Management of common problems in patients with chronic liver disease: a practical guide

Introduction

Chronic liver disease is becoming an increasing problem with the majority of cases the result of alcohol-induced liver damage. Other causes include infection with hepatitis B or C virus, autoimmune liver disease, haemochromatosis, primary biliary cirrhosis, and cirrhosis complicated by non-alcoholic steatohepatitis. This list is by no means a complete one.

Patients with chronic liver disease who are unwell with any illness may initially recover from the acute problem, but their underlying liver disease may then deteriorate. The management of these patients involves both managing the acute problem and also watching out for deterioration in liver function; these should happen simultaneously.

Deterioration in liver function is reflected by worsening jaundice, worsening prothrombin time and international normalized ratio (INR), rising portal hypertension with bleeding oesophageal varices, hepatic encephalopathy, accumulation of ascites, hepatorenal syndrome, hepatopulmonary syndrome, and predisposition to infections and spontaneous bacterial peritonitis.

Worsening prothrombin time and international normalized ratio

This is usually the result of deteriorating known liver disease, alcoholic hepatitis, sepsis, acute hepatitis of any cause, portal vein thrombosis, hepatoma, liver metastasis, biliary obstruction, or Budd–Chiari syndrome.

Investigations should be undertaken to reveal which of the above is responsible for the worsening prothrombin time.

Management begins with correction of any possible vitamin K deficiency with intravenous vitamin K 10 mg per day for 3 days.

Dr RS Kumar Bhamidimarri *is Specialist Registrar in General and Elderly Medicine, Airedale General Hospital, Skipton, Keighley BD20 6TD*

Raised INR does not always need correcting unless the patient is actively bleeding or needs diagnostic, therapeutic or surgical procedures (such as central venous lines, paracentesis, chest drain, lumbar puncture or liver biopsy).

The agents usually used for correcting INR are fresh frozen plasma and prothrombin complex concentrate (O'Shaughnessy et al, 2004). The dose of fresh frozen plasma is 10–15 ml/kg body weight given intravenously, aiming for an INR of less than 1.6 at which most procedures can be done relatively safely. It is important to be aware that each unit of fresh frozen plasma is approximately 300 ml and in situations where fluid overload could be a problem alternative agents like prothrombin complex concentrate should be used. It is important to liaise with a haematologist for the correct dose of prothrombin complex concentrate. Transfusion-related acute lung injury continues to be a potential problem with use of fresh frozen plasma.

Upper gastrointestinal bleed and varices

In patients with chronic liver disease presenting with upper gastrointestinal bleed, the source of the bleed is oesophageal and/or gastric varices until proven otherwise (Habib and Sanyal, 2007). Other sources of upper gastrointestinal bleeding in these patients can include peptic ulcers, oesophagitis, gastritis and Mallory–Weiss tear.

Varices as a source of bleeding in these patients reflects worsening of portal hypertension. It is therefore vital to actively look for causes of worsening portal hypertension. This should begin at initial assessment of these patients. The usual causes of worsening portal hypertension are worsening of cirrhosis, infections including spontaneous bacterial peritonitis, portal vein thrombosis, alcoholic hepatitis, any other acute illness, non-compliance with beta blockers, and development of hepatocellular carcinoma (Blei, 2007).

In the context of liver disease it may be safer to manage patients as having varices as a source of bleeding until proven otherwise. Resuscitate with crystalloids, colloids and blood, and arrange an urgent upper gastrointestinal endoscopy. In patients with elevated prothrombin time use fresh frozen plasma as outlined earlier. Start a proton pump inhibitor (chosen according to local protocols) and in those who are actively bleeding commence prophylactic antibiotics, which should cover gram-negative and anaerobic bacteria.

Commence intravenous terlipressin 1 mg 4-hourly and proceed with oesophagogastroduodenoscopy for both diagnosis and possible endoscopic treatment of the cause of the bleeding. Agents such as octreotide can be used if terlipressin is not available. Patients with an ongoing variceal bleed will need a Sengstaken or Minnesota tube to compress the varices but this should be placed by someone with the necessary experience. Patients with varices will need further oesophagogastroduodenoscopies to tackle the varices by banding or glue injection (Yoshida et al, 2007). If further attempts to control a variceal bleed fail, the patient will need referral for placement of a transjugular intrahepatic portosystemic stent. In patients with varices, non-selective beta-blockers such as propranolol should be commenced if not contraindicated to reduce the risk of future bleeding. Oral nitrates are no longer used for this indication.

