Clinical Practice Guidelines

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis

European Association for the Study of the Liver [1]

Ascites is the most common complication of cirrhosis, and ~60% of patients with compensated cirrhosis develop ascites within 10 years during the course of their disease [1]. Ascites only occurs when portal hypertension has developed [2] and is primarily related to an inability to excrete an adequate amount of sodium into urine, leading to a positive sodium balance. A large body of evidence suggests that renal sodium retention in patients with cirrhosis is secondary to arterial splanchnic vasodilation. This causes a decrease in effective arterial blood volume with activation of arterial and cardiopulmonary volume receptors, and homeostatic activation of vasoconstrictor and sodium-retaining systems (i.e., the sympathetic nervous system and the renin–angiotensin–aldosterone system). Renal sodium retention leads to expansion of the extracellular fluid volume and formation of ascites and edema [3–5]. The development of ascites is associated with a poor prognosis and impaired quality of life in patients with cirrhosis [6,7]. Thus, patients with ascites should generally be considered for referral for liver transplantation. There is a clear rationale for the management of ascites in patients with cirrhosis, as successful treatment may improve outcome and symptoms.

A panel of experts was selected by the EASL Governing Board and met several times to discuss and write these guidelines during 2008–2009. These guidelines were written according to published studies retrieved from Pubmed. The evidence and recommendations made in these guidelines have been graded according to the GRADE system (Grading of Recommendations Assessment Development and Evaluation). The strength of evidence has been classified into three levels: A, high; B, moderate; and C, low-quality evidence, while that of the recommendation into two: strong and weak (Table 1). Where no clear evidence existed, the recommendations were based on the consensus advice of expert opinion(s) in the literature and that of the writing committee.

1. Uncomplicated ascites

1.1. Evaluation of patients with ascites

Approximately 75% of patients presenting with ascites in Western Europe or the USA have cirrhosis as the underlying cause. For the remaining patients, ascites is caused by malignancy, heart failure, tuberculosis, pancreatic disease, or other miscellaneous causes.

1.2. Diagnosis of ascites

The initial evaluation of a patient with ascites should include history, physical examination, abdominal ultrasound, and laboratory assessment of liver function, renal function, serum and urine electrolytes, as well as an analysis of the ascitic fluid.

The International Ascites Club proposed to link the choice of treatment of uncomplicated ascites to a classification of ascites on the basis of a quantitative criterion (Table 2). The authors of the current guidelines agree with this proposal.

A diagnostic paracentesis with an appropriate ascitic fluid analysis is essential in all patients investigated for ascites prior to any therapy to exclude causes of ascites other than cirrhosis and rule out spontaneous bacterial peritonitis (SBP) in cirrhosis. When the diagnosis of cirrhosis is not clinically evident, ascites due to portal hypertension can be readily differentiated from ascites due to other causes by the serum–ascites albumin gradient (SAAG). If the SAAG is greater than or equal to 1.1 g/dl (or 11 g/L), ascites is ascribed to portal hypertension with an approximate 97% accuracy [8,9]. Total ascitic fluid protein concentration should be measured to assess the risk of SBP since patients with protein concentration lower than 15 g/L have an increased risk of SBP [10].

A neutrophil count should be obtained to rule out the existence of SBP [10]. Ascitic fluid inoculation (10 ml) in blood culture bottles should be performed at the bedside in all patients. Other tests, such as amylase, cytology, PCR and culture for mycobacteria should be done only when the diagnosis is unclear or if there is a clinical suspicion of pancreatic disease, malignancy, or tuberculosis [8–11].

Recommendations **A diagnostic paracentesis should be performed in all patients with new onset grade 2 or 3 ascites, and in all patients hospitalized for worsening of ascites or any complication of cirrhosis (Level A1).**

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Clinical Practice Guidelines

Table 1. Grading evidence and recommendations (adapted from the GRADE system).

	Notes	Symbol
Grading of evidence		
High quality evidence	Further research is very unlikely to change our confidence in the estimate of effect	A
Moderate quality evidence	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate	B
Low or very low quality of evidence	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any estimate of effect is uncertain	C
Grading recommendation		
Strong recommendation warranted	Factors influencing the strength of the recommendation included the quality of evidence, presumed patient-important outcomes, and cost	1
Weaker recommendation	Variability in preferences and values, or more uncertainty: more likely a weak recommendation is warranted Recommendation is made with less certainty: higher cost or resource consumption	2

Neutrophil count and culture of ascitic fluid (by inoculation into blood culture bottles at the bedside) should be performed to exclude bacterial peritonitis (Level A1).

It is important to measure ascitic total protein concentration, since patients with an ascitic protein concentration of less than 15 g/L have an increased risk of developing spontaneous bacterial peritonitis (Level A1) and may benefit from antibiotic prophylaxis (Level A1).

Measurement of the serum–ascites albumin gradient may be useful when the diagnosis of cirrhosis is not clinically evident or in patients with cirrhosis in whom a cause of ascites different than cirrhosis is suspected (Level A2).

1.3. Prognosis of patients with ascites

The development of ascites in cirrhosis indicates a poor prognosis. The mortality is approximately 40% at 1 year and 50% at 2 years [7]. The most reliable factors in the prediction of poor prognosis include: hyponatremia, low arterial pressure, increased serum creatinine, and low urine sodium [7,12]. These parameters are not included in the Child-Turcotte-Pugh score (CTP score) and among them, only serum creatinine is included in the Model for end-stage liver disease (MELD score). Furthermore, since serum creatinine has limitations as an estimate of glomerular filtration rate in cirrhosis [13], these scores probably underestimate the mortality risk in patients with ascites [14]. Since allocation for liver transplantation is based on the MELD score in several countries, patients with ascites may not receive an adequate priority in the transplant lists. Therefore, there is need for improved methods to assess prognosis in patients with ascites.

Recommendations **Since the development of grade 2 or 3 ascites in patients with cirrhosis is associated with reduced survival, liver transplantation should be considered as a potential treatment option (Level B1).**

1.4. Management of uncomplicated ascites

Patients with cirrhosis and ascites are at high risk for other complications of liver disease, including refractory ascites, SBP, hyponatremia, or hepatorenal syndrome (HRS). The absence of these ascites-related complications qualifies ascites as uncomplicated [11].

1.4.1. Grade 1 or mild ascites

No data exist on the natural history of grade 1 ascites, and it is not known how frequently patients with grade 1 or mild ascites will develop grade 2 or 3 ascites.

1.4.2. Grade 2 or moderate ascites

Patients with moderate ascites can be treated as outpatients and do not require hospitalization unless they have other complications of cirrhosis. Renal sodium excretion is not severely impaired in most of these patients, but sodium excretion is low relative to sodium intake. Treatment is aimed at counteracting renal sodium retention and achieving a negative sodium balance. This is done by reducing the sodium intake and enhancing the renal sodium excretion by administration of diuretics. Whilst the assumption of the upright posture activates sodium-retaining systems and slightly impairs renal perfusion [15], forced bed rest is not recommended because there are no clinical trials assessing whether it improves the clinical efficacy of the medical treatment of ascites.

1.4.2.1. Sodium restriction. A negative sodium balance can be obtained by reducing dietary salt intake in approximately 10–20% of cirrhotic patients with ascites, particularly in those presenting with their first episode of ascites [16,17]. There are no controlled clinical trials comparing restricted versus unrestricted sodium intake and the results of clinical trials in which different regimens of restricted sodium intake were compared are controversial [17,18]. Nevertheless, it is the current opinion

Table 2. Grading of ascites and suggested treatment.

Grade of ascites	Definition	Treatment
Grade 1 ascites	Mild ascites only detectable by ultrasound	No treatment
Grade 2 ascites	Moderate ascites evident by moderate symmetrical distension of abdomen	Restriction of sodium intake and diuretics
Grade 3 ascites	Large or gross ascites with marked abdominal distension	Large-volume paracentesis followed by restriction of sodium intake and diuretics (unless patients have refractory ascites)

that dietary salt intake should be moderately restricted (approximately 80–120 mmol of sodium per day). A more severe reduction in dietary sodium content is considered unnecessary and even potentially detrimental since it may impair nutritional status. There are no data to support the prophylactic use of salt restriction in patients who have never had ascites. Fluid intake should be restricted only in patients with dilutional hyponatremia.

Recommendations **Moderate restriction of salt intake is an important component of the management of ascites (intake of sodium of 80–120 mmol/day, which corresponds to 4.6–6.9 g of salt/day) (Level B1). This is generally equivalent to a no added salt diet with avoidance of pre-prepared meals.**

There is insufficient evidence to recommend bed rest as part of the treatment of ascites. There are no data to support the use of fluid restriction in patients with ascites with normal serum sodium concentration (Level B1).

1.4.2.2. Diuretics. Evidence demonstrates that renal sodium retention in patients with cirrhosis and ascites is mainly due to increased proximal as well as distal tubular sodium reabsorption rather than to a decrease of filtered sodium load [19,20]. The mediators of the enhanced proximal tubular reabsorption of sodium have not been elucidated completely, while the increased reabsorption of sodium along the distal tubule is mostly related to hyperaldosteronism [21]. Aldosterone antagonists are more effective than loop diuretics in the management of ascites and are the diuretics of choice [22]. Aldosterone stimulates renal sodium reabsorption by increasing both the permeability of the luminal membrane of principal cells to sodium and the activity of the Na/K ATPase pump in the basolateral membrane. Since the effect of aldosterone is slow, as it involves interaction with a cytosolic receptor and then a nuclear receptor, the dosage of antialdosteronic drugs should be increased every 7 days. Amiloride, a diuretic acting in the collecting duct, is less effective than aldosterone antagonists and should be used only in those patients who develop severe side effects with aldosterone antagonists [23].

A long-standing debate in the management of ascites is whether aldosterone antagonists should be given alone or in combination with a loop diuretic (i.e., furosemide). Two studies have assessed which is the best approach to therapy, either aldosterone antagonists in a stepwise increase every 7 days (100–400 mg/day in 100 mg/day steps) with furosemide (40–160 mg/day, in 40 mg/day steps) added only in patients not responding to high doses of aldosterone antagonists or combined therapy of aldosterone antagonists and furosemide from the beginning of treatment (100 and 40 mg/day increased in a stepwise manner every 7 days in case of no response up to 400 and 160 mg/day) [24,25]. These studies showed discrepant findings which were likely due to differences in the populations of patients studied, specifically with respect to the percentage of patients with the first episode of ascites included in the two studies [26]. From these studies it can be concluded that a diuretic regime based on the combination of aldosterone antagonists and furosemide is the most adequate for patients with recurrent ascites but not for patients with a first episode of ascites. These latter patients should be treated initially only with an aldosterone antagonist (i.e., spironolactone 100 mg/day) from the start of therapy and increased in a stepwise manner every 7 days up to 400 mg/day in the unlikely case of no response. In all patients, diuretic dosage should be adjusted to achieve a rate of weight loss of no greater than 0.5 kg/day in patients without peripheral edema and 1 kg/day in those with peripheral edema to prevent diuretic-induced renal failure and/or hyponatremia [27]. Following mobilization of ascites, diuretics should be reduced to maintain patients with minimal or no ascites to avoid diuretic-induced complications. Alcohol abstinence is crucial for the control of ascites in patients with alcohol-related cirrhosis.

