Review article: management of ascites and associated complications in patients with cirrhosis

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SUMMARY

Background
Ascites is the most common complication of cirrhosis, associated with an expected survival below 50% after 5 years. Prognosis is particularly poor for patients with refractory ascites and for those developing complications, including spontaneous bacterial peritonitis (SBP) and hepatorenal syndrome (HRS).

Aim
To provide an evidence-based overview of the pathophysiology, diagnosis and clinical management of ascites secondary to liver cirrhosis.

Methods
Review based on relevant medical literature.

Results
Portal hypertension, splanchnic vasodilatation and renal sodium retention are fundamental in the pathophysiology of ascites formation. The SAAG (serum-ascites albumin gradient) allows reliable assessment of the cause of ascites. The majority of cirrhotic patients with ascites can be managed with dietary sodium restriction in combination with diuretic agents. Large volume paracentesis with albumin suppletion and TIPS are therapeutic options in patients with refractory ascites. Prophylactic antibiotics for SBP should be given in certain patient populations.

Conclusions
Recent advances in the diagnosis and treatment of ascites and associated complications have improved the medical management and poor prognosis of patients with these manifestations of advanced liver disease. Early diagnosis, adequate treatment and focus on prevention of complications remain essential as well as timely referral for liver transplantation.

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INTRODUCTION

Ascites, the accumulation of fluid in the abdomen, is what the Greeks referred to as ‘askos’ or bag. In 2000 BC ascites was a known physical symptom with an established therapy: abdominal paracentesis.

Nearly 50% of patients with liver cirrhosis develop ascites within 10 years of diagnosis. The presence of ascites indicates an advanced stage of liver disease and has important prognostic significance: 50% of patients who develop ascites can be expected to die within 2–5 years of onset. The prognosis for patients with ascites and alcoholic liver disease is considered to be worse than that for those with viral liver disease.

ASCITES

Pathogenesis

In the course of time there have been several hypotheses about how ascites develops in patients with cirrhosis. The currently accepted theory integrates several of the earlier hypotheses and is known as the forward (or arterial vasodilation) theory of ascites formation. The fundamental underlying abnormality is portal hypertension. In patients with cirrhosis and portal hypertension the production of local (splanchnic) vasodilators, especially nitric oxide, is markedly increased. This in turn induces splanchnic arteriolar vasodilatation, which is responsible for both an increase in splanchnic capillary pressure and permeability and a decrease in effective arterial blood volume. The increased production of lymph fluid and the compensatory activation of the renin-angiotensin-aldosterone-system (RAAS) and sympathetic nervous system and hypersecretion of antidiuretic hormone eventually lead to the formation of ascites (Figure 1).

In patients with cirrhosis the blood and plasma volumes are increased. This large intravascular volume is unequally distributed. In most regions the volume remains unaffected, except for the splanchnic area where it is significantly increased, from 19% of the total volume in healthy individuals up to 22–25% in patients with cirrhosis. Central and arterial blood volume on the other hand are markedly decreased. The reduction in arterial pressure, i.e. systemic, diastolic and mean arterial pressure, and effective arterial blood volume are markers for advancement of the disease. In early stages this vasodilatation can be compensated by an increase in plasma volume and cardiac output; when the disease progresses and this compensation is no longer sufficient, there is activation of the RAAS and sympathetic nervous system. An increased absorption of sodium and water has to balance the effect of the splanchnic vasodilation. Aldosterone increases sodium reabsorption in the distal nephron, while the sympathetic nervous system is responsible for an increased reabsorption of sodium in the proximal tubules, loop of Henle and distal and collecting tubules.

With RAAS and sympathetic nervous system activated and an ongoing decrease in effective arterial blood volume, antidiuretic hormone secretion will be stimulated, being responsible for dilutional hyponatraemia. Hyponatraemia only occurs in a late stage of the disease.

Stages of ascites

Patients with ascites can be divided into a group with uncomplicated ascites and a group with refractory ascites (Table 1). Refractory ascites occurs in 5–10% of the patients. It consists of a group with diuretic-resistant ascites (or a reduced response to diuretic treatment), and a group with diuretic-intractable ascites (patients who develop complications due to the diuretic treatment).

