

Guidelines on the management of ascites in cirrhosis

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1.0 INTRODUCTION

Ascites is a major complication of cirrhosis,¹ occurring in 50% of patients over 10 years of follow up.² The development of ascites is an important landmark in the natural history of cirrhosis as it is associated with a 50% mortality over two years,^{2–5} and signifies the need to consider liver transplantation as a therapeutic option.³ The majority (75%) of patients who present with ascites have underlying cirrhosis, with the remainder being due to malignancy (10%), heart failure (3%), tuberculosis (2%), pancreatitis (1%), and other rare causes.⁶ The true prevalence and incidence of cirrhosis of the liver and its complications in the UK are unknown. Mortality from cirrhosis has increased from 6 per 100 000 population in 1993 to 12.7 per 100 000 population in 2000.⁷ Approximately 4% of the general population have abnormal liver function or liver disease⁸ and approximately 10–20% of those with one of the three most common chronic liver diseases (non-alcoholic fatty liver disease, alcoholic liver disease, and chronic hepatitis C) develop cirrhosis over a period of 10–20 years. With a rising frequency of alcoholic and non-alcoholic fatty liver disease, a huge increase in the burden of liver disease is expected over the next few years⁸ with an inevitable increase in the complications of cirrhosis. There have been several changes in the clinical management of cirrhotic ascites over recent years, and the purpose of these guidelines is to promote a consistent clinical practice throughout the UK.

These guidelines are based on a comprehensive literature search, including the results of randomised control trials, systematic reviews, prospective retrospective studies and, in some instances, evidence obtained from expert committee reports. Where possible a judgement is made on the quality of the information used to generate the guidelines, and the specific recommendations have been graded according to the Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001) (see appendices 1 and 2).⁹ These guidelines conform to the international guidelines recently published by the International Ascites Club¹⁰ and are intended for use by physicians. We hope to revise these guidelines in three years time.

2.0 DEFINITIONS

The terms used in this article have been defined by the International Ascites Club.¹¹

Uncomplicated ascites

Ascites that is not infected and which is not associated with the development of the hepatorenal syndrome. Ascites can be graded as follows:

- Grade 1 (mild). Ascites is only detectable by ultrasound examination.
- Grade 2 (moderate). Ascites causing moderate symmetrical distension of the abdomen.
- Grade 3 (large). Ascites causing marked abdominal distension.

Refractory ascites

Ascites that cannot be mobilised or early recurrence of which (that is, after therapeutic paracentesis) cannot be satisfactorily prevented by medical therapy. This includes two different subgroups.

- Diuretic resistant ascites—ascites that is refractory to dietary sodium restriction and intensive diuretic treatment (spironolactone 400 mg/day and frusemide 160 mg/day for at least one week, and a salt restricted diet of less than 90 mmol/day (5.2 g of salt)/day).
- Diuretic intractable ascites—ascites that is refractory to therapy due to the development of diuretic induced complications that preclude the use of an effective diuretic dosage.

3.0 PATHOGENESIS OF ASCITES FORMATION

A detailed description of the pathogenesis of ascites formation is beyond the scope of this article but more detailed reviews are available.^{12–14} There are two key factors involved in the pathogenesis of ascites formation—namely, sodium and water retention, and portal (sinusoidal) hypertension.

3.1 Role of portal hypertension

Portal hypertension increases the hydrostatic pressure within the hepatic sinusoids and favours transudation of fluid into the peritoneal cavity. However, patients with presinusoidal portal hypertension without cirrhosis rarely develop ascites. Thus patients do not develop ascites with isolated chronic extrahepatic portal venous occlusion or non-cirrhotic causes of portal hypertension such as congenital hepatic fibrosis, except following an insult to liver function such as gastrointestinal haemorrhage. Conversely, acute hepatic vein thrombosis, causing postsinusoidal portal hypertension, is usually associated with ascites. Portal hypertension occurs as a consequence of structural changes within the liver in cirrhosis and increased splanchnic blood flow. Progressive collagen deposition and formation of nodules alter the

Abbreviations: TIPS, transjugular intrahepatic portosystemic shunt; SBP, spontaneous bacterial peritonitis; PMN, polymorphonuclear cell

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normal vascular architecture of the liver and increase resistance to portal flow. Sinusoids may become less distensible with the formation of collagen within the space of Disse. While this may give the impression of a static portal system, recent studies have suggested that activated hepatic stellate cells may dynamically regulate sinusoidal tone and thus portal pressure.

Sinusoidal endothelial cells form an extremely porous membrane which is almost completely permeable to macromolecules, including plasma proteins. In contrast, splanchnic capillaries have a pore size 50–100 times less than that of hepatic sinusoids. As a consequence, the trans-sinusoidal oncotic pressure gradient in the liver is virtually zero while it is 0.8–0.9 (80%–90% of maximum) in the splanchnic circulation.¹² Oncotic pressure gradients at such extreme ends of the spectrum minimise any effect the changes in plasma albumin concentration may have on transmicrovascular fluid exchange. Therefore, the old concept that ascites is formed secondary to decreased oncotic pressure is false, and plasma albumin concentrations have little influence on the rate of ascites formation. Portal hypertension is critical to the development of ascites, and ascites rarely develops in patients with a wedged hepatic venous portal gradient of <12 mm Hg.¹⁵ Conversely, insertion of a side to side portacaval shunt to decrease portal pressure often causes resolution of ascites.

3.2 Pathophysiology of sodium and water retention

The classical explanations of sodium and water retention occurring due to “underfill” or “overfill” are oversimplified. Patients may exhibit features of either “underfill” or “overfill” depending on posture or severity of liver disease. One of the key events thought to be critical in the pathogenesis of renal dysfunction and sodium retention in cirrhosis is the development of systemic vasodilatation, which causes a decrease in effective arterial blood volume and a hyperdynamic circulation.¹⁶ The mechanism responsible for these changes in vascular function is unknown but may involve increased vascular synthesis of nitric oxide, prostacyclin, as well as changes in plasma concentrations of glucagon, substance P, or calcitonin gene related peptide.¹⁴

However, the haemodynamic changes vary with posture, and studies by Bernardi *et al* have shown marked changes in secretion of atrial natriuretic peptide with posture, as well as changes in systemic haemodynamics.^{17, 18} In addition, data showing a decreased effective arterial volume in cirrhosis have been disputed.¹⁹ It is agreed however that under supine conditions and in experimental animals, there is an increase in cardiac output and vasodilatation.