1.4.2.3. Complications of diuretic therapy. The use of diuretics may be associated with several complications such as renal failure, hepatic encephalopathy, electrolyte disorders, gynaecomastia, and muscle cramps [20–29]. Diuretic-induced renal failure is most frequently due to intravascular volume depletion that usually occurs as a result of an excessive diuretic therapy [27]. Diuretic therapy has been classically considered a precipitating factor of hepatic encephalopathy, yet the mechanism is unknown. Hypokalemia may occur if patients are treated with loop diuretics alone. Hyperkalemia may develop as a result of treatment with aldosterone antagonists or other potassium-sparing diuretics, particularly in patients with renal impairment. Hyponatremia is another frequent complication of diuretic therapy. The level of hyponatremia at which diuretics should be stopped is contentious. However, most experts agree that diuretics should be stopped temporarily in patients whose serum sodium decreases to less than 120–125 mmol/L. Gynaecomastia is common with the use of aldosterone antagonists, but it does not usually require discontinuation of treatment. Finally, diuretics may cause muscle cramps [28,29]. If cramps are severe, diuretic dose should be decreased or stopped and albumin infusion may relieve symptoms [29].

A significant proportion of patients develop diuretic-induced complications during the first weeks of treatment [24]. Thus, frequent measurements of serum creatinine, sodium, and potassium concentration should be performed during this period. Routine measurement of urine sodium is not necessary, except for non-responders in whom urine sodium provides an assessment of the natriuretic response to diuretics.

Recommendations **Patients with the first episode of grade 2 (moderate) ascites should receive an aldosterone antagonist such as spironolactone alone, starting at 100 mg/day and increasing stepwise every 7 days (in 100 mg steps) to a maximum of 400 mg/day if there is no response (Level A1). In patients who do not respond to aldosterone antagonists, as defined by a reduction of body weight of less than 2 kg/week, or in patients who develop hyperkalemia, furosemide should be added at an increasing stepwise dose from 40 mg/day to a maximum of 160 mg/day (in 40 mg steps) (Level A1). Patients should undergo frequent clinical and biochemical monitoring particularly during the first month of treatment (Level A1).**

Patients with recurrent ascites should be treated with a combination of an aldosterone antagonist plus furosemide, the dose of which should be increased sequentially according to response, as explained above (Level A1).

The maximum recommended weight loss during diuretic therapy should be 0.5 kg/day in patients without edema and 1 kg/day in patients with edema (Level A1).

Clinical Practice Guidelines

The goal of long-term treatment is to maintain patients free of ascites with the minimum dose of diuretics. Thus, once the ascites has largely resolved, the dose of diuretics should be reduced and discontinued later, whenever possible (Level B1).

Caution should be used when starting treatment with diuretics in patients with renal impairment, hyponatremia, or disturbances in serum potassium concentration and patients should be submitted to frequent clinical and biochemical monitoring. There is no good evidence as to what is the level of severity of renal impairment and hyponatremia in which diuretics should not be started. Serum potassium levels should be corrected before commencing diuretic therapy. Diuretics are generally contraindicated in patients with overt hepatic encephalopathy (Level B1).

All diuretics should be discontinued if there is severe hyponatremia (serum sodium concentration <120 mmol/L), progressive renal failure, worsening hepatic encephalopathy, or incapacitating muscle cramps (Level B1).

Furosemide should be stopped if there is severe hypokalemia (<3 mmol/L). Aldosterone antagonists should be stopped if patients develop severe hyperkalemia (serum potassium >6 mmol/L) (Level B1).

1.4.3. Grade 3 or large ascites

Large-volume paracentesis (LVP) is the treatment of choice for the management of patients with grade 3 ascites. The main findings of studies comparing LVP with diuretics in patients with grade 3 ascites are summarized as follows [30–36]: (1) LVP combined with infusion of albumin is more effective than diuretics and significantly shortens the duration of hospital stay. (2) LVP plus albumin is safer than diuretics, the frequency of hyponatremia, renal impairment, and hepatic encephalopathy being lower in patients treated with LVP than in those with diuretics, in the majority of studies. (3) There were no differences between the two approaches with respect to hospital re-admission or survival. (4) LVP is a safe procedure and the risk of local complications, such as hemorrhage or bowel perforation is extremely low [37].

The removal of large volumes of ascitic fluid is associated with circulatory dysfunction characterized by a reduction of effective blood volume, a condition known as post-paracentesis circulatory dysfunction (PPCD) [31,36,38]. Several lines of evidence indicate that this circulatory dysfunction and/or the mechanisms activated to maintain circulatory homeostasis have detrimental effects in cirrhotic patients. First, circulatory dysfunction is associated with rapid re-accumulation of ascites [35]. Secondly, approximately 20% of these patients develop HRS and/or water retention leading to dilutional hyponatremia [31]. Thirdly, portal pressure increases in patients developing circulatory dysfunction after LVP, probably owing to an increased intrahepatic resistance due to the action of vasoconstrictor systems on the hepatic vascular bed [39]. Finally, the development of circulatory dysfunction is associated with shortened survival [36].

The most effective method to prevent circulatory dysfunction after LVP is the administration of albumin. Albumin is more effective than other plasma expanders (dextran-70, polygeline) for the prevention of PPCD [36]. When less than 5 L of ascites are removed, dextran-70 (8 g/L of ascites removed) or polygeline (150 ml/L of ascites removed) show efficacy similar to that of albumin. However, albumin is more effective than these other plasma expanders when more than 5 L of ascites are removed [36]. Despite this greater efficacy, randomized trials have not shown differences in survival of patients treated with albumin compared with those treated with other plasma expanders [36,40,41]. Larger trials would be required to demonstrate a benefit of albumin on survival. Although there are no studies on how fast and when albumin should be given to patients treated with LVP, it seems advisable to administer it slowly to avoid a possible cardiac overload due to the existence of a latent cirrhotic cardiomyopathy and at the end of LVP when the volume of ascites removed is known and the increasing cardiac output begins to return to baseline [42].

As far as alternative plasma volume expanders are concerned, it should be noted that polygeline is no longer used in many countries because of the potential risk of transmission of prions. Despite some evidence of the fact that the use of saline is not associated with an increased risk to develop PPCD after small volume paracentesis [40], there are no randomized controlled studies comparing saline versus albumin in patients who require LVP of less than 5 L. Few data exist on the use of starch as a plasma expander in patients with cirrhosis and grade 3 ascites treated with LVP, while there are some concerns about the possibility for starch to induce renal failure [43] and hepatic accumulation of starch [44].

Furthermore, a recent health economic analysis suggested that it is more cost-effective to use albumin after LVP compared with alternative but cheaper plasma volume expanders since the administration of albumin post-paracentesis is associated with a lower number of liver-related complications within the first 30 days [41].

Although LVP is the treatment of choice for large ascites in patients with cirrhosis, it is important to realise that LVP does not address the underlying cause of the condition, namely renal sodium and water retention. Therefore, patients treated with LVP require diuretic treatment after the removal of ascitic fluid to prevent the re-accumulation of ascites [45].

LVP should be performed under strict sterile conditions using disposable sterile materials. It is generally agreed that there are no contraindications to LVP other than loculated ascites, although studies have excluded several subsets of patients. Hemorrhagic complications after LVP are infrequent. In one study, which also included patients with INR >1.5 and platelet count <50,000/μl, only two patients experienced minor cutaneous bleedings out of 142 paracenteses [46]. The frequency of bleeding complications in patients with coagulopathy after LVP are also reported to be low in other studies and do not support a relation between risk of bleeding and the degree of coagulopathy [37]. Thus, there are no data to support the use of fresh frozen plasma or pooled platelets before LVP, yet in many centers these products are given if there is severe coagulopathy (prothrombin activity less than 40%) and/or thrombocytopenia (less than 40,000/μl). Nevertheless, caution should be exercised in patients with severe coagulopathy and LVP should be avoided in the presence of disseminated intravascular coagulation.

Recommendations **Large-volume paracentesis (LVP) is the first-line therapy in patients with large ascites (grade 3 ascites) (Level A1). LVP should be completed in a single session (Level A1).**

LVP should be performed together with the administration of albumin (8 g/L of ascitic fluid removed) to prevent circulatory dysfunction after LVP (Level A1).

In patients undergoing LVP of greater than 5 L of ascites, the use of plasma expanders other than albumin is not recommended because they are less effective in the prevention of post-paracentesis circulatory dysfunction (Level A1). In patients undergoing LVP of less than 5 L of ascites, the risk of developing post-paracentesis circulatory dysfunction is low. However, it is generally agreed that these patients should still be treated with albumin because of concerns about use of alternative plasma expanders (Level B1).

After LVP, patients should receive the minimum dose of diuretics necessary to prevent the re-accumulation of ascites (Level A1).

1.5. Drugs contraindicated in patients with ascites

The administration of non-steroidal anti-inflammatory drugs (NSAIDs), such as indomethacin, ibuprofen, aspirin, and sulindac to patients with cirrhosis and ascites is associated with a high risk of development of acute renal failure, hyponatremia, and diuretic resistance [47]. The impairment in glomerular filtration rate is due to a reduced renal perfusion secondary to inhibition of renal prostaglandin synthesis. Thus, NSAIDs should not be used in patients with cirrhosis and ascites. This represents an important therapeutic limitation for these patients when analgesis are needed. Preliminary data show that short-term administration of selective inhibitors of cyclooxygenase-2 does not impair renal function and the response to diuretics. However, further studies are needed to confirm the safety of these drugs [48].

Angiotensin-converting enzyme inhibitors, even in low doses, should be avoided in patients with cirrhosis and ascites since they can induce arterial hypotension [49] and renal failure [50]. Likewise, α_1-adrenergic blockers, such as prazosin, should be used with great caution because despite a reduction in portal pressure, they can further impair renal sodium and water retention and cause an increase in ascites and/or edema [51]. Among cardiovascular drugs, dipyridamole should be used with caution since it can induce renal impairment [52]. Aminoglycosides alone or in combination with ampicillin, cephalothin, or mezlocillin should be avoided in the treatment of bacterial infections, because they are associated with high incidence of nephrotoxicity [53,54].

