Response to the NCEPOD report: development of a care bundle for patients admitted with decompensated cirrhosis—the first 24 h

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ABSTRACT

Recently, there has been a significant increase in the prevalence of chronic liver disease in the UK, and as a result, hospital admissions and deaths due to liver disease have also increased. The 2013 National Confidential Enquiry into Patient Outcome and Death (NCEPOD) of patients with alcohol-related liver disease (ARLD) found that less than half the number of patients who died from ARLD received ‘good care’, and avoidable deaths were identified. In order to improve the care of patients admitted with ARLD, the NCEPOD report recommended that a ‘toolkit’ for the acute management of patients admitted with decompensated ARLD be developed and made widely available. As a result, we have developed a ‘care bundle’ for patients admitted with decompensated cirrhosis (of all aetiologies) to ensure that effective evidence-based treatments are delivered within the first 24 h. This care bundle provides a checklist to ensure that all appropriate investigations are undertaken when a patient with decompensated cirrhosis presents and provides clinicians with clear guidance on the initial management of alcohol withdrawal, infection, acute kidney injury, gastrointestinal bleeding and encephalopathy. The first 24 h are particularly important, as early intervention can reduce mortality and shorten hospital stay, and specialist gastroenterology/liver advice is not always available during this period. This review will discuss the care bundle and the evidence base behind the treatment recommendations made.

INTRODUCTION

Over the last 20 years, there has been a significant increase in the prevalence of chronic liver disease in the UK, with the major causes being alcohol-related liver disease (ARLD), hepatitis B and C and obesity-related liver disease.1 There has also been a substantial rise in hospital admissions with complications of liver disease, as well as a steady rise in liver-related deaths in the UK.1,2 Liver disease is now one of the major causes of premature death in the UK.3 Decompensated cirrhosis and acute on chronic liver failure are common causes for hospital admission and are associated with a high mortality rate.4 The 2013 National Confidential Enquiry into Patient Outcome and Death (NCEPOD) of patients with ARLD ‘Measuring the Units’ raised concerns about suboptimal care of patients in hospital with complications of cirrhosis (due to ARLD), which might have contributed to the rise in liver-related mortality.5 The report found that less than half (47%) the patients who died from ARLD received ‘good care’, and avoidable deaths were identified. It is likely that similar findings would be observed for the management of patients with cirrhosis of other aetiologies.

In order to improve the care of patients admitted with ARLD, the NCEPOD report recommended that a ‘toolkit’ for
the acute management of patients admitted with decompensated ARLD be developed and made widely available. As a result, we have developed a ‘care bundle’ for patients admitted with decompensated cirrhosis (of all aetiologies) to ensure that effective evidence-based treatments are delivered within the first 24 h. The first 24 h are particularly important as early intervention for presentations such as sepsis, bleeding or renal dysfunction in patients with cirrhosis can reduce mortality and shorten hospital stay, and specialist gastroenterology/liver advice is not always available during this period. This review will discuss the care bundle and the evidence base behind the treatment recommendations made.

THE CARE BUNDLE

The care bundle is designed to be completed for all patients presenting with decompensated cirrhosis and should be commenced within 6 h of admission. ‘Decompensated cirrhosis’ is defined as an acute deterioration in liver function in a patient with cirrhosis that can manifest with the following: jaundice, increasing ascites, hepatic encephalopathy, renal impairment/ hypovolaemia, gastrointestinal (GI) bleeding, or signs of sepsis. Common precipitants for decompensated cirrhosis are shown in box 1. This care bundle is primarily designed to provide recommendations on management for the first 24 h only. After this period, it is expected that specialist GI/liver input will be available to provide guidance on further management.

BASELINE INVESTIGATIONS

On admission, it is vital that patients presenting with decompensated cirrhosis have a full history and clinical examination to look for the cause of deterioration in liver function, infection or evidence of GI bleeding. The National Early Warning Score should be recorded and used to monitor the patient’s physiological status. Blood tests should be taken to assess liver function, renal function tests, coagulation profile and glucose. As sepsis is a frequent cause of admission, patients should also be screened for infection with clinical examination, urinalysis and urine culture, chest X-ray, blood cultures and C-reactive protein (CRP). Although not always a routine test, serum CRP levels can help detect infection in cirrhotic patients early. One study showed that a CRP level greater than 10 mg/L was predictive of infections in patients with cirrhosis (area under the receiver

Figure 1 The care bundle for decompensated cirrhosis.
operator curve 0.93, sensitivity 84%, specificity 91%), although the CRP can be elevated for other reasons, such as alcoholic hepatitis.9

Additionally, an ascitic tap should be performed for all patients who have clinically detectable ascites to exclude spontaneous bacterial peritonitis (SBP).10 Coagulopathy is not a contraindication to this procedure,3 and measures to correct coagulopathy are NOT required. Ascitic fluid should be sent to the lab for analysis of the fluid: polymorphonuclear (PMN) and white cell count, microscopy and culture, protein and albumin content.11 An abdominal ultrasound should be requested and performed at the earliest opportunity (unless an ultrasound has been conducted in the last month), ideally within 24 h, and should include an assessment of portal vein patency.

