Diagnosis and management of ascites and hepatorenal syndrome (acute kidney injury) in cirrhosis

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Abstract

Ascites is the most common complication of cirrhosis and represents a watershed moment, with patients' median survival falling from >12 years for compensated cirrhosis to approximately 2 years. Treatment aims to reduce sodium intake and increase renal sodium excretion with the aldosterone antagonist spironolactone, starting at 100 mg daily; 60% respond. Renal dysfunction affects as many as 20% of hospitalized patients and is a strong predictor of mortality. Liver transplantation represents the best treatment for hepatorenal syndrome (HRS) yet is rarely available, and a combination of vasoconstrictors and albumin represent the mainstay of treatment. Terlipressin is the most widely used vasoconstrictor, leading to HRS resolution in >50% of patients. The role of transjugular intrahepatic portosystemic shunt insertion or renal replacement therapy for HRS remains uncertain, with further studies needed. These patients are very fragile with a high mortality. Many patients require regular ascitic drainage every 2–4 weeks that is best achieved in a day-case setting. Diuretic medication requires frequent dose adjustment because of coexistent renal impairment. Where ascites persists, liver transplantation or TIPPS should be considered. Finally, given the poor prognosis for many patients, it is important to address end-of-life planning and palliation where appropriate.

Keywords Albumin; diuretics; infection; MRCP; splanchnic vasodilatation; systemic inflammation; terlipressin

Key points

- Unlike other common causes of death, mortality from liver disease continues to rise, with alcohol and obesity the major driving factors since the development of successful treatments for chronic hepatitis C
- Ascites is the most common complication of liver cirrhosis, and patients who develop this often have a median survival of 2 years
- All patients with ascites should be considered for liver transplant referral
- Many patients respond well to salt restriction and diuretic medication, although a number require frequent paracenteses or transjugular intrahepatic portosystemic shunt insertion
- Development of renal dysfunction is a very serious complication with a high short-term mortality; cessation of diuretic medication, treatment with human albumin solution and vasoconstrictors (usually terlipressin) are first-line management in most cases

How common is liver disease?

Liver disease is increasing in prevalence worldwide, with 60,000 people in the UK estimated to have cirrhosis. In contrast to other common diseases in the UK, mortality rates have increased 400% since 1970 and it is now the third most common cause of premature death. Indeed, liver disease is predicted shortly to overtake ischaemic heart disease as the leading cause of working life years lost in the UK. Alcohol remains the primary driver for the vast majority of cirrhosis-related hospital admissions, with a median age of presentation in the early 50s, but obesity is rapidly rising and non-alcoholic steatohepatitis (NASH) will continue to maintain the increasing liver disease mortality. There have, however, been great successes, with the extraordinary effectiveness of oral antiviral regimens against hepatitis C virus leading to campaigns to identify and treat all patients with the virus.

Ascites is the most common complication of cirrhosis or decompensation events, with 5–10% of patients with uncomplicated (compensated) liver cirrhosis per year developing this. Decompensation represents a watershed moment for patients with cirrhosis, with the median survival falling from >12 years for compensated cirrhosis to approximately 2 years.

Definitions

Ascites is the accumulation of fluid within the peritoneal cavity with a volume of at least 25 ml, although >14 litres can collect. Over 75% of cases result from liver cirrhosis and portal hypertension. Other causes include pancreatitis, malignancy or tuberculosis.

Renal dysfunction is common in individuals with ascites, affecting as many as 20% of hospitalized patients, and is a strong predictor of mortality. Renal dysfunction in cirrhosis has been defined as a serum creatinine (sCr) >133 micromol/litre (1.5 mg/dl), and acute kidney injury (AKI) as a 50% increase of sCr to >133 micromol/litre.[1] The main differential diagnoses are hepatorenal syndrome (HRS) and acute tubular necrosis (ATN); if there is no recent use of nephrotoxic drugs, no haematuria, no significant proteinuria, no shock and no structural renal abnormalities, the diagnosis is HRS.