Nephrotoxicity induced by the administration of contrast media is a frequent cause of renal failure in the general population of hospitalized patients. However, it has been shown that cirrhosis with ascites and substantially normal renal function does not appear to be a risk factor for the development of contrast media-induced renal failure [55]. Nevertheless, the possibility that contrast media administration can cause a further impairment of renal function in patients with pre-existing renal failure cannot be excluded.

Recommendations **Non-steroidal anti-inflammatory drugs (NSAIDs) are contraindicated in patients with ascites because of the high risk of developing further sodium retention, hyponatremia, and renal failure (Level A1).**

Drugs that decrease arterial pressure or renal blood flow such as ACE-inhibitors, angiotensin II antagonists, or α1-adrenergic receptor blockers should generally not be used in patients with ascites because of increased risk of renal impairment (Level A1).

The use of aminoglycosides is associated with an increased risk of renal failure. Thus, their use should be reserved for patients with bacterial infections that cannot be treated with other antibiotics (Level A1).

In patients with ascites without renal failure, the use of contrast media does not appear to be associated with an increased risk of renal impairment (Level B1). In patients with renal failure there are insufficient data. Nevertheless, contrast media should be used with caution and the use of general preventive measures of renal impairment is recommended (Level C1).

2. Refractory ascites

2.1. Evaluation of patients with refractory ascites

According to the criteria of the International Ascites Club, *refractory ascites* is defined as "ascites that cannot be mobilized or the early recurrence of which (i.e., after LVP) cannot be satisfactorily prevented by medical therapy" [11,56]. The diagnostic criteria of refractory ascites are shown in Table 3.

Table 3. Definition and diagnostic criteria for refractory ascites in cirrhosis.

Diuretic-resistant ascites	Ascites that cannot be mobilized or the early recurrence of which cannot be prevented because of a lack of response to sodium restriction and diuretic treatment
Diuretic-intractable ascites	Ascites that cannot be mobilized or the early recurrence of which cannot be prevented because of the development of diuretic-induced complications that preclude the use of an effective diuretic dosage
Requisites	
1. Treatment duration	Patients must be on intensive diuretic therapy (spironolactone 400 mg/day and furosemide 160 mg/day) for at least 1 week and on a salt-restricted diet of less than 90 mmol/day
2. Lack of response	Mean weight loss of <0.8 kg over 4 days and urinary sodium output less than the sodium intake
3. Early ascites recurrence	Reappearance of grade 2 or 3 ascites within 4 weeks of initial mobilization
4. Diuretic-induced complications	Diuretic-induced hepatic encephalopathy is the development of encephalopathy in the absence of any other precipitating factor
	Diuretic-induced renal impairment is an increase of serum creatinine by >100% to a value >2 mg/dl (177 μmol/L) in patients with ascites responding to treatment
	Diuretic-induced hyponatremia is defined as a decrease of serum sodium by >10 mmol/L to a serum sodium of <125 mmol/L
	Diuretic-induced hypo- or hyperkalemia is defined as a change in serum potassium to <3 mmol/L or >6 mmol/L despite appropriate measures

Modified with permission from Moore KP, Wong F, Ginès P, et al. The management of ascites in cirrhosis: report on the consensus conference of the International Ascites Club. Hepatology 2003;38:258–266.

Clinical Practice Guidelines

Once ascites becomes refractory to medical treatment, the median survival of patients is approximately 6 months [7,56–59]. As a consequence, patients with refractory ascites should be considered for liver transplantation. The MELD score system predicts survival in patients with cirrhosis [60,61]. However, other factors in patients with cirrhosis and ascites are also associated with poor prognosis, including low arterial pressure, low serum sodium, low urine sodium, and high Child-Pugh score [7,57–61]. Patients with refractory ascites may have a poor prognosis despite a relatively low MELD score (e.g. <18) and this may be of importance with respect to prioritisation for liver transplantation [14]. For these reasons, inclusion of additional parameters in the MELD score, such as serum sodium has been suggested [14,61–65].

Recommendations **The assessment of the response of ascites to diuretic therapy and salt restriction should only be performed in stable patients without associated complications, such as bleeding or infection. (Level B1).**

The prognosis of patients with refractory ascites is poor and therefore they should be considered for liver transplantation (Level B1).

2.2. Management of refractory ascites

Methods for treatment of refractory ascites include LVP with albumin administration, continuing diuretic therapy (if effective in inducing natriuresis), insertion of transjugular intrahepatic portosystemic shunt (TIPS), and liver transplantation. The use of therapies under investigation will also be discussed briefly.

2.2.1. Large-volume paracentesis

A large body of evidence indicates that repeated LVP is an effective and safe therapy of refractory ascites [8,11,56,66]. The administration of albumin prevents circulatory dysfunction associated with LVP (see discussion in a previous section of these guidelines).

2.2.2. Diuretics in patients with refractory ascites

In most patients (>90%), diuretics are not effective in preventing or delaying the recurrence of ascites after LVP since by definition patients have ascites which is refractory to diuretic therapy [56]. Diuretics should be discontinued permanently in patients with diuretic-induced complications (hepatic encephalopathy, renal impairment, or electrolyte abnormalities). In the remaining patients, treatment should be continued only when urinary sodium excretion under diuretic therapy is greater than 30 mmol/day [11].

2.2.3. Transjugular intrahepatic portosystemic shunts (TIPS)

2.2.3.1. Uncontrolled studies. TIPS decompresses the portal system like a side-to-side portocaval shunt inserted between the high pressure portal venous area and the low pressure hepatic venous area [67]. Because of the reduction in portal pressure TIPS has proved to be effective in the control of recurrent ascites. In the short-term, TIPS induces an increase in cardiac output, right atrial pressure, and pulmonary artery pressure leading to a secondary reduction in systemic vascular resistance and effective arterial blood volume [68–79]. With time, the increase in cardiac output that follows a TIPS insertion tends to return to pre-TIPS levels [72,74,75]. Beneficial effects on renal function include increase in urinary sodium excretion and glomerular filtration rate [72,76–78]. In addition, TIPS may have beneficial effects on nitrogen balance and body weight [79–81]. TIPS also improves quality of life, but in randomized studies the degree of improvement is similar to that observed in patients treated with repeated LVP and albumin [82]. TIPS has been successfully used in patients with recurrent hydrothorax but the outcome seems to be highly related to liver function and age [83–86].

A major complication after TIPS insertion is the development of hepatic encephalopathy which occurs in 30–50% of the patients [67,87]. Other complications include shunt thrombosis and stenosis. Uncovered stents are complicated by stenosis in up to approximately 80% of the cases [67,88].

2.2.3.2. Controlled studies. The effects of TIPS on the control of ascites, frequency of encephatlopahty, and survival in the 5 randomised controlled trials so far published is shown in Table 4 [79,89–92]. TIPS was superior to LVP in the control of ascites but was associated with a greater frequency of encephalopathy. Studies showed discrepancies with respect to survival.

The majority of the trials, excluded patients with very advanced disease as indicated by serum bilirubin >5 mg/dl [79,91], INR >2 [91], episodic hepatic encephalopathy >grade 2, or persistent encephalopathy [90], bacterial infections [89,91,92], renal failure [79,89–92], and cardiac and respiratory failure [79,91,92]. Because of insufficient data on efficacy and safety, TIPS cannot be recommended in patients with very advanced liver disease or associated severe extrahepatic diseases.

2.2.3.3. Meta-analyses. Patients in the five above-mentioned randomised controlled clinical trials have variably been included in five meta-analyses yielding almost similar conclusions (Table 5) [93–97]. All meta-analyses agree that recurrence of ascites after 3 and 12 months is lower in patients treated with TIPS compared to that in patients treated with LVP. The frequency of hepatic encephalopathy is higher in the TIPS treated patients in all meta-analyses. Three meta-analyses showed no difference in survival between the TIPS and LVP groups [93,94,96]. One meta-analysis found a trend towards reduced mortality in patients treated with TIPS after having excluded an outlier trial [95] and another meta-analysis found an increased transplant-free survival in the TIPS group [97].

Table 4. Characteristics and results of five multicenter randomised controlled trials comparing transjugular intrahepatic portosystemic shunt (TIPS) and large-volume paracentesis (LVP) in patients with cirrhosis and refractory or recidivant ascites.

Reference	Refractory/recidivant Ascites (%)	Number of patients		Ascites improved (%)		Encephalopathy (%)		Survival (%)	
		TIPS	LVP	TIPS	LVP	TIPS	LVP	TIPS	LVP
Lebrec et al., 1996 [89]	100/0	13	12	38	0	15	6	29	60
Rössle et al., 2000 [79]	55/45	29	31	84	43	23	13	58	32
Ginès et al., 2002 [90]	100/0	35	35	51	17	60	34	26	30
Sanyal et al., 2003 [91]	100/0	52	57	58	16	38	21	35	33
Salerno et al., 2004 [92]	68/32	33	33	79	42	61	39	59	29

Table 5. Main results of 5 meta-analyses on multicenter randomised controlled trials of the effects of transjugular intrahepatic portosystemic shunt (TIPS) and large-volume paracentesis (LVP) on refractory ascites.

Reference	Number of trials included	Number of patients included	Significant heterogeneity among trials	Recurrence of ascites	Encephalopathy	Survival
Albillos et al., 2005 [93]	5	330	Yes	Lower in TIPS group. RR 0.56	Higher in TIPS group. RR 1.72	No difference between groups. RR 0.93
Deltenre et al., 2005 [94]	5	330	No	Lower in TIPS group. $DifE_{4M}$: 0.41, p <0.001 $DifE_{12M}$: 0.35, p <0.001	Higher in TIPS group. DifE: 0.17, p <0.001	No difference between groups $DifE_{1y}$: 0.03, p = 0.7 $DifE_{2y}$: 0.07, p = 0.4
D'Amico et al., 2005 [95]	5	330	Yes	Lower in TIPS group. OR 0.14 (0.7–0.27)	Higher in TIPS group. OR 2.26 (1.35–3.76)	No difference between groups A trend towards better survival in TIPS group OR 0.74 (0.40–1.37)
Saab et al., 2006 [96]	5	330	?	Lower after 3 months in TIPS group. OR 0.07 (0.03–0.18, p <0.01) 12 months OR 0.14 (0.06–0.28, p <0.01)	Higher in TIPS group. OR 2.24 (1.39–3.6) p <0.01	30-days OR 1.0 (0.10–0.06, p = 1) 24 months OR 1.29 (0.65–2.56, p = 0.5)
Salerno et al., 2007 [97]	4	305	No	Lower in TIPS group. 42 versus 89% in LVP group (p <0.0001)	Higher in TIPS group. (1.13 versus 0.63 (p = 0.006)).	Transplant-free survival better in TIPS group (p = 0.035)

$DifE_{4M}$ and $DifE_{12M}$: Difference in effects at 4 and 12 months. $DifE_{1y}$ and $DifE_{2y}$ OR, odds ratio. RR, relative risk.

