Cirrhotic ascites: a review of management

Tharshanan Sivayokan, John F Dillon

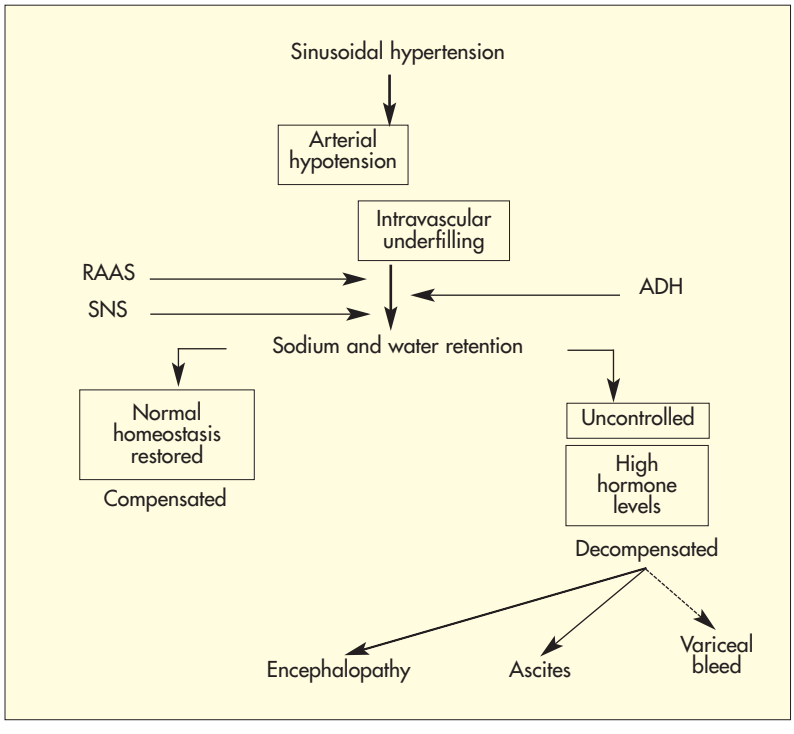
Ascites is a common and debilitating complication of cirrhosis where optimizing management can have satisfying results. New therapeutic and interventional developments have demonstrated improved outcomes. These are reviewed and integrated with established management techniques including consideration of liver transplantation.

Dr Tharshanan Sivayokan is Senior House Officer in Gastroenterology and **Dr John F Dillon** is Consultant Hepatologist, Ninewells Hospital and Medical School, Dundee DD1 9SY

Correspondence to: Dr T Sivayokan

Ascites in cirrhosis occurs as a consequence of portal hypertension. Its onset indicates marked liver damage and carries a mortality approaching 50% at 2 years (D'Amico et al, 1986). The exact mechanisms underlying ascites formation are still unclear. Successful management centres on symptom control that in the early stages is diuretic mediated. Invasive treatment techniques are equally efficacious in improving symptoms, but are reserved for more resistant ascites as they are associated with their own complications and operative mortality.

Figure 1. The peripheral vasodilatation theory. ADH = antidiuretic hormone; RAAS = renin–angiotensin–aldosterone system; SNS = sympathetic nervous system.



THE PERIPHERAL VASODILATATION THEORY

The peripheral vasodilatation theory best explains the abnormalities associated with ascites formation (Schrier et al, 1988). It is based on an amalgamation of the traditional underfill and overflow hypotheses with recognition of a compensated and decompensated (i.e. development of ascites, jaundice, encephalopathy or variceal haemorrhage) disease state.

Sinusoidal portal hypertension is proposed as the primary event, which results in splanchnic arteriolar vasodilation (via as yet unspecified mediators), intravascular underfilling and arterial hypotension. This disruption of homeostasis is detected by high-pressure baroreceptors that stimulate the kidney into retaining sodium and water in order to increase circulating plasma volume and correct the arterial pressure. This involves three principal neurohumoral systems: the renin–angiotensin–aldosterone system (RAAS), sympathetic nervous system (SNS) and antidiuretic hormone (ADH) system.