Evaluation

In the cirrhotic patient the physical examination may reveal splenomegaly, abdominal cutaneous collaterals and other abnormalities, indicating portal hypertension. The abdomen should be examined for ascites (abdominal distension; shifting dullness), and tenderness. In patients with marked ascites, umbilical, inguinal and cicatricial hernias, leg oedema and a poor nutritional status with muscular wasting are common. Pleural effusions, usually right-sided, may be present. Circulatory parameters (blood pressure, central venous pressure, heart rate) should be determined and often point to a hyperdynamic circulation with low blood pressure and tachycardia.

For patients with ascites and clinical deterioration or problems (e.g. fever, encephalopathy, anorexia, abdominal pain, gastrointestinal haemorrhage, renal failure, new hospital admissions) a diagnostic paracentesis should be the standard treatment. Routine investigations include total protein and albumin concentration, total white blood cell count, neutrophil
**Table 1. Stages of ascites**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Severity of ascites</th>
<th>Primary treatment</th>
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<tbody>
<tr>
<td>1</td>
<td>Only detectable by ultrasound</td>
<td>General rules</td>
</tr>
<tr>
<td>2</td>
<td>Moderate ascites; abdominal distension</td>
<td>Diuretic treatment; salt restriction</td>
</tr>
<tr>
<td>3</td>
<td>Massive ascites; marked abdominal distension</td>
<td>Diuretic treatment, therapeutic paracentesis, TIPS</td>
</tr>
<tr>
<td>Refractory</td>
<td>Un-/hyporesponsive to diuretic treatment; side effects of diuretics</td>
<td>Therapeutic paracentesis, TIPS, OLT</td>
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</table>

TIPS, transjugular intrahepatic portosystemic shunts; OLT, orthotopic liver transplantation.

**Figure 1. Pathophysiology of ascites and hepatorenal syndrome.**
count and culture. According to the clinical context analysis may also include cytological examination and measurement of the concentrations of glucose, haemoglobin, amylase, cholesterol and triglycerides. Roughly 15% of patients with cirrhosis develop ascites of non-hepatic origin. Classification of ascites based on the serum albumin ascites gradient (SAAG) has replaced the exsudate–transudate concept and provides a reliable tool to determine whether ascites can be attributed to portal hypertension or has another aetiology. The SAAG is calculated by subtracting the ascitic fluid albumin concentration from the serum albumin concentration. The serum and ascites samples should be obtained at approximately the same time. When the SAAG is <11 g/L the aetiology of ascites is very likely to be of non-portal hypertensive origin; a SAAG of ≥11 g/L is highly suggestive of a portal hypertensive cause but is also found when ascites is caused by right-sided cardiac failure or constrictive pericarditis.

Management of ascites

The management of ascites is determined by the severity of symptoms (Table 1). Presence of ascites per se is not an indication for treatment. In addition, the removal of all ascites is not a therapeutic goal. It is old clinical wisdom that it is better to have a patient ‘wet and wise’ rather than ‘dry and demented’. Another key therapeutic principle is that great attention has to be paid for adequate treatment of the underlying liver disease. Alcohol abstinence in alcoholic liver disease and immuno-suppressives in autoimmune hepatitis may have a dramatic effect on otherwise difficult-to-manage ascites.

For patients with ascites mild-to-moderate dietary sodium restriction (60–90 mmol/day) is usually advised which may result in the disappearance of ascites in up to 15% of cases. A trial that compared low (50 mmol/day) to high sodium content diets (120 mmol/day) showed that in addition to a better compliance, the resolution of ascites in the latter group was more rapid. Especially for those patients who show no or little response to diuretic treatment, strict sodium restriction may be beneficial. However, a major drawback of dietary sodium restriction is that it makes meals less tasty and thus may reduce appetite and caloric intake. This is of great concern for patients who are already severely malnourished. The use of sodium-free salt preparations may occasionally be helpful.

Water restriction should only be considered for patients with dilutional hyponatraemia. The latter is diagnosed when serum sodium is <130 mmol/L in the presence of ascites and/or oedema. In these patients daily fluid intake is usually limited to 1 L. To date no studies have been conducted to document the effectiveness of this restriction.