2.2.4. Peritoneovenous shunt

Due to frequent complications related to surgical insertion, shunt dysfunction, and infections, this treatment has currently very little role in the management of patients with refractory ascites [11].

2.2.5. Other treatments

Since circulatory dysfunction and activation of neuro-humoral systems with sodium and water retention play a major role in the pathogenesis of refractory ascites, there has been an increasing interest in research on drugs that may improve circulatory and renal function, particularly vasoconstrictors and selective antagonists of the V2-receptors of vasopressin, known as vaptans. Vasoconstrictors such as the α_1-adrenergic agonist midodrine or terlipressin improve circulatory and renal function in patients with and without refractory ascites [98–100]. However, large randomized controlled studies have not been reported yet. Terlipressin has the inconvenience of requiring intravenous administration.

In two phase-2 studies the administration of a vaptan, satavaptan, in combination with fixed doses of diuretics, in addition to improving serum sodium levels was associated with weight loss, suggesting an effect of the drug on ascites and/or edema [101,102]. In another phase-2 study, the administration of satavaptan was associated with a reduction of ascites recurrence after LVP [103]. Unfortunately, however, phase-3 randomized, placebo-controlled studies failed to demonstrate a significant beneficial effect of satavaptan in combination with diuretics in the control of ascites and treatment was associated with an increased morbidity and mortality, the causes of which are unclear [104].

Recommendations **Repeated large-volume paracentesis plus albumin (8 g/L of ascites removed) is the first line of treatment for refractory ascites (Level A1). Diuretics should be discontinued in patients with refractory ascites who do not excrete >30 mmol/day of sodium under diuretic treatment.**

TIPS is effective in the management of refractory ascites but is associated with a high risk of hepatic encephalopathy and studies have not been shown to convincingly improve survival compared to repeated large-volume paracentesis (Level A1). TIPS should be considered in patients with very frequent requirement of large-volume paracentesis, or in those in whom paracentesis is ineffective (e.g. due to the presence of loculated ascites) (Level B1).

Resolution of ascites after TIPS is slow and most patients require continued administration of diuretics and salt restriction (Level B1).

TIPS cannot be recommended in patients with severe liver failure (serum bilirubin >5 mg/dl, INR >2 or Child-Pugh score >11, current hepatic encephalopathy ⩾grade 2 or chronic hepatic encephalopathy), concomitant active infection, progressive renal failure, or severe cardiopulmonary diseases (Level B1).

In selected patients TIPS may be helpful for recurrent symptomatic hepatic hydrothorax (Level B2).

3. Spontaneous bacterial peritonitis

SBP is a very common bacterial infection in patients with cirrhosis and ascites [10,105–107]. When first described, its mortality exceeded 90% but it has been reduced to approximately 20% with early diagnosis and treatment [6,108].

3.1. Diagnosis of spontaneous bacterial peritonitis

3.1.1. Diagnostic paracentesis: in whom and when

The diagnosis of SBP is based on diagnostic paracentesis [10]. All patients with cirrhosis and ascites are at risk of SBP and the prevalence of SBP in outpatients is 1.5–3.5% [109,110] and ~10% in hospitalized patients [109]. Half the episodes of SBP are present at the time of hospital admission while the rest are acquired during hospitalization [10].

Patients with SBP may have one of the following [10,109,111]: (1) local symptoms and/or signs of peritonitis: abdominal pain, abdominal tenderness, vomiting, diarrhea, ileus; (2) signs of systemic inflammation: hyper or hypothermia, chills, altered white

Clinical Practice Guidelines

blood cell count, tachycardia, and/or tachypnea; (3) worsening of liver function; (4) hepatic encephalopathy; (5) shock; (6) renal failure; and (7) gastrointestinal bleeding. However, it is important to point out that SBP may be asymptomatic, particularly in outpatients [109,110].

3.1.2. Ascitic fluid cell analysis

Peritoneal infection causes an inflammatory reaction resulting in an increased number of neutrophils in ascitic fluid. Despite the use of sensitive methods, ascites culture is negative in as many as 60% of patients with clinical manifestations suggestive of SBP and increased ascites neutrophil count [10,106–108]. Ascitic fluid neutrophil count is obtained as follows: ascitic fluid is centrifuged, then a smear is stained with Giemsa and total and differential cell counts are made with an optical microscope. This can be done in less than 4 h [10,107,108,112]. Historically, manual counts were recommended, as coulter counter determinations of neutrophil counts were inaccurate at the relatively low levels of neutrophils in ascitic fluid [10]. However, a recent study found excellent correlation between these two techniques, even at low counts, suggesting that automated counting may replace manual counts [113]. The greatest sensitivity for the diagnosis of SBP is reached with a cutoff neutrophil count of 250/mm^3, although the greatest specificity is reached with a cutoff of 500 neutrophils/mm^3 [10,66,107]. Since there may be some delay in obtaining an ascitic fluid cell count, the use of reagent strips (RSs) has been proposed for a rapid diagnosis of SBP (reviewed in [114]). These reagent strips, designed for use in urine, identify leukocytes by detecting their esterase activity via a colorimetric reaction [114]. However, a large, multicenter prospective study has shown that the Multistix 8 SG® RS has a low diagnostic accuracy for the diagnosis of SBP [109]. A critical review of 19 studies comparing RSs (i.e., either Multistix 8 SG®, Nephur®, Combur®, UriScan®, or Aution®) to cytobacteriological methods has shown that RSs have low sensitivity and a high risk of false negative results, in particular in patients with SBP and low neutrophil count [114]. Thus, the use of reagent strips cannot be recommended for the rapid diagnosis of SBP.

3.1.3. Ascitic fluid culture

When culture is positive (~40% of cases), the most common pathogens include Gram-negative bacteria (GNB), usually *Escherichia coli* and Gram-positive cocci (mainly streptococcus species and enterococci) [10,105–108]. A recent study has shown that 30% of isolated GNB are resistant to quinolones and 30% are resistant to trimethoprim–sulfamethoxazole [106]. Seventy percent of quinolone-resistant GNB are also resistant to trimethoprim–sulfamethoxazole [106]. The incidence of SBP due to quinolone-resistant GNB is higher in patients on norfloxacin therapy than in patients 'naïve' for this treatment [106]. The rate of cephalosporin-resistant GNB is low in patients with SBP regardless of norfloxacin prophylaxis [106]. Patients on norfloxacin prophylaxis may develop SBP caused by Gram-positive cocci [10,106–108]. Finally, the epidemiology of bacterial infections differs between community-acquired (in which GNB infections predominate) and nosocomial infections (in which Gram-positive infections predominate) [106].

Patients with an ascitic fluid neutrophil count $\geqslant$250 cells/mm^3 and negative culture have culture-negative SBP [10,115]. Their clinical presentation is similar to that of patients with culture-positive SBP [10,116] and should be treated in a similar manner.

Some patients have 'bacterascites' in which cultures are positive but there is normal ascitic neutrophil count (<250/mm^3) [10]. In some patients bacterascites is the result of secondary bacterial colonization of ascites from an extraperitoneal infection. These patients usually have general symptoms and signs of infection. In other patients, 'bacterascites' is due to the spontaneous colonization of ascites, and they can either be clinically asymptomatic or have abdominal pain or fever. While in some patients, particularly in those who are asymptomatic, bacterascites represents a transient and spontaneously reversible colonization of ascites, in other patients, mainly those who are symptomatic, bacterascites may represent the first step in the development of SBP [10].

3.1.4. Spontaneous bacterial pleural empyema

Infection of a pre-existing hydrothorax, known as spontaneous bacterial pleural empyema, is uncommon although the exact prevalence is unknown [112]. The diagnosis is based on pleural fluid analysis obtained by diagnostic thoracocentesis. In the largest observational study reported so far, the diagnosis of spontaneous bacterial empyema was established when the pleural fluid analysis showed a positive culture and more than 250 neutrophils/mm^3 or a negative culture and more than 500 neutrophils/mm^3, in the absence of lung infection [117]. Pleural fluid culture in blood culture bottles was positive in 75% of cases [117]. Spontaneous bacterial pleural empyema was associated with SBP in ~50% of cases [117].

3.1.5. Secondary bacterial peritonitis

A small proportion of patients with cirrhosis may develop peritonitis due to perforation or inflammation of an intra-abdominal organ, a condition known as secondary bacterial peritonitis. The differentiation of this condition from SBP is important. Secondary bacterial peritonitis should be suspected in patients who have localized abdominal symptoms or signs, presence of multiple organisms on ascitic culture, very high ascitic neutrophil count and/or high ascitic protein concentration, or in those patients with an inadequate response to therapy [112]. Patients with suspected secondary bacterial peritonitis should undergo appropriate radiological investigation such as CT scanning [112]. The use of other tests such as measurement of glucose or lactate dehydrogenase in ascitic fluid has been suggested to help with the diagnosis of secondary bacterial peritonitis [112]. However, there are very limited data on the specificity and sensitivity of these tests in this setting.

Recommendations **A diagnostic paracentesis should be carried out in all patients with cirrhosis and ascites at hospital admission to rule out SBP. A diagnostic paracentesis should also be performed in patients with gastrointestinal bleeding, shock, fever, or other signs of systemic inflammation, gastrointestinal symptoms, as well as in patients with worsening liver and/or renal function, and hepatic encephalopathy (Level A1).**

The diagnosis of SBP is based on neutrophil count in ascitic fluid of >250/mm^3 as determined by microscopy (Level A1). At present there are insufficient data to recommend the use of automated cell counters or reagent strips for the rapid diagnosis of SBP.

Ascitic fluid culture is frequently negative even if performed in blood culture bottles and is not necessary for the

diagnosis of SBP, but it is important to guide antibiotic therapy (Level A1). Blood cultures should be performed in all patients with suspected SBP before starting antibiotic treatment (Level A1).

Some patients may have an ascitic neutrophil count less than 250/mm^3 but with a positive ascitic fluid culture. This condition is known as bacterascites. If the patient exhibits signs of systemic inflammation or infection, the patient should be treated with antibiotics (Level A1). Otherwise, the patient should undergo a second paracentesis when culture results come back positive. Patients in whom the repeat ascitic neutrophil count is >250/mm^3 should be treated for SBP, and the remaining patients (i.e., neutrophils <250/mm^3) should be followed up (Level B1).

Spontaneous bacterial pleural empyema may complicate hepatic hydrothorax. Diagnostic thoracocentesis should be performed in patients with pleural effusion and suspected infection with inoculation of fluid into blood culture bottles (Level A1). The diagnosis is based on positive pleural fluid culture and increased neutrophil count of >250/mm^3 or negative pleural fluid culture and >500 neutrophils/mm^3 in the absence of pneumonia (Level B1).