Disease progression from this point depends on the severity of portal hypertension. In compensated disease with moderate portal hypertension, the increase in plasma volume is adequate to re-establish normal homeostasis, with normal RAAS, SNS and ADH levels, and normal regulation of sodium and water in the kidneys. In decompensated disease hormone levels remain persistently high fuelling continuous sodium and water retention and subsequent ascites formation (*Figure 1*).

DETECTION AND DIAGNOSIS

In patients with new onset ascites identifying aetiology determines successful management. A detailed history may reveal risk factors for liver disease such as excessive alcohol intake, transfu-

sions, tattoos and country of origin. In approximately 20% of cases the cause is not hepatic in origin and relevant medical history may indicate other causes of ascites such as congestive cardiac failure or malignancy.

Important clinical features include a distended abdomen, dullness at the flanks on percussion, shifting dullness and a fluid thrill although these signs are only demonstrable when more than 1500 ml of ascitic fluid is present in the peritoneal cavity. Peripheral pitting oedema, which reduces with bed rest, is also a common feature that can precede the detectable signs of ascites.

An early diagnostic abdominal paracentesis, with analysis of protein, glucose, lactate dehydrogenase, white cell count and cytology, is essential for confirming the cause of ascites and identifying any underlying bacterial peritonitis, whether spontaneous (SBP) or secondary (detailed later). The most common complication of a diagnostic tap is abdominal wall haematoma, which has been demonstrated in only 1% of patients, despite a degree of coagulopathy, and therefore should not prevent its undertaking in all cases (Runyon, 1986).

An ascites albumin level is useful for calculating the serum–ascites albumin gradient (serum albumin minus ascitic fluid albumin) which if greater than 11 g/litre is 97% accurate in diagnosing cirrhotic liver disease with portal hypertension (Runyon et al, 1992).

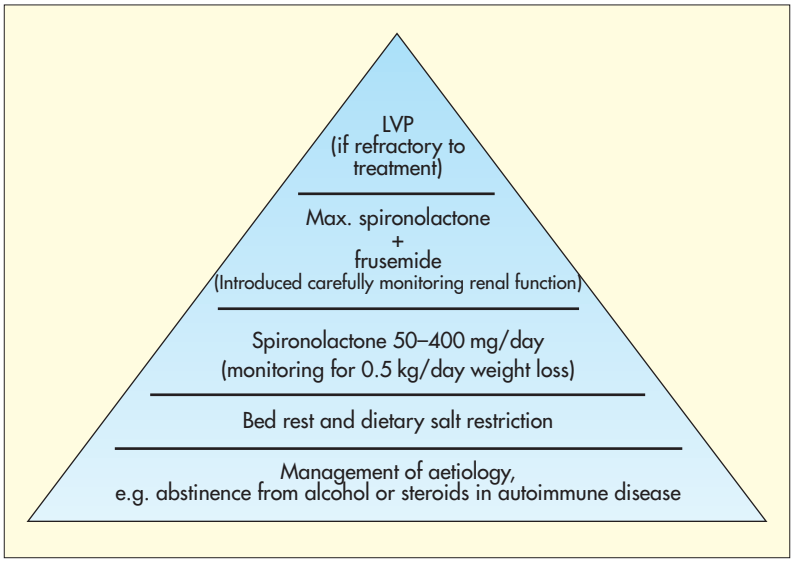
APPROACH TO TREATMENT

Primarily the underlying cause of decompensation must be identified and eliminated. This is particularly important in alcoholic cirrhosis, where abstinence may result in reduced portal pressure and make the ascites more sensitive to pharmacological treatment. Important considerations for treatment include:

