Emergency Management of Acute on Chronic Liver Disease

Dr AJ Portal

Abstract

Chronic liver disease is becoming more common in the UK. There has been much media coverage due to recent change in licensing laws and celebrity figures suffering from cirrhosis. This review highlights the common complications of cirrhosis that frequently present to the acute physician, focussing on initial presentation and subsequent management, based on the current best available evidence.

Keywords

Chronic liver disease, Diagnosis and Management, Ascites, Spontaneous Bacterial Peritonitis, Alcoholic Hepatitis. Hepatic Encephalopathy

Key Points

- Acute decomposition of chronic liver disease is a common problem that often presents to the acute physician.
- Precipitants of sudden decompensation, such as infection, dehydration and GI bleeding should be sought.
- Early initial resuscitation with fluids and antibiotics often forms the mainstay of treatment.
- Referral to a specialist transplant centre should be considered in cases of recurrent decompensation if clinically appropriate.

Introduction

Chronic liver disease (CLD) is a common condition within the general population. In a population study performed in Italy, 17% of those screened were found to have chronic liver disease.[1] CLD is often clinically silent until cirrhosis is advanced, and significant proportions of patients have normal biochemistry. In the United States, the age adjusted death rate from cirrhosis was 9.2 per 100 000, contributing 1.2% of total deaths.[1] Recent data have shown that the prognosis for patients with chronic liver disease admitted to intensive care units is extremely poor.[2]

Portal hypertension is the main complication of liver cirrhosis and is responsible for the majority of the life threatening complications that occur in cirrhosis, including gastrointestinal bleeding, ascites and spontaneous bacterial peritonitis (SBP), hepatorenal syndrome and hepatic encephalopathy. With the exception of gastrointestinal bleeding, the initial management of these conditions will be discussed in this article, as will those of alcoholic hepatitis and the pulmonary manifestations of liver disease.

Alcoholic hepatitis

It is estimated there are around 3500-7000 deaths from alcoholic hepatitis (and/or cirrhosis) each year in the UK.[3, 4] Prognosis is related to the severity of illness at the time of presentation, with 28 day mortality as high as 50% in severe cases.[5] Overall mortality is 15% at 4 weeks and 39% at 1 year.[6]

Diagnosis

Alcoholic hepatitis typically presents with malaise, jaundice, nausea, vomiting and anorexia. There is frequently fever and neutrophilia. Patients may have been drinking up to the time of admission although some will have stopped shortly before as they become too ill to imbibe. On examination, signs of chronic liver disease are often seen. There may also be tender hepatomegaly with or without ascites. Typical laboratory findings are shown in Box 1. Jaundice is always present and is of grave significance in the alcohol abuser, as it implies active inflammation or end stage cirrhosis. Transaminases are usually only mildly elevated. A transaminitis of greater than 500 U/l should cast doubt on the diagnosis.

Liver biopsy is the gold standard of diagnosis but this is seldom practical in the acute setting. Histopathological features of alcoholic hepatitis include ballooning degeneration, fatty change, inflammatory infiltrate, Mallory's hyaline and fibrosis.

Bilirubin	High (>50 µmol/l)
AST	<200 U/l
ALT	<200 U/l (may be normal)
Albumin	Low
Alkaline phosphatase	Mildly elevated
White Cell Count	High
Hb	Often low
MCV	High
INR	Prolonged (implies cirrhosis)
Platelets	Low
Ferritin	High (acute phase reactant)
IgA	High
Creatinine	Variable

Box 1. Biochemical and haematological findings in alcoholic hepatitis

Dr AJ Portal
MBBS, BSc, MRCP
Clinical Research Fellow
Institute of Liver Studies
Kings College Hospital
Denmark Hill
SE5 9RS

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Score given	1	2	3
Age	<50	≥50	-
WCC(10^9/L)	<15	≥15	-
Urea(mmol/L)	<5	≥5	-
PT ratio/INR	<1.5	1.5-2.0	>2.0
Bilirubin (μmol/l)	<125	125-250	>250

Value between 5 and 12 obtained. Score ≥ 9 asssociated with poor prognosis

Box 2. Glasgow Alcoholic Hepatitis Score

Prognosis

The Maddrey Discriminant Function (DF) is the most widely used tool for assessing severity of disease:

DF = 4.6 x (prolongation of prothrombin time in seconds) + bilirubin (μmol/L)/ 17

A score of >32 is associated with a poor prognosis (mortality 50% at 30 days).[7,8] Other prognostic tools, such as the Glasgow Alcoholic Hepatitis Score (GAHS), have recently been validated against the DF (see Box 2).[9] A GAHS score of > 9 is associated with similarly poor outcome. Both of these scoring systems are useful in deciding treatment options such as corticosteroids.