Patients with suspected secondary bacterial peritonitis should undergo appropriate radiological investigation such as CT scanning (Level A1). The use of other tests such as measurement of glucose or lactate dehydrogenase in ascitic fluid cannot be recommended for the diagnosis of secondary bacterial peritonitis (Level B1).

3.2. Management of spontaneous bacterial peritonitis

3.2.1. Empirical antibiotic therapy

Empirical antibiotic therapy must be initiated immediately after the diagnosis of SBP, without the results of ascitic fluid culture [10,107]. Potentially nephrotoxic antibiotics (i.e., aminoglycosides) should not be used as empirical therapy [10]. Cefotaxime, a third-generation cephalosporin, has been extensively investigated in patients with SBP because it covers most causative organisms and because of its high ascitic fluid concentrations during therapy [118–122]. Infection resolution is obtained in 77–98% of patients. A dose of 4 g/day is as effective as a dose of 8 g/day [119]. A 5-day therapy is as effective as a 10-day treatment [123] (Table 6).

Alternatively, amoxicillin/clavulanic acid, first given intravenously then orally, has similar results with respect to SBP resolution and mortality, compared with cefotaxime [122] and with a much lower cost. However, there is only one comparative study with a small sample size and results should be confirmed in larger trials. Ciprofloxacin, given either for 7 days intravenously or for 2 days intravenously followed by 5 days orally, results in a similar SBP resolution rate and hospital survival compared with cefotaxime, but with a significantly higher cost [124]. However, switch therapy (i.e., use of intravenous antibiotic initially, followed by oral step-down administration) with ciprofloxacin is more cost-effective than intravenous cefotaxime [125]. Oral ofloxacin has given similar results as intravenous cefotaxime in uncomplicated SBP, without renal failure, hepatic encephalopathy, gastrointestinal bleeding, ileus, or shock [120]. Cefotaxime or amoxicillin/clavulanic acid are effective in patients who develop SBP while on norfloxacin prophylaxis [10].

If ascitic fluid neutrophil count fails to decrease to less than 25% of the pre-treatment value after 2 days of antibiotic treatment, there is a high likelihood of failure to respond to therapy [10,112]. This should raise the suspicion of an infection caused by bacteria resistant to antibiotic therapy, indicating the need for modification of antibiotic treatment according to *in vitro* sensitivity or on empiric basis or the presence of 'secondary peritonitis'.

***Recommendations*. Empirical antibiotics should be started immediately following the diagnosis of SBP (Level A1).**

Since the most common causative organisms of SBP are Gram-negative aerobic bacteria, such as E. coli, the first line antibiotic treatment are third-generation cephalosporins (Level A1). Alternative options include amoxycillin/clavulanic acid and quinolones such as ciprofloxacin or ofloxacin. However, the use of quinolones should not be considered in patients who are taking these drugs for prophylaxis against SBP, in areas where there is a high prevalence of quinolone-resistant bacteria or in nosocomial SBP (Level B1).

Table 6. Antibiotic therapy for spontaneous bacterial peritonitis in patients with cirrhosis.

Reference	Treatments	Number of patients	Infection resolution (%)	In-hospital survival (%)
Felisart, 1985 [118]	Tobramycin (1.75 mg/kg/8h IV) plus ampicillin (2 g/4h IV)	36	56	61
	versus cefotaxime (2 g/4h IV)	37	85*	73
Rimola, 1995 [119]	Cefotaxime (2 g/6h IV)	71	77	69
	versus cefotaxime (2 g/12h IV)	72	79	79
Navasa, 1996 [120]	Ofloxacin (400 mg/12h PO)	64	84	81
	versus cefotaxime (2 g/6h IV)	59	85	81
Sort, 1999 [121]	Cefotaxime (2 g/6h IV)	63	94	71
	versus cefotaxime (2 g/6h IV) plus IV albumin	63	98	90**
Ricart, 2000 [122]	Amoxicillin/clavulanic acid (1/0.2 g/8h) IV followed by 0.5/0.125 g/8h PO	24	87	87
	versus cefotaxime (1 g/6h IV)	24	83	79
Terg, 2000 [124]	Ciprofloxacin (200 mg/12h IV for 7 days)	40	76	77
	versus ciprofloxacin (200 mg/12h for 2 days, followed by 500 mg/12h PO for 5 days)	40	78	77

* p <0.02 versus tobramycin plus ampicillin.
** p = 0.01 versus cefotaxime alone.

Clinical Practice Guidelines

SBP resolves with antibiotic therapy in approximately 90% of patients. Resolution of SBP should be proven by demonstrating a decrease of ascitic neutrophil count to <250/mm^3 and sterile cultures of ascitic fluid, if positive at diagnosis (Level A1). A second paracentesis after 48 h of start of treatment may help guide the effect of antibiotic therapy.

Failure of antibiotic therapy should be suspected if there is worsening of clinical signs and symptoms and/or no marked reduction or increase in ascitic fluid neutrophil count compared to levels at diagnosis. Failure of antibiotic therapy is usually due to resistant bacteria or secondary bacterial peritonitis. Once secondary bacterial peritonitis has been excluded, antibiotics should be changed according to in vitro susceptibility of isolated organisms, or modified to alternative empiric broad spectrum agents (Level A1).

Spontaneous bacterial empyema should be managed similarly as SBP

3.2.2. Intravenous albumin in patients with spontaneous bacterial peritonitis without septic shock

SBP without septic shock may precipitate deterioration of circulatory function with severe hepatic insufficiency, hepatic encephalopathy, and type 1 hepatorenal syndrome (HRS) [121,126,127] and has approximately a 20% hospital mortality rate despite infection resolution [121,126].

A randomized, controlled study in patients with SBP treated with cefotaxime showed that albumin (1.5 g/kg body weight at diagnosis, followed by 1 g/kg on day 3) significantly decreased the incidence of type 1 HRS (from 30% to 10%) and reduced mortality from 29% to 10% compared with cefotaxime alone. Treatment with albumin was particularly effective in patients with baseline serum bilirubin $\geqslant$68 μmol/L (4 mg/dl) or serum creatinine $\geqslant$88 μmol/L (1 mg/dl). It is unclear whether intravenous albumin is useful in patients with baseline bilirubin <68 μmol/L and creatinine <88 μmol/L, as the incidence of type 1 HRS was very low in the two treatment groups (7% without albumin and 0% with albumin) [121]. Non-randomized studies in patients with SBP also show that the incidence of renal failure and death are very low in patients with moderate liver failure and without renal dysfunction at diagnosis of SBP [128–130]. It is not known whether crystalloids or artificial colloids could replace albumin in the prevention of HRS in patients with SBP. Albumin improves circulatory function in patients with SBP while equivalent doses of hydroxyethyl starch have no such beneficial effect [131]. Clearly, further studies are needed to assess the efficacy of albumin as well as other expanders in the management of SBP. Until further trials are completed, albumin infusion appears a valuable adjunction to the treatment of SBP.

Recommendations **HRS occurs in approximately 30% of patients with SBP treated with antibiotics alone, and is associated with a poor survival. The administration of albumin (1.5 g/kg at diagnosis and 1g/kg on day 3) decreases the frequency of HRS and improves survival (Level A1). It is unclear whether albumin is useful in the subgroup of patients with baseline serum bilirubin <68 μmol/L and creatinine <88 μmol/L (Level B2). Until more information is available, we recommend that all patients who develop SBP should be treated with broad spectrum antibiotics and intravenous albumin (Level A2).**

3.3. Prophylaxis of spontaneous bacterial peritonitis

Since most episodes of SBP are thought to result from the translocation of enteric GNB, the ideal prophylactic agent should be safe, affordable, and effective at decreasing the amounts of these organisms from the gut while preserving the protective anaerobic flora (selective intestinal decontamination) [108]. Given the high cost and inevitable risk of developing resistant organisms, the use of prophylactic antibiotics must be strictly restricted to patients at high risk of SBP. Three high-risk patient populations have been identified: (1) patients with acute gastrointestinal hemorrhage; (2) patients with low total protein content in ascitic fluid and no prior history of SBP (primary prophylaxis); and (3) patients with a previous history of SBP (secondary prophylaxis).

3.3.1. Patients with acute gastrointestinal hemorrhage

Bacterial infection, including SBP, is a major problem in patients with cirrhosis and acute gastrointestinal hemorrhage, occurring in between 25% and 65% of patients with gastrointestinal bleeding [132–141]. The incidence of bacterial infection is particularly high in patients with advanced cirrhosis and/or severe hemorrhage [138,139]. In addition, the presence of bacterial infection in patients with variceal hemorrhage is associated with an increased rate of failure to control bleeding [142,143], rebleeding [136,138], and hospital mortality [139,143–145]. Antibiotic prophylaxis has been shown to prevent infection in patients with gastrointestinal bleeding [10,107,108] and decrease the rate of rebleeding [144]. A meta-analysis [139] of five studies performed in patients with gastrointestinal bleeding [132,134,135,137,140] has shown that antibiotic prophylaxis significantly decreased both the incidence of severe infections (SBP and/or septicemia) and mortality.

Selective intestinal decontamination with norfloxacin (400 mg/12 h orally for 7 days), a quinolone with relatively poor gastrointestinal absorption, and which has antibacterial activity against GNB but not against Gram-positive cocci or anaerobic bacteria, is the most commonly used approach for the prophylaxis of bacterial infections in patients with gastrointestinal hemorrhage [10,107,134]. In recent years, the epidemiology of bacterial infections in cirrhosis has changed, with an increasing incidence of SBP and other infections caused by quinolone-resistant bacteria (see above) [106,146,147]. In addition, a substantial number of infections in patients with gastrointestinal hemorrhage are caused by Gram-positive bacteria likely related to invasive procedures used in these patients [106].

A recent study comparing oral norfloxacin to intravenous ceftriaxone for the prophylaxis of bacterial infection in patients with gastrointestinal bleeding and advanced cirrhosis (at least 2 of the following: ascites, severe malnutrition, encephalopathy, or bilirubin >3 mg/dl) showed that ceftriaxone was more effective than norfloxacin in the prevention of infections [148].

