Management of cirrhotic ascites

Liver disease places a growing burden on health-care systems, causing significant morbidity and mortality. Ascites is the most common complication of cirrhosis (Ginés et al, 1987) and a frequent manifestation of end-stage liver disease. The most common causes of cirrhosis are alcoholic liver disease, non-alcoholic fatty liver disease and chronic viral hepatitis (Blachier et al, 2013). Rising obesity rates mean non-alcoholic fatty liver disease is now the most common liver problem in the western world (Kim and Younossi, 2008), affecting an estimated 20–30% of the population, so ascites is likely to become more common in the future.

However, not all patients with ascites are cirrhotic, other causes including malignancy (10%), heart failure (3%), tuberculosis (2%) and pancreatitis (1%) (Moore and Aithal, 2006). In 5% of patients more than one factor is responsible.

About 60% of those with cirrhosis develop ascites within 10 years (Ginés et al, 1987). Ascites conveys a poor prognosis, with 40% mortality at 1 year, and 50% mortality at 2 years (Guevara et al, 2005). This article focuses on the investigation and management of ascites in patients with cirrhosis; the accompanying article is focussed more specifically on history taking and the clinical examination (Chavda and Bloom, 2015). These patients are often present during the MRCP PACES exam.

Investigations

It is important to emphasize that sepsis is a very common cause of hepatic decompensation. Blood cultures, an ascitic tap, mid-stream urine analysis and chest X-ray are all required in patients in whom sepsis is suspected.

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Blood tests

Check liver function, urea and electrolytes, full blood count, coagulation profile, inflammatory markers and perform a group and save. A lab glucose or BM to check for evidence of the cause of liver disease (hyperglycaemia suggests diabetes which is associated with non-alcoholic fatty liver disease) and as a marker of severity of liver failure (hypoglycaemia).

Urine tests

Urinalysis excludes infection (patients with cirrhosis have suppressed immunity).

Ascitic fluid

A diagnostic paracentesis is the most rapid and cost-effective method of determining aetiology (Runyon, 1994). This should be performed on all those presenting with ascites for the first time, and in those who have acute hepatic decompensation in order to appropriately treat them.

Urgent microscopy should be performed. An ascitic neutrophil count of >250 cells/mm^3 (or a total white cell count of >500 cells/mm^3) is diagnostic of spontaneous bacterial peritonitis.

- Aerobic and anaerobic blood culture bottles should be inoculated with 10 ml ascites each as this greatly increases the yield for microbial culture in patients with infected ascites (see below)
- Send about 100 ml ascitic fluid for cytological investigations if malignant ascites is suspected, which will be diagnostic in up to two-thirds of cases
- Determine the serum albumin–ascites gradient (see below).

Patients with cirrhosis are at an increased risk of refractory ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, hyponatraemia and the hepatorenal syndrome. Around 10–15% of patients with cirrhotic ascites develop spontaneous bacterial peritonitis, which should be identified early as it has an associated high mortality.

The serum albumin–ascites gradient is derived by calculating the difference between serum and ascitic fluid albumin concentrations. The serum albumin–ascites gradient should be <11 g/litre as the serum hydrostatic pressure is balanced by the serum oncotic pressure. In uncomplicated ascites, albumin is unable to leave the circulatory system owing to its molecular size, therefore any rise in serum albumin–ascites gradient is the result of fluid moving into the peritoneal cavity diluting resident albumin.

In cirrhotic ascites, this occurs as a result of portal hypertension, resulting in a serum albumin–ascites gradient >11 g/litre (Moore and Aithal, 2006; Runyon, 2013). Other causes affecting the serum albumin–ascites gradient are shown in *Table 1*. Ascites can also be classified as transudative (<25 g protein/litre) or exudative (>25 g protein/litre), but the serum albumin–ascites gradient is a more specific way of characterizing ascites, with 97% accuracy (Moore and Aithal, 2006).

Imaging

Chest X-ray may be useful to exclude intercurrent sepsis. Ultrasound can be used to confirm the presence and degree of ascites. It can assess the liver parenchyma, the spleen, the biliary tree, the portal and hepatic veins. It facilitates diagnostic or therapeutic paracentesis by identifying easily accessible areas of fluid; this is useful in patients with previous failed paracentesis or severe coagulopathy.