The development of renal vasoconstriction in cirrhosis is partly a homeostatic response involving increased renal sympathetic activity and activation of the renin-angiotensin system to maintain blood pressure during systemic vasodilatation.²⁰ Decreased renal blood flow decreases glomerular filtration rate and thus the delivery and fractional excretion of sodium. Cirrhosis is associated with enhanced reabsorption of sodium both at the proximal tubule and at the distal tubule.²⁰ Increased reabsorption of sodium in the distal tubule is due to increased circulating concentrations of aldosterone. However, some patients with ascites have normal plasma concentrations of aldosterone,²¹ leading to the suggestion that sodium reabsorption in the distal tubule may be related to enhanced renal sensitivity to aldosterone or to other undefined mechanisms.²²

In compensated cirrhosis, sodium retention can occur in the absence of vasodilatation and effective hypovolaemia. Sinusoidal portal hypertension can reduce renal blood flow even in the absence of haemodynamic changes in the systemic circulation, suggesting the existence of a hepatorenal

reflex.^{23, 24} Similarly, in addition to systemic vasodilation, the severity of liver disease and portal pressure also contribute to the abnormalities of sodium handling in cirrhosis.²⁵

4.0 DIAGNOSIS

4.1 Initial investigations

The underlying cause of ascites is frequently obvious from the history and physical examination. However, it is important to exclude other causes of ascites. It should not be assumed that the alcoholic patient has alcoholic liver disease. Therefore, tests must be directed at diagnosing the cause of ascites. The essential investigations on admission include a diagnostic paracentesis with measurement of ascitic fluid albumin or protein, ascitic fluid neutrophil count and culture, and ascitic fluid amylase. Ascitic fluid cytology should be requested when there is a clinical suspicion of underlying malignancy. Other investigations should include abdominal ultrasound scan to evaluate the appearance of the liver, pancreas, and lymph nodes as well as the presence of splenomegaly, which may signify portal hypertension. Blood tests should be taken for measurement of urea and electrolytes, liver function tests, prothrombin time, and full blood count.

4.2 Abdominal paracentesis

The commonest site for an ascitic tap is approximately 15 cm lateral to the umbilicus, with care being taken to avoid an enlarged liver or spleen, and is usually done in the left or the right lower abdominal quadrant.¹² The inferior and superior epigastric arteries run just lateral to the umbilicus towards the mid-inguinal point and should be avoided. For diagnostic purposes, 10–20 ml of ascitic fluid should be withdrawn (ideally using a syringe with a blue or green needle) for inoculation of ascites into two blood culture bottles and an EDTA tube, and the tests outlined below. Complications of ascitic taps occur in up to 1% of patients (abdominal haematomas) but are rarely serious or life threatening.^{26, 27} More serious complications such as haemoperitoneum or bowel perforation are rare (<1/1000 procedures).²⁸ Paracentesis is not contraindicated in patients with an abnormal coagulation profile. The majority of patients with ascites due to cirrhosis have prolongation of the prothrombin time and some degree of thrombocytopenia. There are no data to support the use of fresh frozen plasma before paracentesis although if thrombocytopenia is severe (<40 000) most clinicians would give pooled platelets to reduce the risk of bleeding.

Recommendation

- It is recommended that patients give informed consent for a therapeutic or diagnostic paracentesis. (Level of evidence: 5; recommendation: D.)

4.3 Ascitic fluid investigations

4.3.1 Ascitic fluid neutrophil count and culture

All patients should be screened for the development of spontaneous bacterial peritonitis (SBP), which is present in approximately 15% of patients with cirrhosis and ascites admitted to hospital.^{29–31} An ascitic neutrophil count of >250 cells/mm³ ($0.25 \times 10^9/l$) is diagnostic of SBP in the absence of a known perforated viscus or inflammation of intrabdominal organs. The concentration of red blood cells in cirrhotic ascites is usually <1000 cells/mm³ and bloody ascitic fluid (>50,000 cells/mm³) occurs in about 2% of cirrhotics.³² In approximately 30% of cirrhotics with bloody ascites, there is an underlying hepatocellular carcinoma.³³

Table 1 Serum ascites-albumin gradient (SA-AG)

SA-AG \geq 11 g/l	SA-AG $<$ 11 g/l
Cirrhosis	Malignancy
Cardiac failure	Pancreatitis
Nephrotic syndrome	Tuberculosis

However, in 50% of patients with bloody ascites, no cause can be found.³³ Gram's stain of ascitic fluid is not indicated, as it is rarely helpful.³⁴ The sensitivity of smear for mycobacteria is very poor while fluid culture for mycobacteria has a sensitivity of 50%.³⁵ Several studies have shown that inoculation of ascitic fluid into blood culture bottles will identify an organism in approximately 72–90% of cases whereas sending ascitic fluid in a sterile container to the laboratory will only identify an organism in about 40% of cases of SBP.^{34 36–39}

4.3.2 Ascitic fluid protein and ascitic fluid amylase

Conventionally, the type of ascites is divided into exudates and transudates, in which the ascitic protein concentration is $>$ 25 g/l or $<$ 25 g/l, respectively. The purpose of this subdivision is to help identify the cause of ascites. Thus "malignancy classically causes an exudative ascites and cirrhosis causes a transudate". However, there are many misconceptions in clinical practice. For example, it is often presumed that cardiac ascites is a transudate when this is rarely the case, ascitic protein is $>$ 25 g/l in up to 30% of patients with otherwise uncomplicated cirrhosis,^{32 40–43} and patients with cirrhosis and tuberculous ascites may have a low ascitic protein.⁴⁴ The serum ascites-albumin gradient (SA-AG) is far superior in categorising ascites with 97% accuracy (table 1).^{42 45 46} It is calculated as:

SA-AG = serum albumin concentration – ascitic fluid albumin concentration

As a high ascitic amylase is diagnostic of pancreatic ascites,^{47–49} ascitic fluid amylase should be determined in patients where there is clinical suspicion of pancreatic disease.