The large majority of patients do not respond sufficiently to the above-mentioned measures and require additional treatment with diuretics. Treatment with spironolactone, an aldosterone antagonist, has been shown to be quite effective. The recommended dosage is 100–200 mg/day (maximum dose 400 mg/day), but 25–50 mg can be sufficient. The majority of patients responds sufficiently to treatment with spironolactone alone. Hyperkalaemia and painful gynaecomastia are the most common side effects. When response to spironolactone is insufficient, adjuvant therapy with loop diuretics is often effective. Furosemide is the drug of first choice, with a recommended initial dosage of 20–40 mg/day (max 160 mg/day). With the use of furosemide, beware of hypokalaemia, metabolic hypochloraemic alkalosis, hyponatraemia and hypovolaemia which may lead to renal impairment and precipitate encephalopathy. Spironolactone and furosemide together lead to the disappearance of ascites in approximately 90% of all patients with cirrhosis and ascites. A recent study comparing combination therapy of spironolactone and furosemide with spironolactone monotherapy showed that the two treatment modalities are equally effective in relieving ascites. As spironolactone monotherapy requires fewer dose adjustments, it is a good alternative to the standard combination therapy.

Management of refractory ascites

When patients do not respond to diuretic treatment and sodium restriction or develop side effects of diuretic treatment, they are considered to have refractory ascites. The grave prognosis associated with refractory ascites should always lead to the consideration of liver transplantation. In the interval before liver transplantation or as regular treatment, the therapeutic options are therapeutic paracentesis, transjugular intrahepatic portosystemic shunts (TIPS) or repeated albumin infusion.
Therapeutic paracentesis

Therapeutic large volume paracentesis (LVP) instantaneously relieves symptoms. It is safe to remove all ascitic fluid in a single tap. A suction pump can be used to shorten the duration to 1–2 h. Paracentesis is followed by intravascular and extravascular body fluid redistribution and may lead to rapid mobilization of peripheral oedema. The most common complication is paracentesis-induced circulatory dysfunction (PICD). Up to 5 L of ascitic fluid can be tapped without the need to substitute for the reduced plasma volume. After LVP (>5 L) intravenous administration of plasma expanders is indicated to prevent PICD.

As to what mechanism leads to PICD there is no concrete answer. It is known that paracentesis induces, shortly after the procedure, a decrease in systemic vascular resistance (SVR). This decrease is seen in patients who do not develop PICD, but is even larger in patients who do develop PICD. As plasma volume remains constant, the decrease in SVR after paracentesis triggers further activation of the vasoconstrictor systems, i.e. RAAS and sympathetic nervous system. A comparison of patients who did or did not receive plasma expansion after paracentesis showed that those receiving plasma expansion also exhibited PICD, only later, between days 2 and 6 after paracentesis.

Paracentesis-induced circulatory dysfunction should be avoided as reduced effective arterial blood volume and a drop in arterial blood pressure lead to a decrease in both renal blood flow and glomerular filtration rate. This facilitates the development of complications associated with paracentesis such as hepatorenal syndrome (HRS) and spontaneous bacterial peritonitis (SBP). Although many studies have shown that when plasma expansion is applied during LVP subsequent complications are significantly less severe, the use of plasma expanders in this case is, for some doctors, still controversial. The current gold standard is intravenous albumin, 8 g/L ascitic fluid removed. With this substitution the lowest incidence of PICD is seen.

The use of albumin has been compared with an isotonic saline solution for substitution during paracentesis. Among those patients who had an LVP of more than 6 L the incidence of PICD was significantly higher for those receiving saline (33% vs. 14%). Similar studies have been conducted with other plasma expanders, such as dextran-70 and polygeline; the results obtained in those studies were better than those reported for saline, but albumin remained the best substitution. The drawbacks of albumin are the high cost and the risk of transmitting an infectious agent as human albumin is a blood product. These arguments are responsible for the fact that albumin is not generally used as substitution during LVP (Figure 2).