1. Bed rest in cirrhosis promotes fluid excretion, as standing stimulates the RAAS into retaining sodium and water, but is hard to maintain even within the hospital setting and must be weighed against the benefits of mobilization and hospital bed occupancy
2. Dietary measures should be implemented with concomitant diuretic administration. Sodium restriction of about 100 mmol sodium chloride/day can be effective in preventing the retention of fluid. However, too strict a regimen (minimum requirement 40 mmol sodium chloride/day) is likely to be unpalatable, result in poor compliance and compromise nutrition. Fluid restriction (<1000 ml/day) is only necessary when hyponatraemia of <125 mmol/litre develops. Twenty four-hour urinary sodium collection can be used to assess sodium excretion, as well as likely success of current therapy. If excretion is only 20 mmol/day and sodium chloride is restricted to 100 mmol/day then ascites formation will continue
3. The use of the aldosterone antagonist, spironolactone, underpins the treatment of ascites because of its effectiveness, ease of use and compliance. Administration of 50 mg daily, increasing every few days to a maximum of 400 mg where necessary, can control ascites in 60–70% of cases. Monotherapy with frusemide is less effective in ascites management although it may be a useful adjunct if hyperkalaemia develops. Regular assessment of renal function is particularly important in those with pre-existing renal disease (*Figure 2*)
4. On average 600 ml of ascitic fluid is absorbed from the peritoneal cavity daily. Negative fluid balance should not exceed this, in the absence of peripheral oedema, as the intravascular compartment becomes deplete and may lead to circulatory and metabolic complications
5. Daily measurement of blood urea, creatinine, sodium and potassium along with body weight, aiming for 0.5 kg/day loss, are essential and also provide the best means of monitoring progress.

The onset of encephalopathy, hyponatraemia (<120 mmol/litre) or serum creatinine >150 mg/litre implies diuretic therapy should be stopped and implementation of alternative techniques evaluated. Where side effects with spironolactone occur, e.g. gynaecomastia or impotence, amiloride or triamterene can be substituted although to lesser diuretic effect and greater expense.

Figure 2. Structured approach to treating ascites. LVP = large volume paracentesis.



REFRACTORY ASCITES

The term refractory ascites is given to the condition where maximal medical therapy proves ineffective measured by little or no weight loss, reduced urinary sodium excretion or the onset of diuretic-related side effects. This definition incorporates 'diuretic-resistant ascites' where ascites formation or recurrence is resistant to treatment with dietary sodium restriction and diuretic therapy (Arroyo et al, 1996). At this stage of the disease mortality is 50% at 6 months. Fortunately this occurs in less than 10% of cirrhotics but requires the consideration of invasive techniques (Perez-Ayuso et al, 1983) which currently include large volume paracentesis (LVP), transjugular intrahepatic portosystemic shunt (TIPS), liver transplantation and peritovenous shunting.

Large volume paracentesis

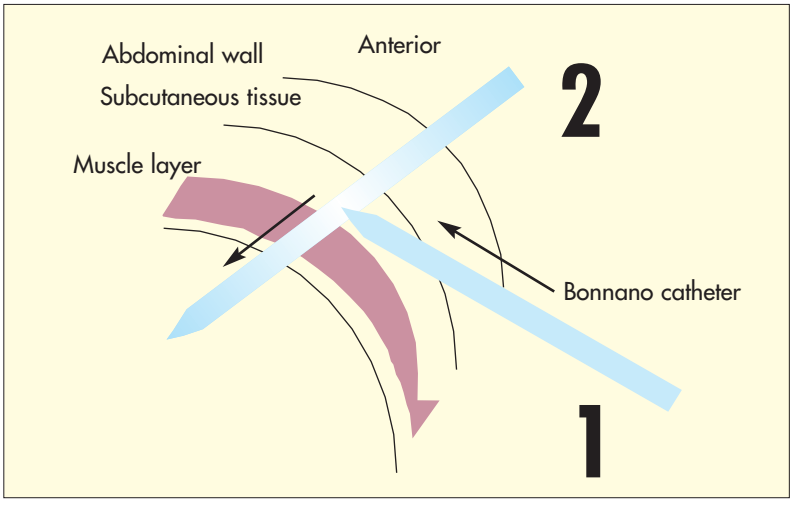
LVP with colloid replacement is the favoured option. At the authors' institution 3 litres of ascites is replaced with 1 unit of 4.5% Alba (Scottish National Blood Transfusion Service, Edinburgh) (containing 42.5–47.5 g/litre albumin with 130–150 mmol Na/litre and 2 mmol potassium chloride). This has made the procedure safer by preventing circulatory collapse and renal failure secondary to rapid fluid loss. Salt-poor albumin or human albumin 20% solution (100 ml contains approximately 190–210 g/litre albumin with 130–150 mmol Na/litre) is a recognized alternative.