4.3.3 Ascitic fluid cytology

Only 7% of ascitic fluid cytologies are positive⁵⁰ yet cytological examination is 60–90% accurate in the diagnosis of malignant ascites, especially when several hundred millilitres of fluid is tested and concentration techniques are used.¹² Clinicians should liaise with their local cytology department to discuss fluid requirements before paracentesis. But ascites fluid cytology is not the investigation of choice for the diagnosis of primary hepatocellular carcinoma.

Recommendations

- The initial ascitic fluid analysis should include serum ascites-albumin gradient in preference to ascitic protein. (Level of evidence: 2b; recommendation: B.)
- Ascitic amylase should be measured when there is clinical suspicion of pancreatic disease. (Level of evidence: 4; recommendation: C.)
- Ascitic fluid should be inoculated into blood culture bottles at the bedside and examined by microscopy for a neutrophil count. (Level of evidence: 2a; recommendation: B.)

5.0 TREATMENT

5.1 Bed rest

In patients with cirrhosis and ascites, assumption of upright posture is associated with activation of the renin-angiotensin-aldosterone and sympathetic nervous system, a reduction in glomerular filtration rate and sodium excretion, as well as a decreased response to diuretics.^{14 51} These effects are even more striking in association with moderate physical exercise.^{52 53} These data strongly suggest that patients should be treated with diuretics while on bed rest. However, there have been no clinical studies to demonstrate increased efficacy of diuresis with bed rest or decreased duration of hospitalisation. As bed rest may lead to muscle atrophy, and other complications, as well as promoting extended stays in hospital, it is not generally recommended for the management of patients with uncomplicated ascites.

Recommendation

- Bed rest is NOT recommended for the treatment of ascites. (Level of evidence: 5; recommendation: D.)

5.2 Dietary salt restriction

Dietary salt restriction alone can create a negative sodium balance in 10% of patients.⁵⁴ Sodium restriction has been associated with lower diuretic requirement, faster resolution of ascites, and shorter hospitalisation.^{55 56} In the past, dietary salt was often restricted to 22 or 50 mmol/day. These diets may lead to protein malnutrition and a similar outcome,⁵⁷ and are no longer recommended. A typical UK diet contains about 150 mmol of sodium per day, of which 15% is from added salt and 70% is from manufactured food.^{58 59} Dietary salt should be restricted to \sim 90 mmol/day (5.2 g) salt by adopting a no-added salt diet and avoidance of pre-prepared foodstuffs (for example, pies). Dieticians' guidance and information leaflets will assist in educating patient and relatives regarding salt restriction. Certain drugs, especially those in the effervescent tablet form, have high sodium contents. Intravenous antibiotics generally contain 2.1–3.6 mmol of sodium per gram with the exception of ciprofloxacin which contains 30 mmol sodium in 200 ml (400 mg) for intravenous infusion. Although in general it is preferable to avoid infusion of fluids which contain salt in patients with ascites, there are occasions, such as the development of hepatorenal syndrome or renal impairment with severe hyponatraemia, when it may be appropriate and indicated to give volume expansion with a crystalloid or colloid. For patients developing hepatorenal syndrome, the International Ascites Club recommend infusion of normal saline.

Recommendation

- Dietary salt should be restricted to a no-added salt diet of 90 mmol salt/day (5.2 g salt/day). (Level of evidence: 2b; recommendation: B.)

5.3 Role of water restriction

There have been no studies on the benefits or harm of water restriction on the resolution of ascites. Most experts agree that there is *no* role for water restriction in patients with uncomplicated ascites. However, water restriction for patients with ascites and hyponatraemia has become

standard clinical practice in many centres. However, there is real controversy about the best management of these patients, and at present we do not know the best approach. Most hepatologists treat these patients with severe water restriction. However, based on our understanding of the pathogenesis of hyponatraemia, this treatment is probably illogical and may exacerbate the severity of effective central hypovolaemia that drives the non-osmotic secretion of antidiuretic hormone (ADH). This may result in further increases in circulating ADH, and a further decline of renal function. Impaired free water clearance is observed in 25–60% of patients with ascites due to cirrhosis,⁶⁰ and many develop spontaneous hyponatraemia.⁶¹ Therefore, some hepatologists, including the authors, advocate further plasma expansion to normalise and inhibit stimulation of ADH release. Studies are needed to determine the best approach.⁶² There are data emerging that support the use of specific vasopressin 2 receptor antagonists in the treatment of dilutional hyponatraemia,^{63–65} but whether this improves overall morbidity and mortality is not yet known. It is important to avoid severe hyponatraemia in patients awaiting liver transplantation as it may increase the risk of central pontine myelinolysis during fluid resuscitation in surgery.

5.4 Management of hyponatraemia in patients on diuretic therapy

5.4.1 Serum sodium ≥ 126 mmol/l

For patients with ascites who have a serum sodium ≥ 126 mmol/l, there should be no water restriction, and diuretics can be safely continued, providing that renal function is not deteriorating or has not significantly deteriorated during diuretic therapy.

5.4.2 Serum sodium ≤ 125 mmol/l

For patients with moderate hyponatraemia (serum sodium 121–125 mmol/l), opinion is divided on what is the next best course of action. The international opinion,¹⁰ in which a consensus of international experts was sought and reported, is that diuretics should be continued. However, there are no or few data to support the best course of action, and our personal view is to adopt a more cautious approach. We believe that diuretics should be stopped once serum sodium is ≤ 125 mmol/l and the patient observed. All experts in the field recommend stopping diuretics if serum sodium is ≤ 120 mmol/l. If there is a significant increase in serum creatinine or serum creatinine is >150 $\mu\text{mol/l}$, we would recommend volume expansion. Gelofusine, haemaccel, and 4.5% albumin solutions contain sodium concentrations equivalent to normal saline (154 mmol/l). This will worsen their salt retention but we take the view that it is better to have ascites with normal renal function than to develop potentially irreversible renal failure. Water restriction should be reserved for those who are clinically euvolaemic with severe hyponatraemia in which free water clearance is decreased, and who are not currently taking diuretics, and in whom serum creatinine is normal.

5.5 Diuretics

Diuretics have been the mainstay of treatment of ascites since the 1940s when they first became available. Many diuretic agents have been evaluated over the years but in clinical practice in the UK this has been mainly confined to spironolactone, amiloride, frusemide, and bumetanide. These are discussed below.