Recommendations **In patients with gastrointestinal bleeding and severe liver disease (see text) ceftriaxone is the prophylactic antibiotic of choice, whilst patients with less severe liver disease may be given oral norfloxacin or an alternative oral quinolone to prevent the development of SBP (Level A1).**

3.3.2. Patients with low total protein content in ascitic fluid without prior history of spontaneous bacterial peritonitis

Cirrhotic patients with low ascitic fluid protein concentration (<10 g/L) and/or high serum bilirubin levels are at high risk of

Table 7. Antibiotic therapy for prophylaxis of spontaneous bacterial peritonitis (SBP) in patients with cirrhosis.[a]

Reference	Type of prophylaxis	Treatments	Number of patients	Number of GNB[b] infections	*p*-value	Incidence of SBP n (%)	*p*-value
Ginès, 1990 [158]	Enrolled only patients with prior SBP[c]	Norfloxacin versus placebo	40 40	1 10	–	5 (12) 14 (35)	0.02
Soriano, 1991 [153]	Enrolled patients without prior SBP and patients with prior SBP[d]	Norfloxacin versus no treatment	32 31	0 9	<0.001	0 (0) 7 (22.5)	<0.02
Singh, 1995 [161]	Enrolled patients without prior SBP and patients with prior SBP[d]	Trimethoprim–sulfamethoxazole versus no treatment	30 30	9 0	–	1 (3) 8 (27)[e]	0.03
Rolachon, 1995 [160]	Enrolled patients without prior SBP and patients with prior SBP[c]	Ciprofloxacin versus placebo	28 32	1 0	–	1 (4) 7 (22)	<0.05
Novella, 1997 [154]	Enrolled only patients without prior SBP[d]	Continuous norfloxacin versus in patient-only prophylaxis	56 53	11 13	–	1 (1.8) 9 (16.9)	<0.01
Grangé, 1998 [155]	Enrolled only patients without prior SBP[c]	Norfloxacin versus placebo	53 54	0 6	<0.04	0 (0) 5 (9)	NA
Fernández, 2007 [156]	Enrolled only patients without prior SBP[c]	Norfloxacin versus placebo	35 33	13 6	–	2 (6) 10 (30)	0.02
Terg, 2008 [157]	Enrolled only patients without prior SBP[c]	Ciprofloxacin versus placebo	50 50	–	–	2 (4) 7 (14)	0.076

NA, not available.
[a] Studies appear in chronological order.
[b] GNB means Gram-negative bacteria.
[c] Randomized, double-blind, placebo-controlled trial.
[d] Randomized, unblinded trial.
[e] Including one patient with spontaneous bacteremia due to *Klebsiella pneumonia.*

developing a first episode of SBP [10,149–152]. Several studies have evaluated prophylaxis with norfloxacin in patients without prior history of SBP (Table 7) [153–157]. One pilot, randomized, open-label trial was performed comparing primary continuous prophylaxis with norfloxacin to inpatient-only prophylaxis in 109 patients with cirrhosis and ascitic fluid total protein level $\leqslant$15 g/L or serum bilirubin level >2.5 mg/dl [154]. SBP was reduced in the continuous treatment group at the expense of more resistance of gut flora to norfloxacin in that group. In another study, 107 patients with ascitic fluid total protein level <15 g/L were randomized in a double-blind manner to receive norfloxacin (400 mg/day for 6 months) or placebo [155]. Of note, the existence of severe liver failure was not an inclusion criterion. The primary endpoint was the occurrence of GNB infections. Norfloxacin significantly decreased the probability of developing GNB infections, but had no significant effect on the probability of developing SBP or survival. However, in this trial, the sample size was not calculated to detect differences in survival. In a third investigation, 68 patients with cirrhosis and low ascites protein levels (<15 g/L) with advanced liver failure [Child-Pugh score $\geqslant$9 points with serum bilirubin level $\geqslant$3 mg/dl or impaired renal function (serum creatinine level $\geqslant$1.2 mg/dl, blood urea nitrogen level $\geqslant$25 mg/dl, or serum sodium level $\leqslant$130 mEq/L)] were randomized in a double-blind, placebo-controlled trial, to receive norfloxacin (400 mg/day for 12 months) or placebo [156]. The primary endpoints of the trial were 3-month and 1-year survival. Norfloxacin significantly improved the 3-month probability of survival (94% versus 62%; $p = 0.03$) but at 1 year the difference in survival was not significant (60% versus 48%; $p = 0.05$). Norfloxacin administration significantly reduced the 1-year probability of developing SBP (7% versus 61%) and HRS (28% versus 41%). In a fourth study, 100 patients with ascitic fluid total protein level <15 g/L were randomized in double-blind, placebo-controlled trial to ciprofloxacin (500 mg/day for 12 months) or placebo [157]. Enrolled patients had moderate liver failure (the Child-Pugh scores were 8.3 ± 1.3 and 8.5 ± 1.5, in the placebo and ciprofloxacin group, respectively). The primary endpoint was the occurrence of SBP. Although SBP occurred in 2 (4%) patients of the ciprofloxacin group and in 7 (14%) patients of the placebo group, this difference was not significant. Moreover, the probability of being free of SBP was not significant ($p = 0.076$). The probability of remaining free of bacterial infections was higher in patients receiving ciprofloxacin (80% versus 55%; $p = 0.05$). The probability of survival at 1 year was higher in patients receiving ciprofloxacin (86% versus 66%; $p < 0.04$). Nevertheless, a type II error cannot be ruled out as the sample size was not calculated to detect differences in survival. The duration of primary antibiotic prophylaxis has not been established.

Recommendations **One double-blind, placebo-controlled, randomized trial performed in patients with severe liver disease (see text) with ascitic fluid protein lower than 15 g/L and without prior SBP showed that norfloxacin (400 mg/day) reduced the risk of SBP and improved survival. Therefore, these patients should be considered for long-term prophylaxis with norfloxacin (Level A1).**

In patients with moderate liver disease, ascites protein concentration lower than 15 g/L, and without prior history of SBP, the efficacy of quinolones in preventing SBP or improving survival is not clearly established. Studies are needed in this field.

3.3.3. Patients with prior spontaneous bacterial peritonitis

In patients who survive an episode of SBP, the cumulative recurrence rate at 1 year is approximately 70% [108]. The probability of survival at 1 year after an episode of SBP is 30–50% and falls to 25–30% at 2 years. Therefore, patients recovering from an episode of SBP should be considered for liver transplantation. There is only one randomized, double-blind, placebo-controlled trial of norfloxacin (400 mg/day orally) in patients who had a previous episode of SBP [158] (Table 7).

Clinical Practice Guidelines

Treatment with norfloxacin reduced the probability of recurrence of SBP from 68% to 20% and the probability of SBP due to GNB from 60% to 3%. Survival was not an endpoint of this study. In an open-label, randomized study comparing norfloxacin 400 mg/day to rufloxacin 400 mg/week in the prevention of SBP recurrence, 1-year probability of SBP recurrence was 26% and 36%, respectively ($p = 0.16$) [159]. Norfloxacin was more effective in the prevention of SBP recurrence due to Enterobacteriaceae (0% versus 22%, $p = 0.01$). Three other studies assessed the effects of ciprofloxacin, trimethoprim–sulfamethoxazole, and norfloxacin, but they included patients with and without previous episodes of SBP [153,160,161] (Table 7). All studies showed a reduced incidence of SBP with antibiotic prophylaxis.

It is uncertain whether prophylaxis should be continued without interruption until liver transplantation or death in all patients with prior SBP or if treatment could be discontinued in patients showing an improvement of liver disease.

Recommendations **Patients who recover from an episode of SBP have a high risk of developing recurrent SBP. In these patients, the administration of prophylactic antibiotics reduces the risk of recurrent SBP. Norfloxacin (400 mg/day, orally) is the treatment of choice (Level A1). Alternative antibiotics include ciprofloxacin (750 mg once weekly, orally) or co-trimoxazole (800 mg sulfamethoxazole and 160 mg trimethoprim daily, orally), but evidence is not as strong as that with norfloxacin (Level A2).**

Patients who recover from SBP have a poor long-term survival and should be considered for liver transplantation (Level A1).

3.3.4. Issues with prolonged antibiotic prophylaxis

As mentioned earlier, prolonged antibiotic prophylaxis (primary or secondary) has led to the emergence of GNB resistant to quinolones and even to trimethoprim/sulfamethoxazole [106]. In addition, there is an increased likelihood of infections from Gram-positive bacteria in patients who have received long-term SBP prophylaxis [156,162]. This underlines the need to restrict the use of prophylactic antibiotics to patients with the greatest risk of SBP. Common sense would suggest that quinolone prophylaxis should be discontinued in patients who develop infection due to quinolone-resistant bacteria. However, there are no data to support this.

4. Hyponatremia

Hyponatremia is common in patients with decompensated cirrhosis and is related to impaired solute-free water excretion secondary to non-osmotic hypersecretion of vasopressin (the antidiuretic hormone), which results in a disproportionate retention of water relative to sodium retention [163–166]. Hyponatremia in cirrhosis is arbitrarily defined when serum sodium concentration decreases below 130 mmol/L [163], but reductions below 135 mmol/L should also be considered as hyponatremia, according to recent guidelines on hyponatremia in the general patient population [167].

Patients with cirrhosis may develop two types of hyponatremia: hypovolemic and hypervolemic. Hypervolemic hyponatremia is the most common and is characterized by low serum sodium levels with expansion of the extracellular fluid volume, with ascites and edema. It may occur spontaneously or as a consequence of excessive hypotonic fluids (i.e., 5% dextrose) or secondary to complications of cirrhosis, particularly bacterial infections. By contrast, hypovolemic hyponatremia is less common and is characterized by low serum sodium levels and absence of ascites and edema, and is most frequently secondary to excessive diuretic therapy.

Serum sodium concentration is an important marker of prognosis in cirrhosis and the presence of hyponatremia is associated with an impaired survival [64,65,168–174]. Moreover, hyponatremia may also be associated with an increased morbidity, particularly neurological complications, and reduced survival after transplantation [175–177], although results of studies show discrepant findings with respect to survival.

4.1. Management of hyponatremia

It is generally considered that hyponatremia should be treated when serum sodium is lower than 130 mmol/L, although there is no good evidence as to what is the level of serum sodium in which treatment should be started.

The treatment of hypovolemic hyponatremia consists of administration of sodium together with identification of the causative factor (usually excessive diuretic administration) and will not be considered further in these guidelines.

The key of the management of hypervolemic hyponatremia is to induce a negative water balance with the aim of normalizing the increased total body water, which would result in an improvement of serum sodium concentration. Fluid restriction has been the standard of care but is seldom effective. It is the clinical experience that fluid restriction is helpful in preventing a further decrease in serum sodium levels, although it is rarely effective in improving serum sodium concentration. The lack of efficacy is probably due to the fact that in practice total daily fluid intake cannot be restricted to less than 1 L/day.

Although hypertonic sodium chloride administration has been used commonly in severe hypervolemic hyponatremia, its efficacy is partial, usually short-lived, and increases the amount of ascites and edema. The administration of albumin appears to improve serum sodium concentration, but more information is needed [178,179].