A pilot study performed by Moreau et al. showed that intravenous administration of terlipressin, a vasopressin pro-drug, is nearly equivalent to albumin in the prevention of PICD. This finding awaits confirmation by additional, larger studies.

Transjugular intrahepatic portosystemic shunt

Transjugular intrahepatic portosystemic shunts are functional side-to-side portocaval shunts that decrease portal pressure and may improve renal sodium excretion. TIPS have been shown to be better in relieving ascites than therapeutic paracentesis. However, there are several disadvantages. First of all, not all patients qualify for TIPS. Patients with a Child-Pugh score ≥12 appear to undergo little benefit from TIPS placement; they have a greater chance of developing complications. The same is true for patients with a bilirubin level of ≥85 µmol/L or a serum creatinine of ≥177 µmol/L. Careful consideration should be given in these patients as to whether TIPS placement is medically feasible, and will presumably increase the prognosis and the quality of life for the individual patient.

There is a 20–30% chance of developing hepatic encephalopathy after TIPS placement. Furthermore, up to 70% of the uncoated stents occlude within the first
The more expensive covered stents have been found to be less prone to these occlusions than uncoated stents.\textsuperscript{24, 25}

There is only one study in which patients with TIPS exhibited a better survival than those receiving therapeutic paracentesis; patients with a Child-Pugh score C were not included in the study. All other studies show no difference in survival between the two treatments.\textsuperscript{3, 26} Patients with preserved liver function exhibit the best improvement after TIPS placement.\textsuperscript{3} Although patients treated with TIPS were expected to have a better quality-of-life than those undergoing repeated therapeutic paracenteses, Campbell \textit{et al.} demonstrated that both treatment groups exhibit the same trend for prognosis and quality-of-life. Complications such as stent occlusion and hepatic encephalopathy competed with the impact of repeated paracentesis on the patient.\textsuperscript{27} It must be noted that the studies which led to this conclusion all used uncoated stents. Studies with the newer covered stents have yet to be conducted.

Peritoneovenous (LeVeen; Denver) shunts have not been demonstrated to be more efficacious than repeated paracenteses and complications, including occlusion, infection and disseminated intravascular coagulation, are frequent. These devices are nowadays seldom used for the treatment of refractory ascites.

Repeated albumin infusion

Repeated administration of albumin (either in combination with or without diuretics) on a (bi)-weekly basis can significantly lower the accumulation rate of ascites.\textsuperscript{25} This approach could be considered for patients who are not eligible for TIPS or liver transplantation and who do not tolerate repeated LVP.\textsuperscript{28, 29}

Liver transplantation

Ascites in patients with cirrhosis indicates an advanced stage of disease and should always lead to careful consideration of all therapeutic options, including liver transplantation. For patients with refractory ascites, liver transplantation will effectively control this problem.\textsuperscript{30}

COMPLICATIONS

Ascites can cause considerable discomfort. Marked fluid accumulation can be accompanied by feelings of fullness at meals, poor appetite, diminished caloric intake and dyspnoea. Other problems are hepatic hydrothorax and the frequent occurrence of hernias. This review focuses on the two major complications of ascites: SBP and HRS.

Spontaneous bacterial peritonitis

Spontaneous bacterial peritonitis is an infection of ascitic fluid in patients with cirrhosis and is defined by an ascitic polymorphonuclear leucocyte (PMN) count of \( \geq 0.25 \times 10^9/L \).\textsuperscript{31} SBP is thought to develop as a result of delayed intestinal transit and increased permeability of the intestinal wall. In this setting bacteria migrate from the intestinal lumen to the mesenteric lymph nodes, a process known as bacterial translocation.\textsuperscript{32} The deficient immune system in cirrhotic patients facilitates colonization of bacteria in the mesenteric lymph nodes. Via the circulation bacteria can travel to other locations, including the ascitic fluid.

Spontaneous bacterial peritonitis is the most common infection in patients with cirrhosis and ascites, with a reported lifetime risk of up to 33%.\textsuperscript{3} SBP is particularly prevalent in cirrhotic patients who are admitted to hospital. In contrast, among asymptomatic patients seen in an outpatient clinic SBP is rare.\textsuperscript{33} Most patients present with fever, abdominal pain, chills, general malaise, loss of appetite, nausea or vomiting. In nearly 50% a change in mental status is detected.