5.5.1 Spironolactone

Spironolactone is an aldosterone antagonist, acting mainly on the distal tubules to increase natriuresis and conserve potassium. Spironolactone is the drug of choice in the initial treatment of ascites due to cirrhosis.⁶⁶ The initial daily dose of

Recommendations

- Serum sodium 126–135 mmol/l, normal serum creatinine. Continue diuretic therapy but observe serum electrolytes. Do not water restrict.
- Serum sodium 121–125 mmol/l, normal serum creatinine. International opinion is to continue diuretic therapy, our opinion is to stop diuretic therapy or adopt a more cautious approach.
- Serum sodium 121–125 mmol/l, serum creatinine elevated (>150 $\mu\text{mol/l}$ or >120 $\mu\text{mol/l}$ and rising). Stop diuretics and give volume expansion.
- Serum sodium ≤ 120 mmol/l, stop diuretics. Management of these patients is difficult and controversial. We believe that most patients should undergo volume expansion with colloid (haemaccel, gelofusine, or voluven) or saline. However, avoid increasing serum sodium by >12 mmol/l per 24 hours.

(Level of evidence: 5; recommendation: D.)

100 mg may have to be progressively increased up to 400 mg to achieve adequate natriuresis. There is a lag of 3–5 days between the beginning of spironolactone treatment and the onset of the natriuretic effect.⁶⁷ Controlled studies have found that spironolactone achieves a better natriuresis and diuresis than a “loop diuretic” such as frusemide.^{68–71} Most frequent side effects of spironolactone in cirrhotics are those related to its antiandrogenic activity, such as decreased libido, impotence, and gynaecomastia in men and menstrual irregularity in women (although most women with ascites do not menstruate anyway). Gynaecomastia can be significantly reduced when the hydrophilic derivative potassium canrenoate is used,⁷² but this is not readily available in the UK. Tamoxifen at a dose 20 mg twice a day has been shown to be useful in the management of gynaecomastia.⁷³ Hyperkalaemia is a significant complication that frequently limits the use of spironolactone in the treatment of ascites.⁷⁴

5.5.2 Frusemide

Frusemide is a loop diuretic which causes marked natriuresis and diuresis in normal subjects. It is generally used as an adjunct to spironolactone treatment because of its low efficacy when used alone in cirrhosis.⁷¹ The initial dose of frusemide is 40 mg/day and it is generally increased every 2–3 days up to a dose not exceeding 160 mg/day. High doses of frusemide are associated with severe electrolyte disturbance and metabolic alkalosis, and should be used cautiously. Simultaneous administration of frusemide and spironolactone increases the natriuretic effect.^{12 28}

5.5.3 Other diuretics

Amiloride acts on the distal tubule and induces diuresis in 80% of patients at doses of 15–30 mg/day.⁷⁵ It is less effective compared with spironolactone or potassium canrenoate.^{71 72} Bumetanide is similar to frusemide in its action and efficacy.⁷⁶

Generally, a “stepped care” approach is used in the management of ascites starting with modest dietary salt restriction, together with an increasing dose of spironolactone. Frusemide is only added when 400 mg of spironolactone alone has proved ineffective.^{77–79} In patients with severe oedema there is no need to slow down the rate of daily weight loss.²⁸ Once the oedema has resolved but ascites persists, then the rate of weight loss should not exceed

~0.5 kg/day.⁸⁰ Over diuresis is associated with intravascular volume depletion (25%) leading to renal impairment, hepatic encephalopathy (26%), and hyponatraemia (28%).⁸¹

Approximately 10% of patients with cirrhosis and ascites have refractory ascites.^{71–82} In patients who fail to respond to treatment, a careful dietary and drug history should be obtained. It is important to ensure that they are not consuming drugs that are rich in sodium, or drugs that inhibit salt and water excretion such as non-steroidal anti-inflammatory drugs.^{83–84} Compliance with dietary sodium restriction should be monitored by measurement of urinary sodium excretion. If urinary sodium exceeds the recommended sodium intake, and the patient fails to respond to treatment, then it can be assumed that the patient is non-compliant.⁸⁵

Recommendations

- Firstline treatment of ascites should be spironolactone alone, increasing from 100 mg/day to a dose of 400 mg/day.
- If this fails to resolve ascites, frusemide should be added in a dose of up to 160 mg/day, but this should be done with careful biochemical and clinical monitoring.

(Level of evidence: 1a; recommendation: A.)

5.6 Therapeutic paracentesis

Patients with large or refractory ascites are usually initially managed by repeated large volume paracentesis. Several controlled clinical studies have demonstrated that large volume paracentesis with colloid replacement is rapid, safe, and effective.^{81–88} The first study demonstrated that serial large volume paracentesis (4–6 l/day) with albumin infusion (8 g/litre of ascites removed) was more effective and was associated with fewer complications and shorter duration of hospitalisation compared with diuretic therapy.⁸⁶ This study was followed by other studies evaluating the efficacy, safety, speed of paracentesis, haemodynamic changes following paracentesis, and need for colloid replacement therapy. Total paracentesis is generally safer than repeated paracentesis,⁸⁹ if volume expansion is administered post-paracentesis. Failure to give volume expansion can lead to post-paracentesis circulatory dysfunction with impairment of renal function and electrolyte disturbances.^{90–93}

Following paracentesis, ascites recurs in the majority (93%) if diuretic therapy is not reinstated, but recurs in only 18% of patients treated with spironolactone.⁹⁴ Reintroduction of diuretics after paracentesis (usually within 1–2 days) does not appear to increase the risk of post-paracentesis circulatory dysfunction.

5.6.1 Haemodynamic changes following paracentesis

Total paracentesis is associated with significant haemodynamic effects.⁹¹ It has been assumed wrongly that total paracentesis of large volumes of ascites (>10 litre) leads to circulatory collapse. Large volume paracentesis (average >10 litre over 2–4 hours) causes a marked reduction in intra-abdominal and inferior vena cava pressure, leading to a decrease in right atrial pressure and an increase in cardiac output. These haemodynamic changes are maximal at three hours. Pulmonary capillary wedge pressure decreases at six hours and continues to fall further in the absence of colloid replacement. On average, blood pressure decreases by ~8 mm Hg.⁹¹ The severity of post-paracentesis circulatory

dysfunction correlates inversely with patient survival.⁹⁵ There are anecdotal reports of some patients with advanced liver disease developing quite severe hypotension post-paracentesis, but this rarely occurs.