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Classically, HRS was considered a functional renal failure caused by intra-renal vasoconstriction resulting from arterial vasodilation and arterial hypotension. For many years, type 1 HRS was defined as rapidly progressive renal failure, with a doubling of sCr to >221 micromol/litre (>2.5 mg/dl) or a halving of creatinine clearance to <20 ml/minute in <2 weeks. Type 2 HRS is slower in onset, not associated with an obvious precipitant and classically defined by an increase in sCr to >133 micromol/litre (>1.5 mg/dl) or a reduction in creatinine clearance to <40 ml/minute and a urine sodium <10 micromol/litre. Most patients who go on to develop type 2 HRS have diuretic-resistant ascites beforehand, in which the kidneys are unable to excrete sufficient sodium to clear ascites despite diuretic medication.

More recently, HRS has been recognized as consequent to haemodynamic *and* inflammatory changes, and it has been acknowledged that AKI can occur in those with underlying chronic kidney disease. Therefore, in the revised classification, type 1 HRS corresponds to HRS-AKI and type 2 corresponds to renal impairment in those who fulfil the criteria of HRS but not AKI.

Epidemiology

The aetiology of liver disease differs according to geographical location. In the developed world, it is most often the result of obesity, non-alcoholic fatty liver disease or NASH, and alcohol excess. In the developing world, chronic viral infection with either hepatitis B or hepatitis C is the leading cause of liver mortality. Globally, about half a billion people suffer from chronic viral hepatitis.

Pathology and pathogenesis

Ascites: splanchnic arterial vasodilation is the major underlying cause of increased water and sodium retention in patients with cirrhosis and ascites. Portal hypertension (defined as a hepatic venous pressure gradient (HVPG) >5 mmHg and clinically significant once HVPG is >10–12 mmHg) causes the release of vasodilators (e.g. nitric oxide, carbon monoxide) in the splanchnic circulation. This reduces the effective circulating volume (ECV), activating baroreceptors and the sympathetic nervous system, renin–angiotensin–aldosterone system (RAAS) and non-osmotic secretion of vasopressin. Cardiac output increases to compensate for the reduced ECV, but as liver disease progresses the heart is unable to cope with the further reduction in ECV, and subsequent activation of the RAAS increases renal reabsorption of sodium and water, leading to the appearance of ascites. The hyperactivation of the sympathetic nervous system triggers an increase in proximal tubular absorption of sodium and water, further increasing ascites. Pathological translocation of bacteria or bacterial products from the gut to the systemic circulation can also contribute by stimulating release of proinflammatory cytokines, leading to additional release of nitric oxide and carbon monoxide, increasing splanchnic arterial vasodilation even further.

Hepatorenal syndrome: pathophysiology involves both hypoperfusion leading to renovascular dysfunction and systemic inflammation caused by bacterial translocation. Increased production of proinflammatory cytokines is associated with renal dysfunction in spontaneous bacterial peritonitis (SBP) and acute-on-chronic liver failure.[2] These processes can drive mitochondrially mediated metabolic downregulation of the kidneys. In patients with severe cholestasis, there can be additional renal tubular injury from excessive bile salts.

Course of the disease

The natural history of cirrhosis is characterized by an asymptomatic course until increasing portal pressure and worsening liver function lead to clinical signs. Patients with compensated cirrhosis generally have a good quality of life and the disease can remain undetected for many years. Decompensation is characterized by the development of ascites, gastrointestinal bleeding, encephalopathy and jaundice. This marks a significant change in disease trajectory, often with rapid progression that is worsened by an increased incidence of bacterial infections, which, when complicated by AKI, with or without HRS, have a particularly poor prognosis.

Diagnosis

Abdominal swelling can develop over days or several weeks. The presence of fluid is confirmed clinically by demonstrating shifting dullness. Precipitating factors include continued excessive alcohol use, a high-sodium diet, infection, development of a hepatocellular carcinoma or splanchnic vein thrombosis. Mild abdominal pain and discomfort are common but, if more severe, should raise the suspicion of SBP. Respiratory distress and difficulty eating accompany tense ascites. Patients can also have non-specific symptoms, particularly weakness, anorexia and fatigue. Other specific symptoms include:[3]

- peripheral oedema
- pleural effusion (usually right-sided), which is infrequently found and arises from the passage of ascites through congenital diaphragmatic defects
- haematemesis and melaena from gastrointestinal haemorrhage
- pruritus caused by cholestasis
- gynaecomastia, loss of libido and amenorrhoea resulting from endocrine dysfunction
- confusion and drowsiness caused by neuropsychiatric complications (portosystemic hepatic encephalopathy).