The pathophysiologically-oriented treatment of hyponatremia consists of improving solute-free water excretion which is markedly impaired in these patients. Early attempts using agents such as demeclocycline or κ-opioid agonists were unsuccessful because of side effects [180–183]. In recent years, the pharmacological approach to treatment of hypervolemic hyponatremia has made a step forward with the discovery of vaptans, drugs that are active orally and cause a selective blockade of the V2-receptors of AVP in the principal cells of the collecting ducts [184–186]. These drugs are effective in improving serum sodium concentration in conditions associated with high vasopressin levels, such as the syndrome of inappropriate antidiuretic hormone secretion (SIADH), heart failure, or cirrhosis [101,184,187–191]. The results of these studies consistently demonstrate that the administration of vaptans for a short period of time (1 week to 1 month in most of the studies) is associated with an increased urine volume and solute-free water excretion and improvement of the low serum sodium levels in 45–82% of patients. No significant changes have been observed in renal function, urine sodium, circulatory function, and activity of the renin–angiotensin–aldosterone system.

The most frequent side effect is thirst. Potential theoretical concerns of the administration of vaptans in patients with cirrhosis include hypernatremia, dehydration, renal impairment, and osmotic demyelination syndrome owing to a too rapid increase in serum sodium concentration. However, in the studies reported, the frequency of hypernatremia, dehydration, and renal impairment has been very low and no case of osmotic demyelination syndrome has been reported. Nevertheless, these complications should be taken into account and treatment should always be started in the hospital with close clinical monitoring and assessment of serum sodium levels, to avoid increases of serum sodium of more than 8–10 mmol/L/day. Vaptans should not be given to patients in an altered mental state (i.e., encephalopathy) who cannot drink appropriate amounts of fluid because of the risk of dehydration and hypernatremia. Vaptans are metabolized by CYP3A enzymes in the liver; therefore, drugs that are strong inhibitors of CYP3A such as ketoconazole, grapefruit juice, and clarithromycin among others, increase the exposure to vaptans and may be associated with large increases in serum sodium concentration. Conversely, drugs that are inducers of the CYP3A system, such as rifampin, barbiturates, and phenytoin, may decrease the effectiveness of vaptans.

Tolvaptan has been recently approved in the USA for the management of severe hypervolemic hyponatremia (<125 mmol/L) associated with cirrhosis, ascites, heart failure, and the SIADH. In Europe the drug is currently only licensed for the treatment of SIADH. Conivaptan is also approved in the USA for the short-term (5 day) intravenous treatment of hypervolemic hyponatremia associated with different conditions. Treatment of tolvaptan is started with 15 mg/day and titrated progressively to 30 and 60 mg/day, if needed, according to changes in serum sodium concentration. In randomized studies, a slightly increased frequency of gastrointestinal bleeding was reported in patients receiving tolvaptan compared to that in patients treated with placebo. No differences in the incidence of other side effects were observed. Nevertheless, it should be pointed out that tolvaptan was given for a period of 1 month and only limited long-term safety data exists with the use of this drug. Long-term, placebo-controlled studies in patients with cirrhosis treated with tolvaptan are clearly needed. No prospective evaluation on the efficacy and safety of conivaptan has been performed in patients with cirrhosis and hyponatremia.

As discussed previously, a phase-3 randomized double-blind placebo-controlled study comparing the efficacy of long-term treatment with satavaptan in combination with diuretics aimed at preventing ascites recurrence in patients with cirrhosis following LVP showed an increased frequency of complications and reduced survival in patients receiving satavaptan compared to those receiving placebo [104].

Recommendations **It is important to differentiate hypovolemic from hypervolemic hyponatremia. Hypovolemic hyponatremia is characterized by low serum sodium concentrations in the absence of ascites and edema, and usually occurs after a prolonged negative sodium balance with marked loss of extracellular fluid. Management consists of administration of normal saline and treatment of the cause (usually diuretic withdrawal) (Level A1).**

Fluid restriction to 1000 ml/day is effective in increasing serum sodium concentration in only a minority of patients with hypervolemic hyponatremia, but may be effective in preventing a further reduction in serum sodium levels (Level A1). There are no data to support the use of either normal or hypertonic saline in the management of hypervolemic hyponatremia (Level A1). Albumin administration might be effective but data are very limited to support its use currently (Level B2).

Treatment with vaptans may be considered in patients with severe hypervolemic hyponatremia (<125 mmol/L). Tolvaptan is licensed in some countries for oral treatment. Conivaptan is only licensed in some countries for short-term intravenous treatment. Treatment with tolvaptan should be started in the hospital and the dose titrated to achieve a slow increase in serum sodium. Serum sodium should be monitored closely particularly during the first days of treatment and whenever the dose of the drug is increased. Rapid increases in serum sodium concentration (>8–10 mmol/day) should be avoided to prevent the occurrence of osmotic demyelination syndrome. Neither fluid restriction nor administration of saline should be used in combination with vaptans to avoid a too rapid increase in serum sodium concentration. Patients may be discharged after serum sodium levels are stable and no further increase in the dose of the drug is required. Concomitant treatment with drugs that are either potent inhibitors or inducers of the CYP3A should be avoided. The duration of treatment with vaptans is not known. Safety has only been established for short-term treatment (1 month) (Level B1).

5. Hepatorenal syndrome

5.1. Definition and diagnosis of hepatorenal syndrome

Hepatorenal syndrome (HRS) is defined as the occurrence of renal failure in a patient with advanced liver disease in the absence of an identifiable cause of renal failure [56]. Thus, the diagnosis is essentially one of exclusion of other causes of renal failure. In 1994 the International Ascites Club defined the major criteria for the diagnosis of HRS and designated HRS into type 1 and type 2 HRS [56]. These were modified in 2007 [192]. The new diagnostic criteria are shown in Table 8. Various new concepts have emerged since the first definition and criteria for HRS were published in 1996 [56]. These are that vasodilatation mainly occurs in the splanchnic arterial bed, that the cardiac output in patients with HRS may be low or normal (infrequently high), but insufficient for the patient's needs, that the most important trigger for the development of type 1 HRS is bacterial infection, and that renal function can be improved by drug therapy [192].

Table 8. Criteria for diagnosis of hepatorenal syndrome in cirrhosis.

Cirrhosis with ascites
Serum creatinine >1.5 mg/dl (133 μmol/L)
Absence of shock
Absence of hypovolemia as defined by no sustained improvement of renal function (creatinine decreasing to <133 μmol/L) following at least 2 days of diuretic withdrawal (if on diuretics), and volume expansion with albumin at 1 g/kg/day up to a maximum of 100 g/day
No current or recent treatment with nephrotoxic drugs
Absence of parenchymal renal disease as defined by proteinuria <0.5 g/day, no microhaematuria (<50 red cells/high powered field), and normal renal ultrasonography

Clinical Practice Guidelines

There are 2 types of HRS. Type 1 HRS is a rapidly progressive acute renal failure that frequently develops in temporal relationship with a precipitating factor for a deterioration of liver function together with deterioration of other organ function. It commonly occurs in severe alcoholic hepatitis or in patients with end-stage cirrhosis following a septic insult such as SBP, although in some patients it may occur in the absence of any identifiable triggering event. Conventionally, type 1 HRS is only diagnosed when the serum creatinine increases more than 100% from baseline to a final level of greater than 2.5 mg/dl (221 μmol/L). Type 2 HRS occurs in patients with refractory ascites and there is a steady but moderate degree of functional renal failure, often with avid sodium retention. Patients with type 2 HRS may eventually develop type 1 HRS either spontaneously or following a precipitating event such as SBP [56]. The renal community has recently re-termed acute renal failure as acute kidney injury (AKI) [193]. However, the applicability and usefulness of the AKI classification in patients with cirrhosis requires full evaluation in prospective studies.

Recommendations **It is important to make the diagnosis of HRS or identify other known causes of renal failure in cirrhosis as early as possible. The causes of renal failure in cirrhosis that should be excluded before the diagnosis of HRS is made include: hypovolemia, shock, parenchymal renal diseases, and concomitant use of nephrotoxic drugs. Parenchymal renal diseases should be suspected if there is significant proteinuria or microhaematuria, or if renal ultrasonography demonstrates abnormalities in kidney size. Renal biopsy is important in these patients to help plan the further management, including the potential need for combined liver and kidney transplantation (Level B1).**

HRS should be diagnosed by demonstrating a significant increase in serum creatinine and excluding other known causes of renal failure. For therapeutic purposes, HRS is usually diagnosed only when serum creatinine increases to >133 μmol/L (1.5mg/dl). Repeated measurement of serum creatinine over time, particularly in hospitalized patients, is helpful in the early identification of HRS (Level B1).

HRS is classified into two types: type 1 HRS, characterized by a rapid and progressive impairment in renal function (increase in serum creatinine of equal to or greater than 100% compared to baseline to a level higher than 2.5 mg/dl in less than 2 weeks), and type 2 HRS characterized by a stable or less progressive impairment in renal function (Level A1).

5.2. Pathophysiology of hepatorenal syndrome

There are four factors involved in the pathogenesis of HRS. These are (1) development of splanchnic vasodilatation which causes a reduction in effective arterial blood volume and a decrease in mean arterial pressure. (2) Activation of the sympathetic nervous system and the renin–angiotensin–aldosterone system which causes renal vasoconstriction and a shift in the renal autoregulatory curve [194], which makes renal blood flow much more sensitive to changes in mean arterial pressure. (3) Impairment of cardiac function due to the development of cirrhotic cardiomyopathy, which leads to a relative impairment of the compensatory increase in cardiac output secondary to vasodilatation. (4) Increased synthesis of several vasoactive mediators which may affect renal blood flow or glomerular microcirculatory hemodynamics, such as cysteinyl leukotrienes, thromboxane A2, F_2-isoprostanes, and endothelin-1, yet the role of these factors in the pathogenesis of HRS remains unknown. An extended discussion of the pathophysiology of HRS is outside the scope of these guidelines and can be found elsewhere [165,195,196].

5.3. Risk factors and prognosis of hepatorenal syndrome

The development of bacterial infections, particulary SBP, is the most important risk factor for HRS [121,127,197,198]. HRS develops in approximately 30% of patients who develop SBP [121]. Treatment of SBP with albumin infusion together with antibiotics reduces the risk of developing HRS and improves survival [121]. The prognosis of HRS remains poor, with an average median survival time of all patients with HRS of approximately only 3 months [195,199]. High MELD scores and type 1 HRS are associated with very poor prognosis. Median survival of patients with untreated type 1 HRS is of approximately 1 month [200].

5.4. Management of hepatorenal syndrome

5.4.1. General measures

All comments made in these guidelines with respect to treatment refer to type 1 HRS unless otherwise specified. Once diagnosed, treatment should be started early in order to prevent the progression of renal failure. General supportive measures include careful monitoring of vital signs, standard liver and renal tests, and frequent clinical assessment as well as management of concomitant complications of cirrhosis. An excessive administration of fluids should be avoided to prevent fluid overload and development/progression of dilutional hyponatremia. Potassium-sparing diuretics should not be given because of the risk of severe hyperkalemia.