Worsening jaundice and alcoholic hepatitis

It is important not to assume that any jaundice is caused by the known liver disease. These patients should be worked up the same way as any patient with jaundice but bearing in mind contextual causes such as paracetamol overdose, sepsis including spontaneous bacterial peritonitis, alcoholic hepatitis, development of hepatoma, portal vein and hepatic vein thrombosis.

The tests should therefore always include alpha fetoprotein, ultrasound of the liver,

and Doppler ultrasound of the portal and hepatic vein. Unless already known check hepatitis A, B, C serology, auto-antibody screen, immunoglobulins, ferritin, transferrin saturation, α-1 antitrypsin, ceruloplasmin, haptoglobin, lactate dehydrogenase and Coombs test.

Consider alcoholic hepatitis in patients who have been abstinent of alcohol for 2–3 weeks but have a history of excessive alcohol consumption (Ceccanti et al, 2006). It is important to recognize this as it has a specific treatment. While there are several scoring systems used to help decide which patients need steroids, the Glasgow Alcoholic Hepatitis score as shown in *Table 1* is used in the author's practice.

Drug treatment with steroids is offered for patients with Glasgow Alcoholic Hepatitis score ≥9 in absence of contraindications (which include sepsis, active gastrointestinal bleed or renal failure). Commence on intravenous methylprednisolone 40 mg once daily (change to oral prednisolone when improving). This needs to be given for a total of 4 weeks if the bilirubin level starts to decrease. Steroids then need to be gradually tapered off. If no decrease in bilirubin level is noted by day 5, steroids should be discontinued.

For patients with contraindications to steroid use as outlined earlier, oral pentoxifylline 400 mg three times a day is used instead. Pentoxifylline was originally used in patients with peripheral vascular disease and is also a suppressor of tumour necrosis factor-alpha. It is now used in patients with severe alcoholic hepatitis mainly for its reno-protective effect, as a result of which it reduces mortality. Pentoxifylline can be continued for 4 weeks even if the bilirubin level does not decrease, as its side-effect profile is better than that of steroids.

Table 1. Glasgow Alcoholic Hepatitis Score

Score	1	2	3
Age (years)	<50	>50	–
White cell count (10^9/litre)	<15	>15	–
Urea (mmol/litre)	<5	>5	–
International normalized ratio	<1.5	1.5–2.0	>2.0
Bilirubin (μmol/litre)	<125	125–250	>250

From Forrest et al (2005)

In these patients diet plays a very important therapeutic role. Early input from a dietician is important and one should have a low threshold to commence nasogastric or nasojejunal feeding. Close monitoring is needed for complications like gastrointestinal bleed, spontaneous bacterial peritonitis, encephalopathy, renal failure, worsening of ascites and sepsis.

Sepsis and spontaneous bacterial peritonitis

Sepsis continues to be a major problem in patients with chronic liver disease and its presentation can be both very subtle and atypical, leading to patients deteriorating quite quickly without prompt recognition and treatment (Wong et al, 2005). The sites of infection are the usual ones (chest, urine and skin), but occult infections can pose a diagnostic challenge (e.g. lung abscess, lung empyema, intra-abdominal collections, septic arthritis, septic discitis, CNS infections).

It is important to consider spontaneous bacterial peritonitis as a differential diagnosis in this subset of patients. Suspect spontaneous bacterial peritonitis in patients with abdominal pain, fever, worsening ascites or worsening encephalopathy (Volk and Marrero, 2006).

The management of these patients should follow standard practice for treating sepsis but must include an urgent ascitic fluid analysis. It is relatively safe to do a diagnostic ascitic tap in a patient with an INR<1.8.