5.6.2 Plasma expansion post paracentesis

One study, which evaluated the haemodynamic and neuro-humoral responses in 12 patients following a single <5 litre total paracentesis concluded that it was safe to omit the use of albumin in these patients.⁹⁶ However, many experts in the field have reservations on basing such a recommendation on a single small unrandomised study. Thus the International Ascites Club recommends that a synthetic plasma expander is used if less than 5 litre is removed, and this recommendation was based on consensus rather than fact.¹⁰ Plasma volume expansion should always be used whenever >5 litre of ascites are removed. Serial paracentesis with and without albumin replacement have been evaluated in patients with tense ascites.⁹⁰ There was a significantly higher rate of renal impairment, significant fall in serum sodium levels, and a marked activation of the renin-angiotensin-aldosterone system in those patients not treated with albumin.⁹⁰

There is still some debate about whether volume expansion should be carried out using albumin or artificial plasma expanders. Analysis of individual, but relatively small and underpowered randomised controlled trials comparing dextran 70 or haemaccel/gelofusine with albumin suggest that these plasma expanders are clinically effective in the prevention of hyponatraemia and renal impairment.^{97–99} However, the use of artificial plasma expanders is associated with a significantly greater activation of renin-angiotensin-aldosterone.⁹⁷ These data suggest that if enough patients were studied, that albumin would prove to be clinically superior to haemaccel or gelofusine or dextrans. Indeed, analysis of data from all published studies also suggests that albumin is more effective in the prevention of hyponatraemia (8% of 482 patients) compared with 17% of 344 patients for other plasma expanders.¹⁰⁰ A recent study by Moreau *et al* suggested that administration of albumin post-paracentesis decreases the number of liver related complications, and that the median hospital cost for a 30 day period was significantly lower (less than 50%) than the cost of those treated with artificial plasma expanders.¹⁰¹ Until further studies are undertaken to compare the efficacy of albumin versus artificial plasma expanders, we would recommend that albumin remains the plasma expander of choice when large volume (>5 litre) paracentesis is undertaken. Albumin (as 20% or 25% solution) should be infused *after* paracentesis of >5 litre is completed at a dose of 8 g albumin/litre of ascites removed.

5.7 Procedure

Paracentesis should be carried out under strict sterile conditions. The cannula should have multiple side perforations, otherwise the end becomes blocked by bowel wall. The needle is usually inserted into the left (preferably) or right lower abdominal quadrant using the “Z” track (skin is penetrated perpendicularly). The needle is advanced obliquely in subcutaneous tissue and then the peritoneal cavity is punctured, with the needle pointing perpendicular to the abdominal wall. This will ensure that the needle track has the puncture site on the skin and the peritoneum that do not overlie each other. All ascitic fluid should be drained to dryness in a single session as rapidly as possible over 1–4 hours, assisted by gentle mobilisation of the cannula or turning the patient on to their side if necessary. In the author’s opinion, the drain should *not* be left in overnight. After paracentesis, the patient should lie on the opposite side for two hours if there is leakage of any remaining ascitic fluid, and/or a suture (ideally purse string) inserted around the site of drainage. These steps help to minimise the risk of ascitic fluid leakage.

Recommendations

- Therapeutic paracentesis is the firstline treatment for patients with large or refractory ascites. (Level of evidence: 1a; recommendation: A.)
- Paracentesis of <5 litre of uncomplicated ascites should be followed by plasma expansion with a synthetic plasma expander and does *not* require volume expansion with albumin (Level of evidence: 2b; recommendation: B.)
- Large volume paracentesis should be performed in a single session with volume expansion being given once paracentesis is complete, preferably using 8 g albumin/litre of ascites removed (that is, ~100 ml of 20% albumin/3 l ascites). (Level of evidence: 1b; recommendation: A.)

5.8 Transjugular intrahepatic portosystemic shunt (TIPS)

As elevated portal pressure is one of the main factors contributing to the pathogenesis of ascites, it is not surprising that TIPS is a highly effective treatment for refractory ascites. It functions as a side to side portocaval shunt that is placed under local anaesthesia and intravenous sedation, and has largely replaced the use of surgically placed portocaval or mesocaval shunts. Numerous uncontrolled studies have been published assessing the effectiveness of TIPS in patients with refractory ascites.^{102–105} In most studies technical success was achieved in 93–100% of cases,^{103 106–108} with control of ascites achieved in 27–92%^{103 108 109} and complete resolution in up to 75% of cases.¹⁰³ TIPS results in a secondary decrease in the activation of the renin-angiotensin-aldosterone system, and increases sodium excretion.¹¹⁰

Prospective randomised trials have shown TIPS to be more effective in controlling ascites compared with large volume paracentesis.^{111–113} However, there is no consensus regarding the impact of TIPS on transplant free survival in patients with refractory ascites. In one study TIPS had no effect on survival¹¹² while others have reported both reduced¹¹¹ as well as improved survival¹¹³ compared with therapeutic paracentesis. Moreover, TIPS also improves the overall nutritional well being of patients, but whether this is simply secondary to control of ascites and improved eating is not clear.^{110 114 115} Hepatic encephalopathy after TIPS insertion occurs in approximately 25% of patients, and the risk is higher in those over the age of 60 years.¹¹⁶ TIPS is associated with less favourable outcome in advanced Child-Pugh class C patients.¹¹¹ TIPS increases the cardiac preload, and hence it may precipitate heart failure in those with pre-existing heart disease.¹¹⁷ TIPS insertion should be considered as a treatment option for patients who require frequent paracentesis (generally >3 a month). TIPS has also been shown to resolve hepatic hydrothorax in 60–70% of patients.^{118–120}

Model for end stage liver disease score, which was originally developed to predict survival following a TIPS procedure,¹²¹ has continued to evolve into a model that predicts prognosis in cirrhosis.¹²² According to the initial TIPS model, a risk score is calculated as

$$R = 0.957 \times \log_e (\text{creatinine mg/dl}) + 0.378 \times \log_e (\text{bilirubin mg/dl}) + 1.120 \times \log_e (\text{international normalised ratio}) + 0.643 \times (\text{cause of cirrhosis})$$

where cause of cirrhosis is coded as 0 for alcoholic or cholestatic liver diseases and 1 for other causes. Please note that old units are used for both creatinine and bilirubin. Patients with a risk score $R > 1.8$ have a median survival of three months after elective TIPS and are considered

unsuitable for the procedure unless it is being performed as a bridge to liver transplantation.¹²¹ Patients with a risk score $R = 1.5$ have a median survival of six months and those with $R = 1.3$ have a median survival of 12 months.