Management

The grading of ascites is important when determining management:

- Mild – only detectable via ultrasound examination
- Moderate – ascites leading to moderate symmetrical distension of the abdomen
- Severe – ascites leading to marked abdominal distension.

Patients with uncomplicated, moderate ascites can be managed as an outpatient (Moore and Aithal, 2006; Runyon, 2013). Treatment is aimed at resolving sodium retention by creating a negative sodium balance.

Around 5–10% of patients show early recurrence of ascites after paracentesis or are poorly controlled despite maximal medical therapy, termed refractory ascites. They can be further divided into diuretic resistant, with no resolution despite salt restriction (<90 mmol/day) and intense diuretic therapy (spironolactone 400 mg/day and furosemide 160 mg/day) for at least 1 week; or diuretic intractable, with complications precluding optimal diuretic use (Moore and Aithal, 2006).

Conservative management

Alcohol cessation

It is important to treat the underlying cause of liver disease. In cases of alcohol-related disease, alcohol cessation is imperative. Ascites can disappear or respond better to medical therapies with abstinence (Runyon, 2013).

Bed rest (not recommended)

It has been suggested that diuretic use with bed rest maximizes fluid loss by minimizing activation of the renin–angiotensin–aldosterone and sympathetic nervous systems (Ginés et al, 1997). However, studies do not demonstrate that it increases the efficacy of diuretics or decreases hospital stay (Moore and Aithal, 2006).

Salt restriction (not used in isolation)

A negative sodium balance can be achieved in 10% of cases of cirrhotic ascites by dietary measures, in particular at presentation (Bernardi et al, 1993). Sodium restriction has been associated with a lower diuretic requirement, faster resolution of ascites and lower hospitalization rates (Gauthier et al, 1986). Dietary salt intake should be restricted to approximately 90 mmol/day (5.2 g salt) (Moore and Aithal, 2006) – more severe restriction could jeopardize nutritional status (Runyon, 2013). The following measures can be used to assist sodium loss:

- No added salt diet
- Avoidance of pre-packaged meals and soups
- Dietetic advice
- Information leaflets
- Signs over the bed.

Compliance can be measured by urinary sodium analysis (see below). Poor dietary compliance is associated with hospital re-admission.

Fluid restriction (controversial)

Experts agree that there is insufficient evidence for water restriction in uncomplicated ascites (Moore and Aithal, 2006, Runyon, 2013). There is controversy over the management of those with hyponatraemia and ascites. Cirrhotic dilutional hyponatraemia occurs as a result of an expanded extracellular fluid volume with increased urinary sodium retention. It is often mild, chronic and not usually a cause of morbidity.

There is no clear evidence for the sodium threshold at which fluid restriction should be enforced, although this is often done when Na+ <120–125 mmol/litre (Runyon, 2013). Cirrhotic patients rarely suffer from symptoms until Na+ <110 mmol/litre, as hyponatraemia develops gradually with little risk of brain damage (Ginès and Cárdenas, 2008); rapid correction can be dangerous and cause demyelination (Runyon, 2013).

Table 1. Interpreting serum ascitic–albumin gradient

High serum ascitic–albumin gradient (>11 g/litre)	Cirrhosis (81%): alcohol (65%), viral (10%), cryptogenic (6%)	
	Heart failure (3%)	
	Pancreatic disease (1%)	
	Rare causes (3%)	Meig's syndrome
		Vasculitis
		Hypothyroidism
		Dialysis Budd–Chiari syndrome
		Constrictive pericarditis
		Nephrotic syndrome
		Serositis
		Spontaneous bacterial peritonitis
Low serum ascitic–albumin gradient (<11 g/litre)	Peritoneal carcinomatosis or metastases (10%)	
	Tuberculosis (2%)	

From Runyon (1992)

Medical management

Diuretics

Only 10% of patients respond to sodium restriction; the aldosterone antagonist spironolactone increases the response to 65% and loop diuretics to 85% (Gerbes, 1993).