Investigations and differential diagnoses

A diagnostic aspiration of 10–20 ml of fluid is mandatory to undergo the following:

- cell count: a neutrophil count >250 cells/mm^3 is diagnostic of an underlying (usually spontaneous) bacterial peritonitis
- Gram stain and culture
- protein measurement: a high serum–ascites albumin gradient of >11 g/litre suggests portal hypertension, and a low gradient <11 g/litre is associated with non-liver disease-related abnormalities of the peritoneum, such as neoplasia (Table 1)
- cytology: to search for malignant cells
- amylase: to exclude pancreatic ascites
- liver and renal tract ultrasonography: to examine liver parenchyma and vascularity and exclude renal tract obstruction.

The serum–ascites albumin gradient

High serum–ascites albumin gradient (>11 g/litre)

- Portal hypertension, e.g. hepatic cirrhosis
- Hepatic outflow obstruction
- Budd–Chiari syndrome
- Hepatic veno-occlusive disease
- Tricuspid regurgitation
- Constrictive pericarditis
- Right-sided heart failure

Low serum–ascites albumin gradient (<11 g/litre)

- Peritoneal carcinomatosis
- Peritoneal tuberculosis
- Pancreatitis
- Nephrotic syndrome

Source: Modified from Chung RT, Iafrate AJ, Amrein PC, et al. Case records of the Massachusetts General Hospital. *New Engl J Med* 2006; **354:** 2166–75.

Table 1

As many as 25% of patients have a cause other than cirrhosis, and the combination of ascitic fluid protein count, liver blood tests and abdominal imaging is able to differentiate this in most cases (Table 1). Liver cirrhosis sometimes coexists with other causes such as metastatic malignancy. Patients can also have intrinsic renal disease with or without HRS-AKI, and this will become more common as NASH increases in prevalence, with patients also affected by hypertension and type 2 diabetes.

Two prospective studies comprising >100 patients each confirmed low ascitic fluid protein concentration as an independent predictor of SBP, a dreaded complication of ascites.[1] Ascitic fluid protein content is believed to mirror host opsonization activity, SBP incidence rates within 2 years of sampling being 20–25% for concentrations <1 g/dl, and <1% for concentrations >1.5 g/dl. These data have, however, been challenged by two recent post-hoc analyses of three large cohorts of hospitalized patients with decompensated cirrhosis that suggested ascitic protein count did not correlate with SBP risk. A UK large-scale clinical trial will shortly start to determine whether primary antibiotic prophylaxis with co-trimoxazole can prevent SBP in patients with a low ascitic fluid protein count.

Management

Ascites

It is important to consider the underlying cause of cirrhosis. Administration of the new direct-acting anti-hepatitis C agents can lead to resolution of ascites, as does >6 months' alcohol cessation in a significant number of patients if this is the primary driver. Effective treatments for NASH are still awaited. Otherwise, treatment is aimed at reducing sodium intake and increasing renal sodium excretion, producing a net reabsorption of fluid from the ascites into the circulating volume. The maximum rate at which ascites can be mobilized is 500–700 ml in 24 hours. It is possible to reduce sodium intake to 40 mmol in 24 hours and maintain a palatable diet with adequate protein and calorie intake. Many drugs, especially penicillins and cephalosporins, contain significant amounts of sodium (up to 50 mmol daily), and sodium-retaining drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids should be avoided. Fluid restriction is unnecessary.

The diuretic of choice is the aldosterone antagonist spironolactone, starting at 100 mg daily. Around 60% of patients respond on this regimen, but the spironolactone dose can be gradually increased to 400 mg daily if necessary, providing there is no hyperkalaemia. Urinary sodium can be used to titrate the dose. The loop diuretic furosemide 40 mg is added if the response is poor; however, this drug has several potential disadvantages, including hyponatraemia, hypokalaemia and volume depletion. Chronic administration of spironolactone can produce gynaecomastia, and if this occurs then amiloride should be substituted at 5–10 mg/day. Diuretics should be temporarily discontinued in the event of hyponatraemia (sodium <128 mmol/litre), a rise in sCr, hyperkalaemia or worsening encephalopathy. Vaptans – vasopressin V_2-receptor antagonists that increase free water clearance – have a small beneficial effect on hyponatraemia and ascites but do not affect mortality, complications of cirrhosis or renal failure; their routine use in cirrhosis cannot be recommended.