The long-term prognosis for patients with SBP is poor, with reported mortality rates at 1 and 2 years of 50–70% and 70–75% respectively.\textsuperscript{24} Patients recovering from an episode of SBP should be con-
sidered as potential candidates for liver transplantation.\textsuperscript{34}

**Diagnosis**

For any cirrhotic patient presenting with new or deteriorating symptoms or clinical problems, the presence of SBP should be considered. Consequently, the threshold to perform diagnostic paracentesis should be low. The diagnosis can be made when the PMN count in ascites is \( \geq 0.25 \times 10^9/L \). In addition, microbiological studies are performed by inoculation of at least 10 mL of ascitic fluid in blood culture bottles in aerobic and anaerobic media. To increase the diagnostic yield this should be done immediately after paracentesis at bedside. The most common isolated microorganisms are Gram-negative bacteria, most often *Escherichia coli* or *Klebsiella* species. Usually, only a single bacterial species is found. Cultures showing multiple organisms indicate the possibility of perforation of a hollow organ.

In up to 60% of patients with SBP according to symptoms and an elevated ascitic fluid PMN count cultures remain negative.\textsuperscript{35} Another important problem is that the results of PMN counts are not immediately available, and this may be a particular problem after office hours. Obviously, the results of microbiological cultures are only available after several days.

Recent studies suggest that diagnosis of SBP may be improved by using reagent strips. The principle of these strips is based on the detection of leucocyte esterase. The esterase in the fluid reacts with an ester on the test strip and in combination with a dye it corresponds to the amount of leucocytes present.\textsuperscript{35, 36} Studies comparing reagent strips with laboratory leucocyte counts revealed a diagnostic sensitivity of the strips of 64–100%. The main advantages of reagent strips are the fact that the results are immediately available and the costs are low.\textsuperscript{35, 37–40}

**Treatment**

Antibiotic treatment should be started as soon as the diagnosis, based on the PMN count in ascites, is made. The recommended and most commonly used antibiotics are third-generation cephalosporins and amoxicillin-clavulanic acid. Cefotaxime (2 g intravenously/day) has been studied the most. This drug has a great advantage because it is not nephrotoxic.\textsuperscript{31} Ceftriaxone is a good alternative. Amoxicillin-clavulanic acid has been reported to be equally effective. As this antibiotic is considerably less expensive, it has been suggested as the first choice for patients not receiving prophylaxis for SBP.\textsuperscript{41} Recommended dosage of amoxicillin-clavulanic acid is 1.2 g every 6 h for 5 days. Patients on antibiotic prophylaxis have a higher chance of carrying a Gram-positive causative micro-organism and cephalosporins are then often considered first choice.\textsuperscript{31}

An important recent finding is that intravenous administration of albumin to patients with SBP reduces the risk of complications such as HRS and may significantly improve survival.\textsuperscript{42–44} This effect may be related to an improvement in cardiac function, due to increased arterial filling and a corresponding reduced arterial vasodilation.\textsuperscript{14} Albumin is the only plasma expander that induces this beneficial effect in SBP, being most prominent in Child-Pugh C patients.\textsuperscript{44, 45}

Few data are available with respect to the safety of LVP in patients with SBP. One trial reported a higher incidence of renal impairment and hyponatraemia after paracentesis but differences were not statistically significant.\textsuperscript{44}

**Risk factors**

The severity of the liver disease is a main risk factor for SBP as nearly all patients have advanced Child-Pugh class B or C cirrhosis. A large volume of ascites is also a risk factor, probably because it is associated with low (\( \leq 10 \) g/L) ascitic fluid protein levels. This is thought to result in reduced opsonization capability of PMN leucocytes and macrophages.

A previous episode of SBP is a major risk factor for recurrent infection. Especially in the first year the recurrence rate is high, up to 70%.\textsuperscript{7, 46} Finally, gastrointestinal haemorrhage is a common initiating event and it is now well established that antibiotic prophylaxis under these circumstances is essential.