The European Association for the Study of the Liver (2010) guidelines recommend an aldosterone antagonist (e.g. spironolactone) for the first presentation of ascites. The initial dose is usually 100 mg/day, increased stepwise every 3–5 days to 400 mg daily, while monitoring serum electrolytes and weight (Moore and Aithal, 2006). If this does not sufficiently control ascites then a loop diuretic should be added (e.g. furosemide starting at 40 mg/day, increased stepwise maximally to 160 mg/day). A ratio of spironolactone to furosemide of 100 mg:40 mg should maintain potassium within the normal range (Runyon, 2013).

Caution must be taken using diuretics in patients with electrolyte disturbances and/or renal failure. In patients without peripheral oedema, medication should be titrated to provide a maximum fluid loss of 0.5 litre/day or 0.5 kg/day. In those with peripheral oedema a maximum of 1 litre/day or 1 kg/day is suggested (Shear et al, 1970). Urinary sodium does not need to be routinely measured but can be used to assess response to diuretics when weight loss is not within the desired range (Runyon, 2013) (*Figure 1*).

Complications of diuretics: The majority of diuretic-associated complications (*Table 2*) occur during the first month (Angeli et al, 2010) and therefore serum creatinine, potassium and sodium levels should be monitored closely during this time (*Table 3*).

Diuretic-induced renal impairment usually occurs as a result of intravascular volume depletion secondary to over-diuresis (Shear et al, 1970). Diuretic use can also

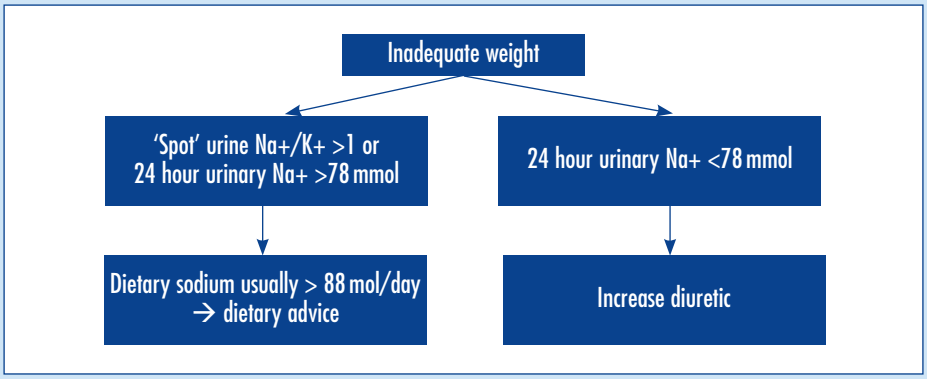

Figure 1. Assessment of response to diuresis.

precipitate hepatic encephalopathy but the exact mechanism is unclear. Diuretics should be withheld in those with acute gastrointestinal haemorrhage, hepatic encephalopathy or renal dysfunction (Runyon, 2013). Hyponatraemia commonly occurs. According to European Association for the Study of the Liver (2010) guidelines, diuretics should be stopped temporarily with Na+ <120–125 mmol/litre; aldosterone agonists stopped when K+ >6 mmol/litre and loop diuretics when K+ <3 mmol/litre. Amiloride 10–40 mg/day can be used as an alternative for men with tender gynaecomastia.

Table 2. Common complications with diuretics

Spironolactone	Hyperkalaemia
	Gynaecomastia
	Reduced libido
Furosemide	Hypokalaemia
	Hyperuricaemia
	Hypomagnesaemia
Both	Hyponatraemia
	Renal impairment
	Muscle cramps
	Hepatic encephalopathy

Table 3. Reasons to reassess diuretic use

Recurrent hepatic encephalopathy
Sodium <120–125 mmol/litre
Creatinine >150–180 μmol/litre
Potassium < 3 or > 6 mmol/litre

From Moore and Aithal (2006), Runyon (2013)

Vaptans

Studies have been performed on a group of drugs calls vaptans (vasopressor receptor analogues) which correct mild hyponatraemia. Some (e.g. tolvaptan, saravaptan) are unsafe in cirrhosis (Wong et al, 2012; Runyon, 2013) and in general they are rarely used.