Paracentesis (drainage of ascites) relieves symptomatic tense ascites. The main complications are hypovolaemia and renal dysfunction (post-paracentesis circulatory dysfunction), which is more likely with >5 litres removal and worse liver function. This is prevented by infusing albumin (8 g/litre of ascitic fluid removed). In practice, up to 20 litres can be removed over 4–6 hours, with albumin infusion.

Renal dysfunction

Several causative factors for renal dysfunction should be avoided (e.g. nephrotoxic drugs, NSAIDs, diuretic-induced excessive diuresis) or treated rapidly (e.g. infections, gastrointestinal bleeding). Contrast imaging should be performed cautiously in patients with ascites. Finally, the increase in intra-abdominal pressure associated with tense ascites can lead to AKI.

The most common cause of AKI in hospitalized patients with decompensated cirrhosis is pre-renal, accounting for approximately 70% of cases. Intra-renal AKI is predominantly ATN, and post-renal AKI is uncommon in cirrhosis. Given that most cases of pre-renal AKI are resolved by volume expansion and post-renal AKI is uncommon, the key is to differentiate HRS-AKI from ATN. However, renal biopsy is rarely performed and the distinction between HRS-AKI and ATN is difficult. Novel biomarkers have recently emerged in this setting and urinary neutrophil gelatinase-associated lipocalin appears the most promising.

The cause of AKI must be investigated urgently to prevent progression, and management commenced immediately. Diuretics and β-adrenoceptor blockers should be discontinued and, most importantly, volume replacement is required in accordance with the cause and the severity of the fluid loss. Patients with diarrhoea or excessive diuresis can be given crystalloids, and those with gastrointestinal bleeding given packed red blood cells to maintain the haemoglobin at 70–90 g/litre. In patients with AKI and tense ascites, therapeutic paracentesis associated with albumin infusion improves renal function. If no obvious cause and HRS-AKI is of AKI stage >1A (increase of sCr 2-fold from baseline), 20% albumin solution at a dose of 1 g/kg of body weight (to a maximum of 100 g) for 2 consecutive days is recommended.

Liver transplantation represents the best treatment for HRS but is rarely available, and a combination of vasoconstrictors and albumin represents the mainstay of treatment. Vasoconstrictors counteract splanchnic arterial vasodilation, and albumin counteracts the reduction in ECV as well as improving cardiac contractility; a dose of 20–40 g/day is recommended. Terlipressin is the most widely used vasoconstrictor, leading to HRS resolution in >50% of cases.[4] Alternatives are the α-adrenergic drug midodrine given orally (2.5 mg up to 12.5 four times a day) with subcutaneous octreotide (125–250 micrograms twice a day) or a continuous intravenous infusion of norepinephrine (0.1–1 mg/hour).

Studies have shown terlipressin to be superior to midodrine plus octreotide and norepinephrine and terlipressin to be equivalent for HRS reversal and 1-month survival. A Cochrane analysis demonstrated a beneficial effect on mortality with terlipressin but an increased risk of serious cardiovascular adverse events. A continuous intravenous infusion of terlipressin was associated with a lower rate of adverse effects than intravenous boluses. Treatment with vasoconstrictors plus albumin should be continued until sCr falls to <133 micromol/litre. HRS recurs in 20% of patients after treatment withdrawal, but re-treatment is often effective.

Transjugular intrahepatic portosystemic shunt (TIPSS) insertion has good theoretical reasons for being an effective treatment for HRS as it reduces portal hypertension and increases cardiac output, improving renal perfusion and sodium and water excretion. In a retrospective matched cohort analysis, TIPSS placement was associated with significant improvement in kidney function compared with serial large-volume paracentesis. This was most prominent in participants with baseline estimated glomerular filtration rates <60 ml/minute/1.73 m^2. Although some patients with HRS can benefit from a TIPSS, this must be balanced against the high risk, particularly for development of hepatic encephalopathy.

The limited data available for the role of renal replacement therapy (RRT) in patients with HRS have not demonstrated a survival benefit and this remains contentious because of the grim prognosis for these patients.[5] For patients on the transplant waiting list, RRT is an appropriate treatment for volume overload, severe metabolic acidosis or hyperkalaemia. Continuous RRT carries a lower risk of hypotension than intermittent haemodialysis, but the best RRT method in cirrhosis is unknown. In non-responders to medical treatment who are candidates for liver transplantation, a simultaneous kidney–liver transplantation can be considered if renal dysfunction is thought unlikely to reverse. In patients not eligible for liver transplantation, the decision for RRT should be made individually and consideration given where appropriate for palliative management.