Benefits over diuretic therapy include speed of draining ascites resulting in a shorter hospital stay. Albumin is the colloid of choice as cheaper alternatives do not provide a survival benefit (Planas et al, 1990). A diuretic regimen must be maintained to prolong benefit. The procedure is summarized in *Table 1*.

TABLE 1.
Large volume paracentesis technique

Lay the patient supine
Percuss the lower right or left abdominal quadrants or use ultrasound marking to locate a safe entry site
Administer subcutaneous local anaesthetic (lidocaine 1%)
Insert a Bonanno (over the needle suprapubic) catheter using a 'Z technique'. (entry of the catheter in the skin and tissues is zig-zagged to reduce ascitic fluid leakage on removal) (*Figure 3*)
Attach an appropriate catheter bag to allow gravity assisted drainage
Prescribe intravenous colloid replacement (e.g. 1 unit Alba 4.5% (Scottish National Blood Transfusion Service, Edinburgh) for every 3 litres of fluid drained)

Figure 3. Z technique when inserting a Bonnano catheter. Position 1 is used until the muscle layer is entered followed by change in angle of the catheter to position 2 until complete penetration of the abdominal wall is achieved.



Transjugular intrahepatic portosystemic shunt

TIPS in the routine management of resistant ascites is still being evaluated. In an early study of 25 patients undergoing this procedure for resistant ascites, survival at 1 year was 29%, far less than that of LVP (Lebrec et al, 1996). Data from a larger cohort have shown an increased survival benefit (without transplantation) with a lesser incidence of ascites at 1 year compared with LVP (Rossle et al, 2000). Gines et al (2002) have demonstrated reduced reaccumulation of ascites and progression to hepatorenal syndrome (HRS) with TIPS; however, encephalopathy was more frequent and survival was not improved. Further supportive data are needed if this is to become a mainstay of treatment.

Liver transplantation

Liver transplantation should be considered in those patients with liver cirrhosis and where there is refractory ascites. It should also be considered after first occurrence of SBP (Rimola et al, 2000). In some centres end-stage alcoholic liver disease is becoming a leading indication for transplantation with similar success rates being achieved with alcoholic-related cirrhosis and autoimmune liver diseases. Such outcomes are not attainable in viral liver cirrhosis because of a high incidence of disease relapse in the transplanted organ.

Peritovenous shunt

The peritovenous shunt system allowed the one-way shunting of ascitic fluid directly to the internal jugular vein. High operative mortality and complications, such as disseminated intravascular coagulation, infection and intraperitoneal fibrosis, mean that it is no longer a generally applicable management option.

SPONTANEOUS BACTERIAL PERITONITIS

This is an infection of the ascitic fluid mediated by translocation of bacteria across intact gut wall. Specific risk factors include ascitic fluid protein concentration <10 g/litre, variceal haemorrhage and previous episode of SBP. Occurring in up to 27% of those with ascites during hospital admissions it carries a mortality of 30% at 1 year (Altman et al, 1995). Diagnosis is best made by differential cell count of the ascitic fluid obtained by paracentesis.

A polymorphonuclear (PMN) leucocyte count >500/ml, or >250/ml with a positive Gram stain for a single organism, is diagnostic of SBP and indicates the need for urgent antibiotic treatment. Culture of ascitic fluid (using blood culture bottles) and peripheral blood will allow more specific treatment once a causative organism is identified (*Table 2*). In a bloody tap or haemorrhagic ascites where the red cell count is greater than 10 000 a correction of 1 PMN per 250 red blood cells should be made.

The most appropriate antibiotic is a third generation cephalosporin given intravenously, i.e. cefotaxime (2 g/8 hr), which covers 95% of the causative organisms including *Escherichia coli*, *Klebsiella pneumoniae* and pneumococcus without causing nephrotoxicity or superinfections. A short 5-day course is equally efficacious as the traditional 10-day regimen (Runyon et al, 1991). Follow-up diagnostic paracentesis is only required if symptoms become atypical, the likely organism changes or if cultures are positive but the PMN count is <250/ml.