Paracentesis

Large volume ascites is best managed with large volume paracentesis (Moore and Aithal, 2006). Ultrasound is mandatory in patients with previous failed attempts or severe coagulopathy. Large volume paracentesis should be performed under strict sterile conditions in a single session (Moore and Aithal, 2006). It is advised to leave an ascitic drain in for <6 hours to minimize the risk of spontaneous bacterial peritonitis (Runyon, 2013). There is no need to clamp the drain.

Patients require diuretics and sodium restriction after large volume paracentesis to prevent re-accumulation in those that are diuretic sensitive (Fernández-Esparrach et al, 1997; Runyon, 2013). Repeated large volume paracentesis is indicated for refractory ascites.

Removal of large volumes of ascites can lead to a condition called post-paracentesis circulatory dysfunction (Ginès et al, 1988, 1996) which is associated with higher mortality (Ginès et al, 1996) and a rapid re-accumulation of ascites (Solá et al, 1994). Approximately 20% of these patients develop hepatorenal syndrome and/or water retention leading to severe dilutional hyponatraemia (Ginès et al, 1988). Portal pressure can increase as a result of post-paracentesis circulatory dysfunction which can cause further complications. A patient is at risk of developing post-paracentesis circulatory dysfunction when more than 5 litres of ascites is drained (Moore and Aithal, 2006).

The issue of albumin replacement for paracentesis is somewhat controversial. Numerous studies have shown that large volume paracentesis with albumin replacement is more effective than diuretics alone in the treatment of large volume ascites (Ginès et al, 1988, 1996; Solá et al, 1994). The administration of albumin with large volume paracentesis is associated with a lower number of liver-related complications in the subsequent 30 days compared to artificial plasma expanders (Moreau et al, 2006), and it also reduces hospital stay (Ginès et al, 1988). However, one study has shown that those not receiving albumin have changes in electrolyte and creatinine levels but no overall change in morbidity or mortality (Ginès et al, 1988). There is currently no study large enough to definitively address this issue. In view of this, it is usual practice to administer human albumin solution 100 ml 20% (8 g albumin/litre) for every 2 litres of ascites drained in those with cirrhotic ascites to try and counteract post-paracentesis circulatory dysfunction (Moore and Aithal, 2006).

Paracentesis is contraindicated in loculated ascites and should be avoided in patients with disseminated intravascular coagulation (Runyon, 2013). Haemorrhagic complications are rare and there are no data to support limits for coagulation parameters where paracentesis should be avoided (Runyon, 1986). Although there is limited evidence to support the use of blood products before large volume paracentesis, many units still adopt this when severe coagulopathies are present. Large volume paracentesis is considered a safe procedure and has a complication rate <1/1000. Complications include bowel perforation and haemorrhage into the peritoneum (Webster et al, 1996; Pache and Bilodeau, 2005).

Treatment of spontaneous bacterial peritonitis

Spontaneous bacterial peritonitis is diagnosed when the ascitic neutrophil count is >250 cells/mm^3 or total white cell count is >500 cells/mm^3 without an intra-abdominal or surgically treated cause (Moore and

Aithal, 2006; Runyon, 2013). To maximize the chances of a more accurate diagnosis, inoculate blood culture bottles before giving antibiotics (Moore and Aithal, 2006; Runyon, 2013), although negative cultures do not refute the diagnosis.

Empiric antibiotics must be started, without delay awaiting culture results. A broad spectrum antibiotic covering the three most common organisms (*Escherichia coli*, *Klebsiella pneumoniae* and *Streptococcus pneumoniae*) should be used (Felisart et al, 1985). Cefotaxime is one of the most extensively studied but other antibiotics such as ceftriaxone, co-amoxiclav and ceftazidime are equally effective (Moore, and Aithal, 2006). Albumin 1.5 g/kg should be given within 6 hours of diagnosis and albumin 1 g/kg should be given on the third day to reduce mortality from 29% to 10% (Runyon, 2007).