Recommendation

- TIPS can be used for the treatment of refractory ascites requiring frequent therapeutic paracentesis or hepatic hydrothorax with appropriate assessment of risk benefit ratio. (Level of evidence: 1b; recommendation: B.)

6.0 PROGNOSIS

The development of ascites is associated with a mortality of 50% within two years of diagnosis.^{2–5} Once ascites becomes refractory to medical therapy, 50% die within six months.¹²³ Despite improving fluid management and patient quality of life while awaiting liver transplantation, treatments such as therapeutic paracentesis and TIPS do not improve long term survival without transplantation for most patients.^{103 124 125} Therefore, when any patient with cirrhosis develops ascites, suitability for liver transplantation should be considered. Attention should be given to renal function in patients with ascites as pre-transplant renal dysfunction leads to greater morbidity and delayed recovery following liver transplantation and is associated with a prolonged stay in the intensive care unit and hospital.^{126–128}

Recommendation

- Liver transplantation should be considered in patients with cirrhotic ascites. (Level of evidence: 1C; recommendation: B.)

7.0 SPONTANEOUS BACTERIAL PERITONITIS

Spontaneous bacterial peritonitis (SBP) is the development of a monomicrobial infection of ascites in the absence of a contiguous source of infection. SBP is a frequent and serious complication of cirrhotic patients with ascites. The prevalence of SBP in cirrhotic hospitalised patients with ascites ranges between 10% and 30%.^{29–31} When first described, its mortality exceeded 90% but in-hospital mortality has been reduced to approximately 20% with early diagnosis and prompt treatment.⁸⁵

7.1 Diagnosis

Patients with SBP are frequently asymptomatic.^{129 130} However, a significant proportion have some symptoms such as fever, mild abdominal pain, vomiting, or confusion. Diagnosis should also be suspected in those who present with hepatic encephalopathy, impairment of renal function, or peripheral leucocytosis without any obvious precipitating factor. A diagnostic paracentesis is mandatory in all patients with cirrhosis requiring hospital admission.³¹

7.1.1 Ascitic fluid analysis

The diagnosis of SBP is confirmed when ascitic neutrophil count is >250 cells/mm³ ($0.25 \times 10^9/l$) in the absence of an intra-abdominal and surgically treatable source of sepsis. A cutoff of 250 neutrophils/mm³ has the greatest sensitivity although a cutoff of 500 neutrophils/mm³ has greater

specificity.^{131–134} In patients with haemorrhagic ascites with a fluid red blood cell count of $>10\,000/\text{mm}^3$ (due to concomitant malignancy or traumatic tap), subtraction of one neutrophil per 250 RBC should be made to adjust for the presence of blood in ascites.³¹ Historically, neutrophil counts have been carried out by oncall microbiologists, as coulter counter determinations of neutrophil counts were inaccurate at the relatively low but pathological levels of neutrocytosis in ascitic fluid (for example, polymorphonuclear cell (PMN) count of $500\text{ cells}/\text{mm}^3$). However, one recent study found excellent correlation between these two techniques, even at low counts, suggesting that automated counting may replace manual counts.¹³⁵ Gram's stain of a smear of sediments obtained after centrifugation of ascites fluid is rarely helpful and should not be routinely requested.³⁴

7.1.2 Ascitic fluid culture

This has been discussed before under ascitic fluid investigations (see above). Patients with “culture negative neutrocytic ascites” (PMN count $>250\text{ cells}/\text{mm}^3$ ($0.25 \times 10^9/\text{l}$)) have a similar clinical presentation to those with culture positive SBP.^{136–137} As both groups of patients are associated with significant morbidity and mortality,^{136–137} they should be treated in a similar fashion. Some patients have “mono-microbial bacterascites” in which cultures are positive but there is normal ascitic neutrophil count.¹³⁸ Such infections are thought to occur relatively commonly, and the majority are eradicated by the body's natural defence mechanisms (for example, opsonic and complement mediated bactericidal activity).^{138–139} When a positive culture is obtained, a further ascitic tap with a neutrophil count should be obtained. If the neutrophil is normal and patient is asymptomatic, then ignore the positive culture, but re-culture.^{138–140} If the neutrophil count is $>250\text{ cells}/\text{mm}^3$, then treat as per SBP.

Recommendations

- A diagnostic paracentesis should be performed in all cirrhotic patients with ascites on hospital admission. (Level of evidence 1a; recommendation A.)
- A diagnostic paracentesis should be performed in all cirrhotic patients with ascites in those who have signs and symptoms of peritoneal infection, including the development of encephalopathy, renal impairment, or peripheral leucocytosis without a precipitating factor. (Level of evidence: 2b; recommendation: C.)
- Ascitic fluid should be inoculated into blood culture bottles at the bedside. (Level of evidence: 2a; recommendation: B.)

7.2 Treatment

7.2.1 Antibiotics

The commonest organisms isolated in patients with SBP include *Escherichia coli*, gram positive cocci (mainly streptococcus species) and enterococci. These organisms account for approximately 70% of all cases of SBP.^{85–141} Cefotaxime has been the most extensively investigated in patients with SBP because it covers 95% of the flora isolated from ascitic fluid and achieves high ascitic fluid concentrations during therapy.^{28–142} Five days of treatment with cefotaxime is as effective as 10 day therapy,¹⁴³ and low dose (2 g twice daily) is similar in efficacy to the higher doses (2 g four times daily).¹⁴⁴ Other cephalosporins, such as ceftriaxone and ceftazidime as well as co-amoxiclav (amoxicillin plus

clavulanic acid), have been shown to be as effective as cefotaxime in resolving SBP.^{31–145} In patients who are “well” (asymptomatic), with bowel sounds, SBP can be treated with oral antibiotics.²⁷ Under these circumstances either oral ciprofloxacin (750 mg twice daily) or oral co-amoxiclav (1000/200 mg amoxicillin/clavulanic acid three times daily), subject to renal function, is logical.