Alcohol
Seventy per cent of patients in the UK, admitted with cirrhosis, have alcohol as the major aetiological factor.12 The patient’s current and previous alcohol history (in units/day: box 2), time of last drink and any symptoms of alcohol withdrawal should be documented.5 For patients with current excessive alcohol consumption, parenteral thiamine and other B vitamins (Pabrinex: two pairs of vials three times daily for 3 days) should be given to treat thiamine deficiency and reduce the risk of Wernicke’s encephalopathy or Korsakoff’s syndrome.13 Patients who have symptoms of alcohol withdrawal or are at high risk of alcohol withdrawal, seizures or delirium tremens should be assessed with a validated tool for alcohol withdrawal, such as the revised Clinical Institute Withdrawal Assessment—Alcohol (CIWA-Ar) scale, and be treated with a symptom-triggered regimen of benzodiazepines.13 14

Infections
Patients with cirrhosis have impaired defence against bacteria due to immune dysfunction, and as a result, bacterial infections are one of the most frequent reasons for admission and are associated with a high mortality rate.8 15 16 A careful assessment for infection is critical in all patients admitted with decompensated cirrhosis, as prompt treatment with antibiotics improves prognosis.17 The most common infections in cirrhotics are SBP, followed by urinary tract infections and pneumonia,8 18 and Gram-negative bacilli, such as *Escherichia coli*, are the most frequently encountered pathogens.19 There has been a recent increase in the prevalence of infections with multidrug resistant bacteria in patients with cirrhosis, which emphasises the importance of taking the appropriate samples for culture and sensitivity, so patients can have their antibiotics modified accordingly.20 Importantly, patients with cirrhosis do not always display typical signs of infection, such as pyrexia or rise in CRP, so clinicians must have a high index of suspicion for infection. Once suspected clinically, infection should be treated promptly with broad spectrum antibiotics as per hospital protocol.

SBP is defined as infection of the ascitic fluid in the absence of a secondary cause, such as intestinal perforation, and occurs in approximately 10% of hospitalised patients with cirrhosis.1 15 16 Although abdominal pain and fever are commonly seen in patients with SBP symptoms are frequently absent.21 It is, therefore, recommended that all patients presenting with ascites have a diagnostic ascitic tap to exclude SBP on admission to hospital, or if there is deterioration in their clinical status.5 10 11 Diagnosis of SBP is made when the absolute number of PMN cells is $>250/\text{mm}^3$ of ascitic fluid.22 Upon diagnosis, SBP should be empirically treated with broad spectrum antibiotics, such as third-generation cephalosporin (cefotaxime or ceftriaxone), co-amoxiclav or ciprofloxacain, according to hospital policy, with modifications made in light of subsequent culture results.8 10 11 Patients with SBP are at high risk of developing hepatorenal syndrome (HRS) and should have intravenous albumin administered to prevent worsening of renal function.10 Studies have shown that intravenous albumin 1.5 g/kg

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### Box 1 Definition of decompensated cirrhosis and common precipitants

- **Decompensated cirrhosis**—deterioration in liver function that can manifest with the following:
  - Jaundice
  - Increasing ascites
  - Hepatic encephalopathy
  - Renal impairment/hypovolaemia
  - Signs of sepsis/hypovolaemia

- **Common precipitants of decompensated cirrhosis:**
  - Gastrointestinal bleeding (variceal and non-variceal)
  - Infection/sepsis (spontaneous bacterial peritonitis, urine, chest, cholangitis, etc)
  - Alcoholic hepatitis
  - Acute portal vein thrombosis
  - Development of hepatocellular carcinoma
  - Drugs (alcohol, opiates, NSAIDs, etc)
  - Ischaemic liver injury (sepsis or hypotension)
  - Dehydration

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### Box 2 Definition of units of alcohol

- One unit of alcohol = 10 mL of alcohol or 8 g of alcohol
- Example: a 500 mL can of 5% Beer = 25 mL of alcohol = 2.5 units of alcohol
- The maximum recommended weekly alcohol consumption is 21 units for men and 14 units for women.
at diagnosis and 1 g/kg at 72 h reduces the incidence of HRS from 30% to 10% and reduces mortality from 29% to 10%.23

