phosphate, potassium and magnesium should be monitored daily, and electrolytes replaced orally or intravenously as appropriate. Pabrinex (intravenous thiamine) should be prescribed if there is evidence of inadequate nutrition, or in patients who consume excessive alcohol, to reduce the risk of Wernick's encephalopathy.²⁹

Escalation of care / end-of-life care

For cirrhotic patients who fail to respond to initial management or deteriorate, consider escalation of care to a high dependency / intensive care environment to optimise their treatment. Outcomes from the intensive care unit are reasonably good (overall >50% survival to hospital discharge), particularly for acutely reversible complications, such as a GI bleed or encephalopathy.³⁰ It is important to regularly review progress of patients to avoid prolonged futile admissions. Escalation or palliative care plans should be clearly documented by the specialist teams to avoid difficult decisions for on-call teams.

Conclusions

Decompensated cirrhosis is a common disorder presenting to acute medical units and has high mortality. A systematic approach, with the aid of a care bundle, can ensure patients receive appropriate management of their complications. ■

Conflicts of interest

The authors have no conflicts of interest to declare.

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