Treatment

General measures:

- Patients should be admitted unless the disease is mild and abstinence from alcohol can be guaranteed.
- All patients should be fed early, either orally or NG. Thiamine (in the form of pabrinex) should be given twice daily for 5 days to prevent Wernicke-Korsakoff syndrome and provide other vitamin supplementation.[10]
- Patients should be screened for bacterial infections, including ascitic tap to exclude SBP. Broad-spectrum antibiotics should be started early if infection is suspected.
- Renal and liver function should be monitored on a daily basis, as hepatorenal syndrome is extremely common in severe cases.
- Patients should be reviewed by the GI / Hepatology team early in their clinical course.

Specific measures:

Few specific treatments have been shown to influence outcome in CLD. Treatments such as insulin and glucagon, propylthiouracil, colcichine and penicillamine have all been trialled but have failed to show convincing results.

- **Corticosteroids (prednisolone 40mg od).** There has been much debate on the use of steroids in alcoholic hepatitis. A recent review identified that patients with a DF of ≥32 given steroids for one month had a survival benefit at 28 days compared with placebo.[11] An early fall in bilirubin was also a predictor of response to steroids i.e. if no fall at 7 days patients would be unlikely to respond thus the decision to continue should be judged cautiously and balanced against the risk of sepsis.
- **Pentoxyfilline**. Tumour necrosis factor α (TNF α) is a mediator of hepatic inflammation in alcoholic hepatitis. Pentoxifylline (400mg tds) was shown to improve survival by preventing development of hepatorenal syndrome.[12] In those that died, hepatorenal syndrome was far more prevalent in the placebo group.

Ascites and Spontaneous Bacterial Peritonitis

Ascites

Ascites is an extremely common complication of cirrhosis. Patients may present with extreme discomfort, dyspnoea and/or general malaise. For large volume tense ascites paracentesis is the treatment of choice, being both safe and effective.[13] Drainage volumes of ≥5 L is associated with circulatory dysfunction post paracentesis. These patients are at risk of developing hyponatraemia, rapid reaccumulation of ascites and hepatorenal syndrome.[14] This can be prevented by plasma expansion using either colloid or crystalloid for volumes ≤5L and colloid (such as albumin) for volumes ≥5L.[15] A recent pilot study also showed efficacy for use of terlipressin 1mg at 0,8 and 16 hours.[16] The catheter draining the ascites should not be left in situ for more than 12 hours due to the risk of secondary infection.

Spontaneous Bacterial Peritonitis (SBP)

Any patient with ascites presenting acutely to hospital is at risk of SBP. This condition carries a significant morbidity and mortality as it is associated with hepatorenal syndrome, variceal bleeding and hepatic encephalopathy.

SBP may present with signs of sepsis, abdominal pain and ileus. In some patients it may manifest as worsening liver function tests, hepatic encephalopathy or renal failure. In a small number it may be clinically silent.

Diagnosis of SBP depends on an ascitic tap, with a polymorphonuclear (PMN) count of ≥250/mm^3. Inoculation of fluid into blood culture bottles improves the likelihood of identifying the infecting organism, which helps tailor subsequent antibiotic therapy.

The initial treatment of SBP should include:[17]

General measures

- Antipyretics – avoiding NSAIDS (due to nephrotoxicity).
- Intravenous fluid – albumin
- Broad spectrum antibiotics – cefotaxime 2g tds for at least 5 days.

Prevention of complications

- Hepatic encephalopathy – lactulose
- Gastrointestinal bleeding – acid suppression; endoscopic therapy
- Renal dysfunction – cessation of diuretics. Use of albumin to prevent development of HRS and avoidance of unnecessary large volume paracentesis.

The use of albumin and cefotaxime has been shown to improve survival in one study, decreasing mortality from 29% to 10% when compared with cefotaxime alone.[18] Whether other colloids or crystalloids would have had the same effect has yet to be determined by large randomised controlled trials. Therefore at the current time the International Ascites Club advocates the use of albumin as the colloid of choice.[17]

Hepatorenal syndrome

Renal failure commonly occurs in cirrhosis for a variety of reasons. Patients can become hypovolaemic secondary to over-diuresis, suffer a nephrotoxic insult as a result of contrast agents or non steroidal anti-inflammatory drugs or suffer shock secondary to haemorrhage or sepsis. Renal impairment can also develop in the absence of the above and this is known as hepatorenal syndrome (HRS).