The ascitic fluid must be sent for cell count, bacterial culture, albumin level, and at least 10 ml should be put into blood culture bottles at the bed side, which increases the chance of growing the organism. Ascitic fluid white cell count >500/μl (mm^3) or neutrophils >250/μl (mm^3) favours spontaneous bacterial peritonitis unless there has been recent antibiotic exposure in which case a lower cell count may be seen.

For suspected spontaneous bacterial peritonitis, commence cefuroxime, cefotaxime or ciprofloxacin and metronidazole along with appropriate fluid management. Also commence 1–2 units of 20% human albumin solution intravenously on day 1, 3 and 5. Draining ascites with spontaneous bacterial peritonitis needs to be considered, particularly if the abdomen is tensely distended. This needs very close monitoring of all blood parameters including full blood count, serum electrolytes, bilirubin, clotting and C-reactive protein. Worsening of jaundice, INR, portal hypertension, ascites, renal function and encephalopathy can complicate the course of the illness.

Commence long-term spontaneous bacterial peritonitis prophylaxis with norfloxacin 400 mg once a day orally in patients who have any one or more of an episode of spontaneous bacterial peritonitis, ascitic fluid albumin < 10 g/litre, recurrent variceal bleeds and encephalopathy.

Worsening ascites and therapeutic paracentesis

In the context of chronic liver disease worsening ascites is usually caused by worsening of underlying liver disease, development of spontaneous bacterial peritonitis, non-compliance with diuretics and fluid restriction, and resistant ascites (Blei, 2007). It is important to consider portal vein thrombosis, hepatoma, tuberculosis and non-cirrhotic causes for worsening ascites. Worsening ascites is also an inevitable consequence during the management of these patients when they are treated for an acute illness where intravenous fluids are usually given.

Investigations in these patients should address the above queries and should always include sending ascitic fluid for biochemical and microbiological analysis, checking alpha fetoprotein, and Doppler ultrasound of portal and hepatic veins.

The ascitic fluid must be sent for urgent cell count, culture sensitivity (put at least 10 ml of fluid in blood culture bottles at bedside), stain and culture for acid-fast bacilli and albumin level. The serum ascitic albumin gradient must always be calculated: if <10 this indicates an exudative fluid and if >10 indicates the fluid is a transudate, usually as a result of portal hypertension.

The management of these patients aims for a weight loss of 0.5 kg per day in those with no peripheral oedema and 1.0 kg per day in those who also have severe peripheral oedema. It is therefore essential to weigh these patients daily.

In patients whose ascites is substantial or tense, therapeutic paracentesis as detailed below will be the first line of action, but for others begin with fluid restriction of 1–1.5 litre per day, progressing to medications. Spironolactone initiated at 50 mg per day can be gradually increased to a maximum of 400 mg per day. A loop diuretic like furosemide can be added to spironolactone starting with 20 mg per day, which can be increased up to 160 mg per day. If painful gynaecomastia becomes a problem with spironolactone, amiloride 5–10 mg per day can be used instead. Close monitoring of serum electrolytes and urine output is essential.

For patients who need therapeutic paracentesis aim for an INR of <1.6 using either fresh frozen plasma or prothrombin complex. Begin by administering three units of 20% human albumin solution intravenously and drain 6 litres of the fluid. Give a further unit of 20% human albumin solution for every 2 litres of fluid drained. Aim to drain to dryness, unless there are concerns about renal impairment or potential cardiovascular instability, in which case drain for symptom relief. Refrain from leaving the drains in-situ for long periods because of the very high risk of sepsis.

Continue to closely monitor these patients, watching out for developing complications such as sepsis, including spontaneous bacterial peritonitis, variceal gastrointestinal bleed, renal failure and hepatic encephalopathy. In those with recurrent and resistant ascites refer for TIPS and assessment for liver transplant (Senzolo et al, 2006).

Renal failure and hepatorenal syndrome

Renal failure continues to be a major problem in patients with advanced liver disease. The initial work-up and treatment of renal failure is no different to that in patients without liver disease.

Hepatorenal syndrome is diagnosed after exclusion and/or treatment of other causes of renal failure including pre-renal failure, hypovolaemia, sepsis, drug adverse effects, intrinsic renal disease and obstructive uropathy (Wadei et al, 2006). The two types of hepatorenal syndrome are type 1 which is characterized by doubling of the serum creatinine to >200 μmol/litre in less than 2 weeks and type 2 which is chronic and more slowly progressive over months.