Prophylaxis of norfloxacin 400 mg daily on hospital admission is recommended in those with low protein ascites (<10 g/dl) and previous SBP (Gines et al, 1990). In patients who have a low ascites protein concentration and no previous episode of SBP the benefit of prophylaxis in hospital is unclear, although some physicians choose to treat with a daily regimen. Continuation of prophylactic measures outwith hospital is recommended in patients with a history of SBP (Rimola et al, 2000). In those patients developing SBP while on prophylaxis the causative organism is a quinolone-resistant Gram-negative bacilli or Gram-positive cocci, both of which respond well to the aforementioned intravenous treatment.

Bowel perforation, infection and inflammation are common causes of secondary peritonitis, which can be difficult to distinguish from SBP in the context of ascites. *Table 3* gives a guide for when such aetiology should be sought.

HEPATORENAL SYNDROME

This condition is associated with end-stage liver disease, developing in 18% of decompensated cirrhotics at 1 year increasing to 39% at 5 years (Gines et al, 1993). It can be defined as renal failure in the presence of progressive liver failure where there are no other pathological or anatomical causes. Theories to its development centre on renal vasoconstriction secondary to altered haemodynamic control systems, involving the RAAS, SNS, ADH and prostaglandins, as a result of splanchnic vasodilatation.

The international ascites club has defined two types relating to severity of deterioration. In type 1 disease there is a doubling of the serum creati-

TABLE 2.
Key points for managing spontaneous bacterial peritonitis

Diagnostic paracentesis on all admissions with ascites
Urgent differential cell count, glucose, protein and lactate dehydrogenase
Ascitic fluid sample for culture (in blood culture bottles with further peripheral sample)
Treat for spontaneous bacterial peritonitis if polymorphonuclear leucocyte count >500/ml or >250/ml with a positive Gram stain
Use a 5-day intravenous cefotaxime (2 g/8 hr) regimen
Consider norfloxacin prophylaxis at discharge

TABLE 3.
Indicators of secondary peritonitis

No response to antibiotics or no fall in ascitic fluid polymorphonuclear leucocyte count
More than one organism isolated
Ascitic fluid glucose <5 mmol/litre, protein >10 g/litre and lactate dehydrogenase greater than that of the serum

From Rimola et al (2000)

nine to >250 μmol/litre or a 50% fall in creatinine clearance to <20 ml/min in 2 weeks. Type 2 indicates a less rapid deterioration with serum creatinine >150 μmol/litre or creatinine clearance <40 ml/min (Arroyo et al, 1996).

Mortality at 2 weeks is 80%, falling to 10% at 3 months (Gines et al, 1993). The delicate balance between hepatic and renal function is easily lost with infection, over-diuresis and the use of nephrotoxic substances such as aminoglycosides, non-steroidal anti-inflammatory drugs (NSAIDs) and contrast media. Other risk factors include SBP, prolonged antibiotic therapy and gastrointestinal bleeding resulting in hypovolaemia.

Successful treatment relies on liver transplantation. Short-term maintenance aims to increase renal blood flow either by splanchnic vasoconstriction or direct renal vasodilatation. Terlipressin (0.5–2 mg/4 hours intravenously with concomitant intravenous albumin) has, in a pilot study, been shown to reverse HRS and improve mean arterial blood pressure without the ischaemic side effects of its predecessors (Uriz et al, 2000). The administration of N-acetylcysteine (150 mg/kg over 2 hours intravenously, followed by continuous infusion of 100 mg/kg/day for 5 days) has also, in a pilot trial, produced improved renal function in alcoholic-induced HRS (Holt et al, 1999). Future management may lie with TIPS which, despite being in the early stages, is demonstrating improved post-procedure survival (Brensing et al, 2000).

CONCLUSION

The complex circulatory abnormalities of liver cirrhosis make management difficult. Uncomplicated disease requires careful balance of pharmacological therapies with regular monitoring of serum hepatic and renal markers. The onset of refractory ascites calls for more invasive measures, such as LVP, for symptomatic relief. There should be a high level of suspicion at all times for SBP, particularly at hospital admission, and a diagnostic tap is essential. The onset of HRS signifies end-stage disease, with high mortality, whose deterioration can only temporarily be halted. Liver transplantation should be borne in mind throughout the disease progression as it offers a potential cure with improved long-term survival. **HM**

KEY POINTS

- Obtain a detailed history and examination to ascertain the disease aetiology leading to ascites formation.
- Early abdominal diagnostic paracentesis and exclusion of spontaneous bacterial peritonitis is mandatory.
- Implement bed rest, dietary and diuretic measures to treat the ascites.
- Response to therapy can be monitored with a target of 0.5 kg/day weight loss.
- In refractory disease proceed to large volume paracentesis.
- Consider liver transplantation in resistant disease or hepatorenal syndrome.