Prognosis, explanation to the patient and follow-up

Patients with complicated ascites represent a very fragile population with a high mortality and a high risk of early readmission. Patients in whom alcohol is the predominant cause need urgent cessation therapy with a realistic opportunity for ascites to resolve. Many patients require regular ascitic drainage every 2–4 weeks, best achieved in a day-case setting. Diuretic medication requires frequent dose adjustment because of coexistent renal impairment. In patients with persistent ascites, liver transplantation or TIPPS should be considered.

A peritoneum–bladder conduit, by means of an implantable, rechargeable, battery-powered pump (Alfapump®), has been developed for use in patients with resistant ascites. This removes ascites from the peritoneal cavity into the urinary bladder, to be eliminated in the urine. Early studies have shown a reduction in the need for large-volume paracentesis, but several complications, including pain and infection, occurred.

Patients require surveillance for the development of hepatocellular carcinoma with 6-monthly ultrasonography and screening endoscopy for varices. Finally, given the poor prognosis for many patients, it is important to address end-of-life planning and consider palliative measures where appropriate.

Prevention of hepatorenal syndrome with human albumin solution

A large randomized controlled trial in patients admitted to hospital with SBP showed that treatment with 20% albumin (1.5 mg/kg^{-1} on day 1, and 1 mg/kg^{-1} on day 3) prevented HRS-AKI, although the control group were given no fluid. A more recent trial of the same regimen of albumin in patients with infections other than SBP was stopped early because of the increased incidence of pulmonary oedema in the treatment group. The recent ANSWER trial of weekly *outpatient* albumin infusions (200 ml of 20% albumin) compared with standard medical therapy (no fluids) demonstrated a reduced incidence of renal dysfunction and HRS type 1 during the 18-month trial period. However, weekly outpatient albumin infusions represent a substantial logistical challenge and this approach has not yet been introduced in the UK.

Future directions

The management of patients with ascites with or without renal dysfunction is complex, currently hospital-based and highly resource-intensive. The development of new models of specialist care that are outpatient-based and prevention-focused are urgently required to improve the survival and quality of life in this increasing group of patients. ◆

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FURTHER READING

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 53-year-old man presented with a 5-day history of a painful swollen abdomen. He had a long history of excessive alcohol consumption.

On clinical examination, he was jaundiced and there was tense ascites, but the liver was not palpable.

Investigations

- Serum creatinine 145 micromol/litre (60–110)
- Ascitic tap showed an elevated polymorphonuclear cell count of >750/mm^3

Question 1

What is the most important immediate management step after antibiotic treatment?

A. Only administer intravenous fluids if the mean arterial pressure falls below 70mmHg
B. Administer fluid resuscitation using crystalloids
C. Administer fluid resuscitation with 5% human albumin solution
D. Administer fluid resuscitation with 1.5 mg/kg human albumin solution
E. Administer fluid resuscitation with a synthetic colloid such as hydroxyethylstarch or gelatin

Question 2

A 45-year-old man presented with symptoms and signs of alcoholic hepatitis. After 24 hours he deteriorated with a reduction in his conscious level.

Investigation

- Creatinine 175 micromol/litre (60–110) (100 on admission)

What is the next best step in his management?

A. Commence terlipressin and 20% human albumin solution
B. Organize ultrasound of the renal tract and ask for a renal opinion
C. Commence diuretic medication
D. Organize a contrast-CT scan of the abdomen
E. Commence antibiotics

Question 3

A 65-year-old man presented for review after admission for spontaneous bacterial peritonitis on a background of alcoholic cirrhosis. He was well but still has some residual swelling of the abdomen. On clinical examination there was a small amount of free fluid detectable in the abdomen.

What is now the most appropriate management action?

A. He should be prescribed secondary antibiotic prophylaxis
B. He should aim for a salt free diet
C. He should be given high dose spironolactone for 6 months
D. He should be referred for liver transplant assessment
E. He should restrict his fluid intake to 1.5 litres/day to control his ascites