There is a 70% chance of spontaneous bacterial peritonitis recurrence at 1 year. The 1-year survival following one episode of spontaneous bacterial peritonitis is 30–50% and 2-year survival is 25–30% (Altman et al, 1995). Therefore secondary prophylaxis should be provided, with oral antibiotics such as norfloxacin 400 mg/day or ciprofloxacin 500 mg/day (Moore and Aithal, 2006; Runyon, 2013). Primary prophylaxis can be initiated for those who are deemed high risk with ascitic fluid protein <10 g/litre (Moore and Aithal, 2006; Runyon, 2013).

Liver transplant

Liver transplant should be considered early for those with complications from cirrhosis. Cirrhotic patients should be referred for assessment for liver transplantation when they develop signs of hepatic dysfunction (Child-Turcotte Pugh score ≥7 or Model for End-Stage Liver Disease score ≥10; in the UK, UKELD score >49 is the standard parameter) or when a severe complication occurs (ascites, variceal bleeding or hepatic encephalopathy). All patients with spontaneous bacterial peritonitis should be considered for liver transplant as the 2-year survival following an acute episode is 25–30% (Altman et al, 1995). Special attention must be given to pre-transplant renal function as reduced function is associated with poorer outcomes (Murray and Carithers, 2005).

Transjugular intrahepatic portosystemic shunt

Hepatic venous pressure gradient is the gold standard for measuring portal hypertension; a value of >12 mmHg is clinically significant (Said et al, 2012), associated with complications such as ascites and oesophageal varices. Transjugular intrahepatic portosystemic shunt decompresses the portal system by shunting high pressure portal flow to lower pressure hepatic veins. It is useful in the management of recurrent ascites. However, 30–50% subsequently develop hepatic encephalopathy, and it has not been shown to significantly improve survival compared to large volume paracentesis (Runyon, 2013). It is recommended in those who require frequent large volume paracentesis or in those with loculated ascites (Runyon, 2013). Owing to limited data on safety and efficacy it is not recommended in patients with extremely advanced liver disease.

KEY POINTS

- Ascites is a common complication of cirrhosis and is associated with increased mortality and morbidity.
- Patients should be comprehensively screened for sepsis.
- Perform an ascitic tap for novel or worsening ascites.
- Use the conservative measure of salt restriction for all patients with ascites.
- For moderate ascites couple salt restriction with diuretics.
- In large volume ascites use salt restriction, diuretics and large volume paracentesis.
- Spontaneous bacterial peritonitis confers a high mortality.
- Refractory ascites is hard to manage, requiring repeated paracentesis, transjugular intrahepatic portosystemic shunt or liver transplant.

Conclusions

Liver disease is common and ascites is a common complication. Treatment should be divided into conservative, medical and interventional. Ascites carries a high morbidity and mortality and therefore evaluation for liver transplant should be considered early (*Table 4*). BJHM

Table 4. Indications for referral for liver transplant

Non-cholestatic liver disease	Chronic hepatitis C
	Chronic hepatitis B
	Autoimmune hepatitis
	Alcoholic liver disease
Cholestatic liver disease	Primary biliary cirrhosis
	Primary sclerosing cholangitis
	Biliary atresia
	Alagille syndrome
	Non-syndromic paucity of the intrahepatic bile ducts
	Cystic fibrosis
	Progressive familial intrahepatic cholestasis
Metabolic causes of cirrhosis	Alpha-1-antitrypsin deficiency
	Wilson disease
	Non-alcoholic steatohepatitis and cryptogenic cirrhosis
	Hereditary haemochromatosis
	Tyrosinaemia
	Glycogen storage disease type IV
	Neonatal haemochromatosis
Metabolic disorders causing severe extrahepatic morbidity	Amyloidosis
	Hyperoxaluria
	Urea cycle defects
	Disorders of branch chain amino acids
Primary liver malignancies	Hepatocellular carcinoma
	Hepatoblastoma
	Fibrolamellar hepatocellular carcinoma
	Haemangioendothelioma
Fulminant hepatic failure	Re-transplantation
	Miscellaneous
	Budd–Chiari syndrome
	Metastatic neuroendocrine tumours
	Polycystic disease

From Murray and Carithers (2005)

Conflict of interest: none.

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