Resolution of infection in SBP is associated with an improvement in symptoms and signs. However, for those patients who do not improve, treatment failure should be recognised early. A reduction in ascitic fluid neutrophil count of less than 25% of the pretreatment value after two days of antibiotic treatment suggests failure to respond to therapy.³¹ This should raise the suspicion of “secondary peritonitis” (secondary to perforation or inflammation of intra-abdominal organs) and indicate further evaluation or modification of antibiotic treatment according to in vitro sensitivity or on an empiric basis. The presence of multiple organisms in ascitic fluid is strongly suggestive of perforated bowel, and needs further urgent investigation.³¹ Although algorithms, including estimation of ascetic fluid protein, glucose, lactate dehydrogenase, carcinoembryonic antigen, and alkaline phosphatase levels have been proposed to distinguish “secondary peritonitis” from SBP,^{146–147} erect chest x ray and abdominal computed tomography scan are the most useful in practice.

7.2.2 Albumin infusion in SBP

Development of renal impairment occurs in 30% of patients with SBP and is one of the strongest predictors of mortality in SBP.¹⁴⁶ A recent study suggests that cefotaxime plus albumin improves survival and decreases the incidence of renal impairment to 10%.¹⁴⁹ This study has since been criticised as the control group were not given an equivalent amount of fluid as crystalloid. A further study has demonstrated that treatment with albumin is associated with significant improvement in circulatory function and lower frequency of endothelial dysfunction compared with equivalent doses of hydroxyethyl starch.¹⁵⁰ But the latter study was not powered to compare clinical outcomes such as renal failure and mortality. We believe that further studies are required before making any formal recommendations about the use of albumin in SBP. However, if patients have an increased serum creatinine or a rising serum creatinine, we would support infusing 1.5 g albumin/kg in the first six hours, followed by 1 g/kg on day 3, which is the regimen adopted by the Barcelona group in their study on the use of albumin in SBP.¹⁴⁹

7.2.3 Total paracentesis for SBP

There are no data on the role of total paracentesis in the management of SBP.

Recommendations

- In patients with an ascitic fluid neutrophil count of $>250\text{ cells}/\text{mm}^3$, empiric antibiotic therapy should be started. (Level of evidence: 1b; recommendation: A.)
- Third generation cephalosporins such as cefotaxime have been most extensively studied in the treatment of SBP and have been shown to be effective. (Level of evidence: 1a; recommendation: A.)
- Patients with SBP and signs of developing renal impairment should be given albumin at 1.5 g albumin/kg in the first six hours followed by 1 g/kg on day 3. (Level of evidence: 2b; recommendation: B.)

7.3 Prophylaxis

For patients who have never had SBP and in whom ascitic fluid protein concentration is low (<10 g/l), there is no consensus among experts regarding primary prophylaxis.³¹ In patients who survive an episode of SBP, the cumulative recurrence rate at one year is approximately 70%.⁸⁵ Probability of survival at one year after an episode of SBP is 30–50% and falls to 25–30% at two years.^{151–152} Therefore, patients recovering from an episode of SBP should always be considered as a potential candidate for liver transplantation. In patients who had one episode of SBP, oral norfloxacin (400 mg/day) reduces the probability of recurrence of SBP from 68% to 20% and the probability of SBP due to gram negative bacilli from 60% to 3%.¹⁵³ However, studies of antibiotic prophylaxis using norfloxacin or ciprofloxacin in patients with low ascites fluid protein concentration (<15 g/l) have included a heterogeneous group of patients with and without previous episodes of SBP.^{154–155} In the UK many centres use once daily ciprofloxacin as prophylaxis against SBP, although many also use norfloxacin. One study reported that patients with cirrhosis on long term quinolone prophylaxis developed more gram positive bacterial infections (79%), including methicillin resistant *Staphylococcus aureus*, compared with predominantly gram negative infections (67%) in those who were not on prophylaxis.¹⁵⁶

Recommendations

- Patients recovering from one episode of SBP should receive prophylaxis with continuous oral norfloxacin 400 mg/day (or ciprofloxacin at 500 mg once daily). (Level of evidence: 1b; recommendation: B.)
- All patients with SBP should be considered for referral for liver transplantation. (Level of evidence: 1c; recommendation: B.)

8.0 CONCLUSIONS

The development of ascites is an important landmark in the natural history of cirrhosis. Adequate management of ascites is important, not only because it improves quality of life in patients with cirrhosis, but also prevents serious complication such as SBP. However, treatment of ascites does not significantly improve survival. Therefore, development of ascites should be considered as an indication for transplantation. Liver transplantation is the ultimate treatment of ascites and its complications.

Summary of recommendations: management of ascites in cirrhosis

Diagnosis

- It is recommended that patients give informed consent for a therapeutic or diagnostic paracentesis.
- The initial ascitic fluid analysis should include serum ascites-albumin gradient in preference to ascitic protein.
- Ascitic amylase should be measured when there is clinical suspicion of pancreatic disease.
- Ascitic fluid should be inoculated into blood culture bottles at the bedside and examined by microscopy for a neutrophil count.

Treatment

- Bed rest is not recommended for the treatment of ascites.
- Dietary salt should be restricted to a no added salt diet of 90 mmol salt/day (5.2 g salt/day).

Hyponatraemia

- Serum sodium 126–135 mmol/l, normal serum creatinine. Continue diuretic therapy, but observe serum electrolytes. Do not water restrict.
- Serum sodium 121–125 mmol/l, normal serum creatinine. International opinion is to continue diuretic therapy, our opinion is to stop diuretic therapy or adopt a more cautious approach.
- Serum sodium 121–125 mmol/l, serum creatinine elevated (>150 µmol/l or >120 µmol/l and rising). Stop diuretics and give volume expansion.
- Serum sodium ≤120 mmol/l, stop diuretics. The management of these patients is difficult and controversial. We believe that most patients should undergo volume expansion with colloid (haemaccel, gelofusine, or voluven) or saline. However, avoid increasing serum sodium by >12 mmol/l per 24 hours.

Diuretics

- Firstline treatment of ascites should be spironolactone alone, increasing from 100 mg/day to a dose of 400 mg/day.
- If this fails to resolve ascites, frusemide should be added in a dose of up to 160 mg/day but this should be done with careful biochemical and clinical monitoring.