Diagnosis

HRS is a functional impairment of renal function and the kidneys are histologically normal. There is severe renal vasoconstriction in the setting of splanchnic vasodilatation and effective systemic hypovolaemia. HRS is a diagnosis of exclusion (see Box 3) and carries a poor prognosis. Type 1 HRS develops suddenly (usually as a result of an acute insult such as sepsis) and carries a median survival of 1.7 weeks without intervention.[19] Type 2 HRS follows a more indolent course and develops over weeks or months, with a median survival of 6-12 months. Referral to a renal transplant centre should be considered.

Management

In the acute setting, cirrhotic patients with renal failure should be assessed as follows:

- Assess for signs of hypovolaemia or shock. If present give plasma expander (colloid or crystalloid).
- Stop all potentially nephrotoxic drugs and diuretics.
- Septic screen and commencement of appropriate antibiotics.
- Urinalysis for proteinuria and/or haematuria, suggesting parenchymal cause for renal dysfunction
- Renal ultrasound to exclude obstruction or parenchymal disease

1. Low glomerular filtration rate, as indicated by serum creatinine greater than 1.5 mg/dl or 24-hour creatinine clearance lower than 40 ml/min
2. Absence of shock, ongoing bacterial infection, fluid losses and current treatment with nephrotoxic drugs
3. No sustained improvement in renal function (decrease in serum creatinine to 1.5 mg/dl or less or increase in creatinine clearance to 40 ml/min or more) following diuretic withdrawal and expansion of plasma volume with 1.5 l of a plasma expander
4. Proteinuria lower than 500 mg/day and no ultrasonographic evidence of obstructive uropathy or parenchymal renal disease

Box 3. Major criteria for diagnosis of HRS.[20]

Terlipressin	0.5mg / 4 hourly IV Increasing to 1mg then 2mg every 3 days if no response. Given until reversal of HRS / maximum 15 days
Albumin	20%. 20g/100ml. 1g/kg body weight day1 Then 20-40g/day thereafter

Box 4. Suggested doses for albumin and terlipressin in HRS[21]

Once HRS has been diagnosed, there are now treatment strategies that have been proven to affect outcome and potentially allow a bridge to transplantation in certain patients. Use of systemic vasoconstrictors with plasma expanders has been shown to reverse renal failure in small prospective trials.[21-25] Terlipressin and albumin are most commonly used in the UK (Box 4). This combination improves GFR and decreases serum creatinine in 60-75% of patients with type 1 HRS.[26]

Prognosis

Outcome is poor in patients with HRS. Survival in type 1 HRS is <10%, a reflection of their end stage liver disease. Those with a higher Child Pugh score, unsurprisingly, fare badly.[28] The ultimate treatment for HRS is liver transplantation in those patients that are suitable. Bridges to transplantation may include the above, transjugular intrahepatic porto-systemic shunt (TIPSS) and molecular adsorbents recycling system (MARS) in selected patients.

Hepatic encephalopathy

Hepatic encephalopathy (HE) affects up to 70% of cirrhotic patients and is defined as:

- an acute confusional state that can lead to the development of coma (acute encephalopathy).
- recurrent episodes of altered mental status in the absence of a precipitant (recurrent encephalopathy) or neurological defects that do not completely reverse (persistent encephalopathy).
- mild cognitive defects only apparent on psychometric or neurophysiological testing (minimal or subclinical encephalopathy).[28]

It is widely believed that HE is caused by failure of the liver to detoxify nitrogenous substances, either through hepatocyte failure or hepatic bypass via portosystemic shunts. These chemicals have an adverse effect on neurotransmission and alter consciousness and behaviour.

Hepatic encephalopathy is graded as follows (based on the West Haven Criteria)[29]:

- **Grade 0 - Clinically normal mental status** but may have minimal changes in memory, concentration, intellectual function, and coordination. Asterixis absent.

- **Grade 1 - Mild confusion, asterixis sometimes detected.** Euphoria or depression; decreased attention span; slowing of ability to perform mental tasks; irritability; and disordered sleep pattern (i.e. inverted sleep pattern).
- **Grade 2 - Drowsiness, lethargy, slurred speech and asterixis.** Gross deficits in ability to perform mental tasks, obvious personality changes, inappropriate behavior, and intermittent disorientation.
- **Grade 3 - Somnolent but rousable.** Unable to perform mental tasks, disorientation about time and place, marked confusion, amnesia, occasional fits of rage, present but incomprehensible speech. Asterixis usually absent.
- **Grade 4 - Coma** with or without response to painful stimuli.