Recommendations **Monitoring: Patients with type 1 HRS should be monitored carefully. Parameters to be monitored include urine output, fluid balance, and arterial pressure, as well as standard vital signs. Ideally central venous pressure should be monitored to help with the management of fluid balance and prevent volume overload. Patients are generally better managed in an intensive care or semi-intensive care unit (Level A1).**

Screening for sepsis: Bacterial infection should be identified early, by blood, urine and ascitic fluid cultures, and treated with antibiotics. Patients who do not have signs of infection should continue taking prophylactic antibiotics, if previously prescribed. There are no data on the use of antibiotics as empirical treatment for unproven infection in patients presenting with type 1 HRS (Level C1).

Use of beta-blockers: There are no data on whether it is better to stop or continue with beta-blockers in patients with type 1 HRS who are taking these drugs for prophylaxis against variceal bleeding (Level C1).

Use of paracentesis: There are few data on the use of paracentesis in patients with type 1 HRS. Nevertheless, if patients have tense ascites, large-volume paracentesis with albumin is useful in relieving patients' discomfort (Level B1).

Use of diuretics: All diuretics should be stopped in patients at the initial evaluation and diagnosis of HRS. There are no data to support the use of furosemide in patients with ongoing type 1 HRS. Nevertheless furosemide may be useful to maintain urine output and treat central volume overload if present. Spironolactone is contraindicated because of high risk of life-threatening hyperkalemia (Level A1).

5.4.2. Specific therapies

5.4.2.1. Drug therapy. The most effective method currently available is the administration of vasoconstrictor drugs. Among the vasoconstrictors used, those that have been investigated more extensively are the vasopressin analogues particularly terlipressin [195,201–209]. The rationale for the use of vasopressin analogues in HRS is to improve the markedly impaired circulatory function by causing a vasoconstriction of the extremely dilated splanchnic vascular bed and increasing arterial pressure [210,211]. A large number of studies, randomized and non-randomized, have shown that terlipressin improves renal function in patients with type 1 HRS. Treatment is effective in 40–50% of patients, approximately (reviewed in [195,210]). There is no standardized dose schedule for terlipressin administration because of the lack of dose-finding studies. Terlipressin is generally started at a dose of 1 mg/4–6 h and increased to a maximum of 2 mg/4–6 h if there is no reduction in serum creatinine of at least 25% compared to the baseline value at day 3 of therapy. Treatment is maintained until serum creatinine has decreased below 1.5 mg/dl (133 μmol/L), usually around to 1–1.2 mg/dl (88–106 μmol/L). Response to therapy is generally characterized by a slowly progressive reduction in serum creatinine (to below 1.5 mg/dl–133 μmol/L), and an increase in arterial pressure, urine volume, and serum sodium concentration. Median time to response is 14 days and usually depends on pre-treatment serum creatinine, the time being shorter in patients with lower baseline serum creatinine [212]. A serum bilirubin less than 10 mg/dl before treatment and an increase in mean arterial pressure of >5 mm Hg at day 3 of treatment are associated with a high probability of response to therapy [212]. Recurrence after withdrawal of therapy is uncommon and retreatment with terlipressin is generally effective. The most frequent side effects of treatment are cardiovascular or ischemic complications, which have been reported in an average of 12% of patients treated [195,210]. It is important to emphasize that most studies excluded patients with known severe cardiovascular or ischemic conditions. In most studies, terlipressin was given in combination with albumin (1 g/kg on day 1 followed by 40 g/day) to improve the efficacy of treatment on circulatory function [213].

Treatment with terlipressin has been shown to improve survival in some studies but not in others. A recent systematic review of randomized studies using terlipressin as well as other vasoconstrictors has shown that treatment with terlipressin is associated with an improved short-term survival [214]. Most clinical trials on the use of terlipressin have excluded patients with ongoing sepsis. The effectiveness of terlipressin in the treatment of HRS with concomitant sepsis is unknown. Finally, treatment with terlipressin in patients with type 2 HRS is also associated with an improvement of renal function [209,215]. Nevertheless, there is still limited information on the use of terlipressin in these patients.

Vasoconstrictors other than vasopressin analogues that have been used in the management of type 1 HRS include noradrenaline and midodrine plus octreotide, both in combination with albumin. Midodrine is given orally at doses starting from 2.5 to 75 mg/8 h and octreotide 100 μg/8 h subcutaneously, with an increase to 12.5 mg/8 h and 200 μg/8 h, respectively, if there is no improvement in renal function. Although this approach has been shown to improve renal function, the number of patients reported using this therapy is very small [216,217]. Noradrenaline (0.5–3 mg/h) is administered as a continuous infusion and the dose is increased to achieve a raise in arterial pressure and also improves renal function in patients with type 1 HRS [218]. Unfortunately, the number of patients treated with noradrenaline is also small and no randomized comparative studies with a control group of patients receiving no vasoconstrictor therapy have been performed to evaluate its efficacy.

There have been few studies on prevention of HRS. Short-term treatment (4 week) with pentoxifylline (400 mg three times a day) in a randomized double-blind study was shown to prevent the development of HRS in patients with severe alcoholic hepatitis [219]. In a more recent study, long-term treatment with pentoxifylline was not associated with an improved survival but with reduced frequency of some complications of cirrhosis, including renal failure, yet this was not the primary endpoint of the study [220]. More studies are needed to assess the usefulness of pentoxifylline in the prevention of HRS in patients with cirrhosis. Finally, as discussed previously a randomized double-blind study showed that norfloxacin (400 mg/day) reduced the incidence of HRS in advanced cirrhosis [156].

5.4.2.2. Transjugular intrahepatic portosystemic shunts. Transjugular intrahepatic portosystemic shunts (TIPS) have been reported to improve renal function in patients with type 1 HRS [77,221]. However, the applicability of TIPS in this setting is very limited because many patients have contraindications to the use of TIPS. More studies are needed to evaluate the use of TIPS in patients with type 1 HRS. TIPS has also been shown to improve renal function and the control of ascites in patients with type 2 HRS [90]. However, TIPS has not been specifically compared with standard medical therapy in these latter patients.

5.4.2.3. Renal replacement therapy. Both hemodialysis or continuous venous hemofiltration, have been used to treat patients with type 1 HRS [222,223]. However, published information is very scant and in most studies patients with type 1 HRS have not been differentiated from patients with other causes of renal failure. Moreover, no comparative studies have been reported between renal replacement therapy and other methods of treatment, such as vasoconstrictor drugs. Circumstances that call for an immediate treatment with renal replacement therapy, such as severe hyperkalemia, metabolic acidosis, and volume overload are infrequent in patients with type 1 HRS, particularly in the early stages. There are isolated reports and a small randomized study suggesting that the so-called artificial liver support systems, either the molecular adsorbents recirculating system (MARS) or Prometheus, may have beneficial effects in patients with type 1 HRS [224,225]. However, these approaches should still be considered investigational until more data are available.

5.4.2.4. Liver transplantation. Liver transplantation is the treatment of choice for both type 1 and type 2 HRS, with survival rates of approximately 65% in type 1 HRS [226]. The lower survival rate compared to patients with cirrhosis without HRS is due to the fact that renal failure is a major predictor of poor outcome after transplantation. Moreover, patients with type 1 HRS have a high mortality whilst on the waiting list and ideally should be given priority for transplantation.

There seems to be no advantage in using combined liver–kidney transplantation versus liver transplantation alone in patients with HRS, with the possible exception of those patients who have been under prolonged renal support therapy (>12 weeks) [227,228].

Clinical Practice Guidelines

Although not studied prospectively, treatment of HRS before transplantation (i.e., with vasoconstrictors) may improve outcome after transplantation [229]. The reduction in serum creatinine levels after treatment and the related decrease in the MELD score should not change the decision to perform liver transplantation since the prognosis after recovering from type 1 HRS is still poor.

Recommendations **Management of type 1 hepatorenal syndrome**

Drug therapy of type 1 hepatorenal syndrome Terlipressin (1 mg/4–6 h intravenous bolus) in combination with albumin should be considered the first line therapeutic agent for type 1 HRS. The aim of therapy is to improve renal function sufficiently to decrease serum creatinine to less than 133 μmol/L (1.5 mg/dl) (complete response). If serum creatinine does not decrease at least 25% after 3 days, the dose of terlipressin should be increased in a stepwise manner up to a maximum of 2 mg/4 h. For patients with partial response (serum creatinine does not decrease <133 μmol/L) or in those patients without reduction of serum creatinine treatment should be discontinued within 14 days (Level A1).

Contraindications to terlipressin therapy include ischemic cardiovascular diseases. Patients on terlipressin should be carefully monitored for development of cardiac arrhythmias or signs of splanchnic or digital ischemia, and fluid overload, and treatment modified or stopped accordingly. Recurrence of type 1 HRS after discontinuation of terlipressin therapy is relatively uncommon. Treatment with terlipressin should be repeated and is frequently successful (Level A1).

Potential alternative therapies to terlipressin include norepinephrine or midodrine plus octreotide, both in association with albumin, but there is very limited information with respect to the use of these drugs in patients with type 1 HRS (Level B1).

Non-pharmacological therapy of type 1 hepatorenal syndrome: Although the insertion of TIPS may improve renal function in some patients, there are insufficient data to support the use of TIPS as a treatment of patients with type 1 HRS.

Renal replacement therapy may be useful in patients who do not respond to vasoconstrictor therapy, and who fulfill criteria for renal support. There are very limited data on artificial liver support systems, and further studies are needed before its use in clinical practice can be recommended (Level B1).

Management of type 2 hepatorenal syndrome

Terlipressin plus albumin is effective in 60–70% of patients with type 2 HRS. There are insufficient data on the impact of this treatment on clinical outcomes (Level B1).

Liver transplantation

Liver transplantation is the best treatment for both type 1 and type 2 HRS. HRS should be treated before liver transplantation, since this may improve post-liver transplant outcome (Level A1).

Patients with HRS who respond to vasopressor therapy should be treated by liver transplantation alone. Patients with HRS who do not respond to vasopressor therapy, and who require renal support should generally be treated by liver transplantation alone, since the majority will achieve a recovery of renal function post-liver transplantation. There is a subgroup of patients who require prolonged renal support (>12 weeks), and it is this group that should be considered for combined liver and kidney transplantation (Level B2).

Prevention of hepatorenal syndrome

Patients who present with SBP should be treated with intravenous albumin since this has been shown to decrease the incidence of HRS and improve survival (Level A1).

There are some data to suggest that treatment with pentoxifylline decreases the incidence of HRS in patients with severe alcoholic hepatitis and advanced cirrhosis and treatment with norfloxacin decreases the incidence of HRS in advanced cirrhosis, respectively. Further studies are needed (Level B2).

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