Therapeutic paracentesis

- Therapeutic paracentesis is the firstline treatment for patients with large or refractory ascites.
- Paracentesis of <5 litre of uncomplicated ascites should be followed by plasma expansion with a synthetic plasma expander (150–200 ml of gelofusine or haemaccel), and does *not* require volume expansion with albumin.
- Large volume paracentesis should be performed in a single session with volume expansion being given once paracentesis is complete, preferably using 8 g albumin/l of ascites removed (that is, ~100 ml of 20% albumin/3 l ascites).

TIPS procedure

- TIPS could be used for the treatment of refractory ascites requiring frequent therapeutic paracentesis or hepatic hydrothorax with appropriate assessment of risk benefit ratio.

Liver transplantation

- Liver transplantation should be considered in patients with cirrhotic ascites.
- All patients with SBP should be considered for referral for liver transplantation.

Spontaneous bacterial peritonitis (SBP)

Diagnosis

- A diagnostic paracentesis should be performed in all cirrhotic patients with ascites on hospital admission.
- A diagnostic paracentesis should be performed in all cirrhotic patients with ascites in those who have signs and symptoms of peritoneal infection including the development of encephalopathy, renal impairment, or peripheral leucocytosis without a precipitating factor.
- Ascitic fluid should be inoculated into blood culture bottles at the bedside.

Treatment

- In patients with ascitic fluid neutrophil count of >250 cells/mm³, empiric antibiotic therapy should be started.
- Third generation cephalosporins such as cefotaxime have been most extensively studied in the treatment of SBP and have been shown to be effective.
- Patients with SBP and signs of developing renal impairment should be given albumin at 1.5 g albumin/kg in the first six hours followed by 1 g/kg on day 3.

Prophylaxis

- Patients recovering from one episode of SBP should receive prophylaxis with continuous oral norfloxacin 400 mg/day (or ciprofloxacin at 500 mg once daily).

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10. 0 APPENDIX 1

Table A2 summarises the levels of evidence according to the Oxford Centre for Evidence-based Medicine.

Level	Therapy/prevention/aetiology/harm	Prognosis	Diagnosis	Differential diagnosis/symptom prevalence study	Economic and decision analyses
1a	SR (with homogeneity*) of RCTs	SR (with homogeneity*) of inception cohort studies; CDR† validated in different populations	SR (with homogeneity*) of level 1 diagnostic studies; CDR† with 1b studies from different clinical centres	SR (with homogeneity*) of prospective cohort studies	SR (with homogeneity*) of level 1 economic studies
1b	Individual RCT (with narrow confidence interval)	Individual inception cohort study with ≥80% follow up; CDR† validated in a single population	Validating¶ cohort study with good§ reference standards; or CDR† tested within 1 clinical centre	Prospective cohort study with good follow up§§	Analysis based on clinically sensible costs or alternative systematic reviews of the evidence and including multi-way sensitivity analyses
1c	All or none‡	All or none case series	Absolute SpPin and SnNout‡‡	All or none case series	Absolute better value or worse value analysis***
2a	SR (with homogeneity*) of cohort studies	SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity*) of level >2 diagnostic studies	SR (with homogeneity*) of level 2b and better studies	SR (with homogeneity*) of level >2 economic studies
2b	Individual cohort study (including low quality RCT (<80% follow up))	Retrospective cohort study of follow up of untreated controls in an RCT; Derivation of CDR† or validation on split samples¶¶ only	Exploratory¶ cohort study with good§ reference standards; CDR† after derivation; or validated only on split samples¶¶ or databases	Retrospective cohort study, or poor follow-up	Analysis based on clinically sensible costs or alternatives; limited reviews of the evidence, or single study; and including multi-way sensitivity analysis
2c	"Outcomes" research, ecological studies	"Outcomes" research		Ecological studies	Audit or "outcomes" research
3a	SR (with homogeneity*) of case control studies		SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies
3b	Individual case control study		Non-consecutive study, or without consistently applied reference standards	Non-consecutive study, or very limited population	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations
4	Case series (and poor quality cohort and case-control studies**)	Case series (and poor quality prognostic cohort studies††)	Case control study, poor or non-dependent reference standards	Case series or supervised reference standards	Analysis with no sensitivity analysis
5	Expert opinion without explicit critical appraisal or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal or based on physiology, bench research, or "first principles"	Expert opinion without explicit critical appraisal or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal or based on physiology, bench research or "first principles"

SR, Systematic review; RCT, randomised controlled trial.
 *Homogeneity means a systematic review that is free from worrisome variations (heterogeneity) in the results between individual studies.
 †Clinical decision rules are algorithms or scoring systems leading to a diagnostic category or prognostic estimation.
 ‡All patients died before the therapy became available, but some survive now on it, or some died before therapy became available, but none now die on it.
 ¶Validating studies test the quality of a diagnostic test, based on prior evidence. An exploratory study collects information and (for example, using a regression analysis) identifies which factors are significant
 §Good, better, bad, and worse refer to the comparison between treatments in terms of their clinical benefit and risks.
 **Poor quality cohort study is one that failed to define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded) objective way in both exposed and non-exposed individuals, and/or failed to identify and control for confounders and/or to complete long follow up. Poor quality case control study is one that failed to define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded) objective way in both cases and controls, and/or failed to identify and control for confounders.
 ††Poor quality prognostic cohort study is one with biased sampling in favour of patients who already had the target outcome, or outcomes were measured in <80%, or outcomes were determined in an unblinded non-objective way, or there was no correction for the confounders.
 ‡‡An "absolute SpPin" is a diagnostic finding whose specificity is so high that a positive result confirms the diagnosis. "Absolute SnNout" is a diagnostic finding whose sensitivity is so high that negative results rule out the diagnosis.
 ¶¶Split sample validation is achieved by collecting all the information in a single tranche and then dividing this into "derivation" and "validation" samples.
 §§Good follow up is >80%, with adequate time for alternative diagnosis to emerge (for example, 1–8 months acute, 1–5 years chronic).
 ***Better value treatments are clearly as good, but cheaper or better at the same or reduced cost. Worse value treatments are as good and more expensive, or worse and equally/more expensive

11. 0 APPENDIX 2

Table A2 summarises the grades of recommendations.

A	Consistent level 1 studies
B	Consistent level 2 or 3 studies or extrapolations from level 1 studies
C	Level 4 studies or extrapolations from level 2 and 3 studies
D	Level 5 evidence or troublingly inconsistent studies at any level