Assessment

In the acute medical setting, cirrhotic patients may present with altered consciousness for a variety of reasons. Non hepatic causes need to be excluded and precipitants of hepatic encephalopathy should be identified and treated (Box 5). Patients should be assessed as follows:

1. Assess ABC and appropriate actions.
2. Disability – assess Glasgow coma score (GCS). If ≤8, may require airway protection.
3. Assess grade of encephalopathy.
4. Identify and treat obvious precipitants ie metabolic disturbance /dehydration, GI bleed or infection.
5. If diagnosis in doubt (i.e. suspicion of intracranial event) CT head may be needed and LP if infection suspected (N.B. taking due note of coagulation parameters and assessing individual risk). Electroencephalogram (EEG) may be useful in ruling out other causes but is usually impractical in the emergency setting.
6. Keep well hydrated and, if necessary, place NG tube.

Treatment

- **Provision of supportive care.** Close observation and careful nursing are needed to prevent injury to the patient. Nutrition should be started early and if the patient is unable to swallow an NG tube should be placed. Protein restriction worsens pre-existing malnutrition and is therefore not recommended.[28] Zinc deficiency is common in malnourished patients and administration of oral zinc supplements improves the activity of the urea cycle in experimental models.[30]

- **Reduction of nitrogenous products and absorption from gut.** Lactulose is the most commonly used non absorbable disaccharide. It changes the colonic pH and favours ammonia uptake by bacteria. The aim is to produce 3 soft stools per day. Antibiotics can also be used to decontaminate the gut. Choices in the acute setting include neomycin and metronidazole. Side effects can occur. A large recent meta-analysis of lactulose failed to show that it improved mortality.[31] It was noted that there were insufficient quality trials to support use of lactulose and that antibiotics may be more effective. However, until further evidence is forthcoming, lactulose remains the first line of treatment.

GI Bleeding – exclude melaena. May need NG tube.
Infection – cultures including ascites (SBP) and broad spectrum antibiotics
Metabolic - renal failure, alkalosis (facilitates conversion of NH_4^+ to NH_3), dehydration, over-diuresis.
Constipation (increases intestinal production and absorption of ammonia)
Psychoactive medications – benzodiazepines, opioids, sedatives.
Excessive dietary protein – rare cause of hepatic encephalopathy.

Box 5. Precipitants of hepatic encephalopathy – and treatment

Hepatic encephalopathy occurs in a large number of cirrhotic patients. In a certain subgroup, transplantation may also be an option and development of hepatic encephalopathy should trigger referral for transplant assessment once the patient has recovered from the acute episode.

The Breathless Patient with CLD

Cirrhotic patients commonly present to hospital with shortness of breath. This may reflect co-existent pathology, such as pulmonary embolism, respiratory tract infection or pulmonary oedema. There are, however certain conditions more specific to cirrhotics, of which the acute physician should be aware.

Ascites and hepatic hydrothorax

Tense ascites may be complicated by dyspnoea due to diaphragmatic splinting. Even in the presence of SBP, this would be an indication for paracentesis if shortness of breath is severe.

10% of patients with ascites will develop a hepatic hydrothorax (>500ml of fluid within the pleural cavity in the absence of cardiopulmonary disease).[32] This is thought to be due to small defects in the diaphragm that allow flow from the abdomen to the thorax. In 2/3 of cases the effusion will be right sided.

Treatment is as for ascites. Initially, sodium restriction and diuretics should be commenced unless creatinine is elevated or sodium < 130mmol/L. If there is severe respiratory compromise, then thoracocentesis should be performed. Spontaneous bacterial empyema is diagnosed if the fluid has a neutrophil count of ≥500/mm^3 or a count of ≥250/mm^3 combined with a positive culture. Any patient with a hydrothorax presenting with fever, pleuritic pain, encephalopathy or unexplained deterioration in renal function should have this diagnosis excluded. Chest drain insertion is contraindicated in these patients, who should be treated with broad spectrum antibiotics. TIPSS may be required.

Portopulmonary hypertension and Hepatopulmonary syndrome

The term *portopulmonary hypertension* is used to describe the development of pulmonary hypertension in association with portal hypertension with or without liver disease. It manifests itself as right sided heart failure and usually results in worsening ascites and peripheral oedema in the cirrhotic patient. Hepatopulmonary syndrome is a progressive debilitating complication of end stage liver disease, diagnosed by the presence of cirrhosis, hypoxaemia and pulmonary vasodilatation. Patients may be clubbed, cyanotic and have dyspnoea, platypnoea or orthodeoxia. Pulmonary vasodilatation is usually diagnosed by double contrast echo or 99mTC macro-aggregated lung perfusion scan. Both of these conditions may present acutely, and if other more common diagnoses are excluded should promote prompt referral to a specialist. Both conditions are now considered indications for consideration of orthotopic liver transplantation.

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