**Prophylaxis**

Primary antibiotic prophylaxis is indicated for patients with cirrhosis and gastrointestinal haemorrhage either from portal hypertensive or non-portal hypertensive causes. There is no consensus as to whether patients with low ascitic fluid protein concentration (<10 g/L) should receive prophylaxis. Secondary prophylaxis – prevention of recurrent SBP – is indicated for all patients following a first episode of SBP.\textsuperscript{1, 29}
Quinolones are usually preferred, i.e. norfloxacin (1dd 400 mg) or ciprofloxacin (750 mg weekly) after the first episode. For patients who received prophylactic quinolones after the first episode of SBP, the recurrence rate after the first year decreased from 70% to 20%.

Hepatorenal syndrome

Hepatorenal syndrome is a condition characterized by renal vasoconstriction and progressive renal failure in the absence of structural kidney abnormalities. It is one of the most feared complications in patients with cirrhosis. The incidence of HRS is approximately 10% for hospitalized cirrhotic patients. The chance of developing HRS when cirrhosis and ascites are present is 20% in the first year, increasing to 40% in the fifth year. According to the severity and clinical course, HRS can be subdivided into HRS type 1 and type 2.

Hepatorenal syndrome type 1 is the most severe and, if left untreated, the prognosis is extremely poor. Renal failure develops rapidly, in days to weeks, often after a triggering event, and patient survival is limited to 1–2 weeks. The second type develops slowly, usually in patients with refractory ascites. The reported mean survival for type 2 is 6 months.

A key feature of HRS is severe renal vasoconstriction. This is probably a final consequence of marked splanchnic vasodilatation, caused by local vasodilators such as nitric oxide, in patients with cirrhosis and portal hypertension. Splanchnic vasodilation in turn leads to an activation of the RAAS and sympathetic nervous system and increased production or activity of local vasoconstrictors in the kidney. Although this is counterbalanced by increased activity of renal vasodilator mediators to maintain renal perfusion and glomerular filtration rate, vasoconstriction predominates and results in the development of HRS.

The RAAS and sympathetic nervous system are further activated by arterial underfilling caused by splanchnic vasodilation. When renal vasoconstriction, caused by the activation of the two systems, can no longer be compensated HRS develops (Figure 1).

In most cases HRS type 1 develops after a triggering event. The most common event is infection and up to 20% of patients with SBP may develop HRS. LVP without albumin administration and gastrointestinal bleeding are also precipitating events. Important iatrogenic triggers are the administration of radiological contrast agents, nephrotoxic antibiotics (aminoglycosides) and non-steroidal anti-inflammatory drugs.

The diagnosis of HRS is based on exclusion of other potential causes of renal failure in the patient with cirrhosis (Table 3). The International Ascites Club has developed major and minor criteria for the diagnosis of HRS (Table 4).

<table>
<thead>
<tr>
<th>Table 3. Causes of renal failure in patients with liver cirrhosis</th>
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<tbody>
<tr>
<td>Dehydration</td>
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<tr>
<td>Shock (haemorrhagic/septic)</td>
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<tr>
<td>Nephrotoxic drugs</td>
</tr>
<tr>
<td>Intrinsic kidney disease</td>
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<tr>
<td>Acute tubular necrosis</td>
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<tr>
<td>Hepatorenal syndrome</td>
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<th>Table 4. Diagnostic criteria for HRS as proposed by the International Ascites Club</th>
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<tbody>
<tr>
<td><strong>Major criteria</strong></td>
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<tr>
<td>Low GFR, as indicated by serum creatinine &gt;132 mmol/L</td>
</tr>
<tr>
<td>Exclusion of shock, bacterial infection, volume depletion, use of nephrotoxic drugs</td>
</tr>
<tr>
<td>No improvement in renal function despite stopping diuretics and volume repletion</td>
</tr>
<tr>
<td>No proteinuria or ultrasonic evidence of obstructive uropathy or parenchymal renal disease</td>
</tr>
<tr>
<td>Serum sodium concentration &lt;130 mmol/L</td>
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</tbody>
</table>