Conflict of interest: none.

Altman C, Grange JD, Amiot X et al (1995) Survival after a first episode of spontaneous bacterial peritonitis: prognosis of potential candidates for orthoptic liver transplantation. *J Gastroenterol Hepatol* **10:** 47–50

Arroyo V, Gines P, Gerbes AL et al (1996) Definitions and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. *Hepatology* **23:** 164–76

Brensing KA, Textor J, Perz J et al (2000) Long term outcome after transjugular intrahepatic portosystemic stent-shunt in non-transplant cirrhotics with hepatorenal syndrome: a phase II study. *Gut* **47:** 288–95

D'Amico G, Morabito A, Pagliaro L et al (1986) Survival and prognostic indicators in compensated and decompensated cirrhosis. *Dig Dis Sci* **31:** 468–75

Gines P, Rimola A, Planas R et al (1990) Norfloxacin prevents spontaneous bacterial peritonitis recurrence in cirrhosis: results of a double-blind, placebo controlled trial. *Hepatology* **12:** 716–24

Gines A, Escorsell A, Gines P et al (1993) Incidence, predictive factors and prognosis of hepatorenal syndrome in cirrhosis with ascites. *Gastroenterology* **105:** 229–36

Gines P, Uriz J, Calahorra B et al (2002) Transjugular intrahepatic portosystemic shunting versus paracentesis plus albumin for refractory ascites in cirrhosis. *Gastroenterology* **123**(6): 1839–47

Holt S, Goodier D, Marley R et al (1999) Improvement in renal function in hepatorenal syndrome with N-acetylcysteine. *Lancet* **353:** 294–5

Lebrec D, Giuily N, Hadengue A et al (1996) Transjugular intrahepatic portosystemic shunts: comparison with paracentesis in patients with cirrhosis and refractory ascites: a randomized trial. *J Hepatol* **25:** 135–44

Perez-Ayuso RM, Arroyo V, Planas R et al (1983) Randomized comparative study of efficacy of furosemide vs. spironolactone in non-azotemic cirrhotic ascites. *Gastroenterology* **84:** 961–8

Planas R, Gines P, Arroyo V et al (1990) Dextran 70 versus albumin as plasma expanders in cirrhotic patients with tense ascites treated with total paracentesis. *Gastroenterolgy* **99:** 1736–44

Rimola A, Garcia-Tsao G, Navasa M et al (2000) Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: a consensus document. International Ascites Club. *J Hepatol* **32**(1): 142–53

Rossle M, Ochs A, Gulberg V et al (2000) A comparison of paracentesis and transjugular intrahepatic portosystemic shunting in patients with ascites. *N Engl J Med* **342:** 1701–7

Runyon BA (1986) Low-protein-concentration ascitic fluid is predisposition to spontaneous bacterial peritonitis. *Gastroenterology* **91:** 1343–6

Runyon BA, McHutchison JG, Antillon MR, Akriviadis EA, Montano AA (1991) Short-course vs long-course antibiotic treatment of spontaneous bacterial peritonitis: a randomised control trial of 100 patients. *Gastroenterology* **100:** 1737–42

Runyon BA, Montano AA, Akriviadis EA, Antillon MR, Irving MA, McHutchinson JG (1992) The serum-ascites albumin gradient is superior to the exudate-transudate concept in the differential diagnosis of ascites. *Ann Intern Med* **117:** 215–20

Schrier RW, Arroyo V, Bernadi M, Epstein M, Henriksen JH, Rodés J (1988) Peripheral arterial vasodilatation hypothesis: a proposal for the initiation of renal sodium and water retention in cirrhosis. *Hepatology* **8:** 1151–7

Uriz J, Gines P, Cardenas A et al (2000) Terlipressin plus albumin infusion: an effective and safe therapy of hepatorenal syndrome. *J Hepatology* **33:** 43–8