**Acute kidney injury and/or hyponatraemia**

Acute kidney injury (AKI) is estimated to occur in approximately 20% of hospitalised patients with cirrhosis, and is associated with a poor prognosis.24 25 Several definitions of AKI exist, but the National Institute of Health and Care Excellence (NICE) recommends the use of the modified RIFLE (Risk Injury Failure Loss and End stage renal disease) criteria that were devised by the Acute Kidney Injury Network to detect subjects at risk of AKI.26 27 AKI is defined if any of the following criteria are met: (1) an absolute rise in serum creatinine of ≥26 μmol/L within 48 h; (2) a ≥50% increase in serum creatinine known or presumed to have occurred in the last 7 days; (3) a fall in urine output to <0.5 mL/kg/h for 6 h.27 It should be noted that patients with cirrhosis frequently have low baseline creatinine levels, as many have reduced muscle bulk and malnutrition. Therefore, some patients with creatinine levels within the normal range can have a significantly reduced glomerular filtration rate.

AKI in patients with cirrhosis is commonly multifactorial, but prerenal AKI is most common (45%), followed by acute tubular necrosis and glomerulonephritis (32%), HRS (23%) and rarely postrenal (<1%).25 It is important to identify the cause of AKI, as the underlying cause has implications on prognosis. Type 1 HRS (acute) carries a particularly poor prognosis with mortality rates approaching 100% without treatment. HRS is a diagnosis of exclusion, and current diagnostic criteria are shown in box 3.28 It is important to note that before a diagnosis of HRS can be made patients need to have their diuretics and nephrotoxic medications suspended and be volume expanded with albumin, so a diagnosis of HRS can usually not be made within the first 24 h. If HRS is subsequently diagnosed, patients should be treated with intravenous albumin and terlipressin, as this has been shown to reduce mortality in patients with HRS.29

Early intervention in patients with AKI can prevent further deterioration in renal function leading to renal failure. Initial management of AKI should include suspension of all diuretics and nephrotoxic drugs.30 31 Patients should be fluid-resuscitated with 0.9% saline or 5% albumin, giving boluses of 250 mL with regular volume status reassessment aiming to achieve euvoilaemia with a urine output of >0.5 mL/kg/h based on dry weight.32 33 Accurate fluid balance monitoring and daily weight charts should be commenced. Usually 1–2 L of intravenous fluid will correct most losses and render the patient euvoilaemic. If after 6 h the target urine output is not achieved, or the patient’s clinical parameters are worsening, then escalation to high-dependency care for more invasive monitoring, inotropic support or renal support should be considered.

Hyponatraemia is common in patients with decompensated cirrhosis and can be caused by multiple factors including: hormonal dysregulation of salt and water balance in response to portal hypertension, dehydration, treatment with diuretics, infections and excessive use of hypotonic fluids, such as 5% dextrose.10 Patients with serum sodium levels <125 mmol/L are at risk of seizures. A careful history, clinical examination, medication review and review of other biochemistry are essential to determine the cause of hyponatraemia. Assessment of the patient’s volume status is fundamental, and subjects who are hypovolaemic should be fluid-resuscitated. Patients with hypervolaemic hyponatraemia should be treated with fluid restriction. However, it should be noted that some patients with significant ascites, peripheral oedema and low serum albumin levels who appear hypervolaemic are actually intravascularly deplete, and treatment with intravenous albumin can correct the hyponatraemia.34 Correction of hyponatraemia should be slow (<10 mmol/L increase per 24 h), as rapid changes in serum sodium can precipitate osmotic demyelination syndrome.

**Box 3 Diagnostic criteria for hepatorenal syndrome**

- Cirrhosis with ascites
- Serum creatinine >133 μmol/L
- No improvement of serum creatinine to <133 μmol/L after at least 2 days with diuretic withdrawal and volume expansion with albumin (1 g/kg up to a maximum of 100 g/day)
- Absence of shock
- No current treatment with nephrotoxic drugs
- Absence of parenchymal kidney disease as indicated by proteinuria (>500 mg/day) or microhaematuria (>50 red blood cells per high-power field) and/or a normal renal ultrasonography
Transfusion of red blood cells is indicated when the haemoglobin (Hb) falls below 7 g/dL, aiming for an Hb of 8 g/dL. It has been recently shown that a restrictive blood transfusion strategy (transfuse when Hb <7 g/dL) had lower mortality compared with a liberal strategy (transfuse when Hb <9 g/dL) in patients with cirrhosis and with GI bleeding. The liberal strategy also increased the portal pressure over 5 days, thus increasing the potential for rebleeding. Coagulation abnormalities are common in patients with cirrhosis and may require correction in patients with active bleeding. Although not evaluated in randomised controlled trials, correction of blood clotting abnormalities is recommended by NICE when the international normalised ratio (INR) is >1.5 (fresh frozen plasma), platelet count is <50×10^9/L (platelets) or fibrinogen <1.0 g/L (cryoprecipitate). Consider giving intravenous vitamin K in patients with cirrhosis and with a prolonged prothrombin time, as vitamin K deficiency is common due to malnutrition and chronic cholestasis.