The initial treatment of hepatorenal syndrome entails a decent fluid challenge with at least 1 litre of intravenous fluid unless the patient has an adequately filled central volume status. When it comes to choice of intravenous fluids, either crystalloids or colloids can be used, but increasingly human albumin solution is being used. Commence intravenous terlipressin 0.5 mg, 4-hourly along with at least 2 units of 20% human albumin solution per day (Schmidt and Ring-Larsen, 2006). Accurate fluid balance measurement along with close monitoring of serum electrolytes, bilirubin, prothrombin time, full blood count and C-reactive protein is important. If electrolytes improve, continue this regimen until the serum creatinine levels normalize.

If no improvement in renal function is seen, increase terlipressin every third day to 1 mg, 1.5 mg and then 2 mg 4-hourly aiming for a total maximum daily dose of 12 mg. Stop this regimen if no response and consider referral for liver transplant assessment. Some of these patients may need renal replacement therapy as a bridge to liver transplant.

At all stages of management one should watch out for other developing complications such as sepsis, including spontaneous bacterial peritonitis, gastrointestinal bleed, worsening ascites and precipitation of hepatic encephalopathy.

Confused, drowsy patient and hepatic encephalopathy

The evaluation of confused and/or drowsy patients should be as for any patient but it important to bear in mind hepatic encephalopathy as an important cause (Detry et al, 2006).

The evaluation should exclude the mimickers of hepatic encephalopathy like drug effects (e.g. chlordiazepoxide, opiates, sedatives), alcohol intoxication, intracranial events (e.g. meningitis, subdural bleed, encephalitis), sepsis, electrolyte disturbances and Wernicke's encephalopathy.

The investigations and management should focus on excluding and treating the above mimickers starting with discontinuing culprit medication, administering intravenous thiamine, diagnostic ascitic tap to exclude spontaneous bacterial peritonitis, and additional relevant measures. If no improvement is noted in either the confusion or drowsiness then hepatic encephalopathy is likely.

For patients with hepatic encephalopathy commence oral lactulose solution adjusting the dose to ensure the bowels are loose with at least two to three motions a day. Consider either oral neomycin 500 mg once a day for 7 days or oral metronidazole 400 mg three times a day for the same duration if there are concerns about renal function (Festi et al, 2006). If no improvement, refer these patients for assessment for liver transplant (Mas, 2006). Closely monitor serum electrolytes, bilirubin, prothrombin time and urine output as in these patients it is not unusual to have other signs of worsening liver function.

Pulmonary oedema and hepatopulmonary syndrome

Pulmonary oedema can pose a major problem during the management of patients with advanced liver disease. Usually it is the result of iatrogenic fluid excess in the context of hypoalbuminaemia, portal hypertension and alcohol cardiomyopathy in patients with excess alcohol intake.

It is not uncommon to see non-cardiogenic pulmonary oedema, i.e. adult respiratory distress syndrome, or transfusion-

KEY POINTS

- Chronic liver disease is increasing, with the majority of cases caused by excess alcohol intake.
- In acutely ill patients with known chronic liver disease, there could be deterioration of liver function.
- Worsening of liver function is reflected by worsening of jaundice, prothrombin time, and rising portal hypertension with bleeding oesophageal varices, hepatic encephalopathy, accumulation of ascites, hepato-renal syndrome, hepato-pulmonary syndrome, and predisposition to infections and spontaneous bacterial peritonitis.

related acute lung injury in the context of sepsis and use of blood products like fresh frozen plasma and human albumin solution. The management of these patients is supportive with some needing non-invasive or even invasive positive pressure ventilation.

Consider hepatopulmonary syndrome in cirrhotic patients with oxygen saturation on room air less than 97% with no other explanation for it (Varghese et al, 2007). Some of these patients may be considered for transjugular intrahepatic porto-systemic stent and assessment for liver transplantation.

Conclusions

Patients with chronic liver disease, the majority of which is alcohol related, continue to be admitted onto medical wards. This article is intended as a handy guide for trainees and residents working on these wards. **BJHM**

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