HRS, hepatorenal syndrome; GFR, glomerular filtration rate. * Only major criteria are required for the diagnosis of HRS.
Treatment

Patients with HRS type 1 require intensive monitoring. Diuretics should be stopped together with other potential nephrotoxic drugs and precipitating factors should be treated adequately. Diagnostic paracentesis is indicated to rule out SBP. Therapeutic LVP may have an adverse effect and should preferably be avoided. Part of the initial therapeutic approach is a fluid challenge with an albumin (1 g/kg) solution or 1–1.5 L of normal isotonic saline as in HRS type 1 hypovolaemia is frequently present and many patients respond to this simple measure. The fluid challenge should be performed cautiously, with a maximum albumin load of 100 g to avoid fluid overload.

The aim of pharmacological treatment is improving renal blood flow. This can be achieved by drugs that act on the splanchnic circulation and by plasma expansion. Most experience has been obtained with terlipressin, a vasopressin prodrug, in combination with albumin. Other drugs that have been used are ornipressin, octreotide and midrodine but their efficacy has not yet been well documented.

All drugs have been shown to be more effective when given in combination with albumin. When HRS is treated with both albumin and terlipressin before liver transplantation the chance of recovery after liver transplantation is comparable to that of patients without HRS prior to transplantation.

Small studies have shown promising perspectives for endothelin blockers and N-acetylcysteine, but they should be more extensively studied before they can be generally introduced for this indication.

Renal support (continuous haemofiltration, haemodialysis) can occasionally be used as a bridge until hepatic recovery has occurred or until liver transplantation had been performed. When recovery is highly unlikely or transplantation is not feasible renal support is not indicated. It is important to note that the same principle should be followed with respect to vasoconstrictor therapy.

Patients with HRS type 1 may improve after TIPS implantation but it is as yet not clear whether this is more effective than treatment with terlipressin and albumin and whether benefit of TIPS can be expected only in specific subgroups of patients.

In patients with HRS type 2 refractory ascites is usually the main clinical problem and patients should be treated accordingly. TIPS insertion may result in a decrease in the amount of ascites and improvement in renal function. Few data are available on the efficacy of vasoconstrictor or other specific medical therapies.

Prevention

An important aspect of the management of HRS type II is to avoid possible precipitants of HRS type I, particularly variceal bleeding, SBP and other infections, nephrotoxic drugs and hypovolaemia.

Two trials have shown that for SBP, administration of albumin markedly reduces the incidence of HRS. Treatment with pentoxifylline has been reported to reduce significantly the incidence of HRS in patients with acute alcoholic hepatitis. Further studies are needed to confirm this finding.

SUMMARY

Patients with concomitant cirrhosis and ascites have a poor prognosis and without liver transplantation there is a 2- to 5-year mortality rate of 50%, depending on the aetiology. Most respond well to general lifestyle rules and diuretic treatment. For the small group of patients with refractory ascites repeated LVP or TIPS placement is a good palliative treatment option. Before TIPS placement patients should be carefully screened as there is a substantial group that is likely to develop complications following the procedure.

Large volume paracentesis should be replaced by a plasma expander to prevent inherent complications; albumin has yielded the best results for this indication.

Patients with (refractory) ascites have a chance of developing several complications. SBP and HRS are complications which, without early detection and treatment, can lead to severe morbidity and mortality. It is therefore important to screen ascitic fluid for signs of infection and to closely monitor the renal function. Antibiotic treatment should be initiated as soon as possible to prevent further deterioration of the patient. Those patients at risk of developing SBP should receive prophylactic antibiotic treatment.

There are two types of HRS. The first develops rapidly and has a very poor prognosis. The second type develops gradually in patients with refractory ascites. Combination treatment with albumin and a vasoconstrictor in HRS type 1 yields the best survival data and is superior to either of the drugs alone as a monotherapy; for patients for whom the liver disease can be influenced, e.g. alcohol, this treatment can subdue
the activity of the hepatitis, helping the patient to recover. For those patients whose aetiological factor for the liver disease is not responsive to the different treatment regimens, e.g. the patient with SBP who develops the HRS, liver transplantation is the only treatment option.

REFERENCES