In patients with suspected variceal bleeding, terlipressin (2 mg four times daily) should be administered intravenously as soon as possible to control bleeding. Terlipressin is a vasopressin analogue that reduces portal pressure by inducing splanchnic vasoconstriction and has been shown to improve control of bleeding, as well as reduce all-cause mortality in patients with cirrhosis and with variceal bleeding. Significant adverse events with terlipressin are uncommon, but because of its vasoconstrictor activity it should be used with caution in patients with known or suspected ischaemic heart disease or peripheral vascular disease and those older than 65 years of age, making a baseline ECG mandatory. For patients who have a contraindication to terlipressin (or if terlipressin is unavailable), a continuous intravenous infusion of octreotide is an alternative. Once patients have been adequately resuscitated, endoscopy should be performed at the earliest opportunity (ideally within 6–12 h, but not more than 24 h) to determine the cause of bleeding and perform endotherapy as indicated. Bacterial infections, particularly SBP, are common in patients with cirrhosis in the first 7 days post-GI bleeding, occurring in 25%–65% of patients. Prophylaxis with antibiotics post-GI bleed have been shown to reduce short-term mortality, as well as the risk of rebleeding, septicaemia and SBP. It is, therefore, recommended that patients with cirrhosis and GI bleeding (variceal and non-variceal) receive prophylaxis with a broad spectrum antibiotic, such as cefotaxime or ceftazidime, as per hospital protocol, as soon as possible. Patients with advanced cirrhosis (any two of the following: ascites, severe malnutrition, encephalopathy or jaundice) are at highest risk of developing infection and should receive the antibiotics intravenously. Importantly, there appears to be no increase in the incidence of Clostridium difficile infection in patients receiving antibiotic prophylaxis for variceal bleeding compared with the hospital medical population.

Encephalopathy (delirium)

Encephalopathy is another common complication in patients with cirrhosis. A careful assessment of the cause of encephalopathy should be undertaken looking for causes such as infection, electrolyte disturbance, occult bleeding, constipation or sedative drugs. For patients with grade 4 encephalopathy (coma) consider orotracheal intubation to reduce the risk of developing aspiration pneumonia. In conscious patients, oral lactulose (20 mL–30 mL four times per day) should be administered aiming for 2 soft stools per day. For patients with a reduced conscious level, phosphate enemas or lactulose administered by nasogastric tube should be considered. Consider a CT head examination in patients where the confusion is unexplained to exclude intracranial pathology, such as subdural haematoma.

Other considerations

In the recent UK audit of blood component use in cirrhosis, thrombotic events occurred in 3% of patients. Thromboprophylaxis with low-dose, low molecular weight heparin (LMWH), is therefore recommended to reduce the risk of thrombosis, unless the patient is bleeding or has a platelet count less than 50×10^9/L. Recent evidence suggests that even with apparent abnormalities on blood testing suggestive of a hypocoagulable state (prolonged prothombin time), patients with cirrhosis typically have normal clot-forming capacity provided the platelet count is >50×10^9/L, and some patients with advanced cirrhosis are actually hypercoagulable. Changes in the balance of the hepatic production of procoagulant and anticagulant blood clotting factors in cirrhosis are believed to be responsible for this phenomenon. Although thromboprophylaxis with LMWH has not been specifically trialled in hospitalised patients with decompensated cirrhosis to prevent thromboembolism, a previous study demonstrated that the administration of enoxaparin 4000 µg/day for 48 weeks reduced the risk of portal vein thrombosis, liver decomposition and mortality, and no haemorrhagic side effects were seen.

Malnutrition and nutritional deficiency are common in hospitalised patients with cirrhosis. Moreover, reduced caloric intake in hospitalised patients with cirrhosis is an independent risk factor for short-term mortality. Therefore, a nutritional assessment should be performed early in the admission and, if indicated, nutritional supplementation (oral or nasogastric) should be prescribed. Close monitoring of electrolytes (phosphate, magnesium, potassium and calcium) is mandatory as refeeding syndrome is common. Low electrolyte levels should be corrected promptly.
CONCLUSIONS
The recent NCEPOD report on ARLD highlighted that the management of some patients with decompensated cirrhosis in the UK was suboptimal. In order to address these concerns, we have developed a ‘care bundle’ for patients admitted with decompensated cirrhosis, to ensure the appropriate initial investigations and interventions are conducted at an early stage when specialist advice may not be available. It is hoped that this care bundle will help improve the care of patients admitted to hospital with decompensated cirrhosis across the UK, but this will need to be formally evaluated. This care bundle could also be a focus for audit, nationally regarding the management of patients with decompensated cirrhosis.

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