Netherlands
The Journal of Medicine

REVIEW

Ascites in cirrhosis: a review of management and complications

J.J. Kuiper*, H.R. van Buuren, R.A. de Man

Department of Gastroenterology and Hepatology, Erasmus MC University Medical Centre, Rotterdam, the Netherlands, *corresponding author: tel.: +31 (0)10-463 59 42, fax: +31 (0)10-436 59 16, e-mail: j.j.kuiper@erasmusmc.nl

ABSTRACT

Ascites is the most common manifestation in cirrhotic patients, and is associated with a reduced survival rate. Management of ascites is primarily focused on sodium restriction and diuretic treatment to which most patients respond appropriately. For the small group of patients who do not respond sufficiently, interventions such as large volume paracentesis and transjugular intrahepatic portosystemic shunt placement should be considered.

Most important in the management of cirrhotic patients with ascites is prevention of complications. Spontaneous bacterial peritonitis and hepatorenal syndrome are severe complications with a poor prognosis when not detected and treated in an early stage. In all hospitalised patients with ascites, an infection of the ascitic fluid should be ruled out. For those patients at risk of developing spontaneous bacterial peritonitis, in particular patients after a first episode and patients with gastrointestinal bleeding, antibiotic prophylaxis should be given. To prevent the hepatorenal syndrome, substitution with albumin is essential, both in patients who experience an episode of spontaneous bacterial peritonitis and in patients treated with large volume paracentesis. For those patients unresponsive to standard treatment regimens, liver transplantation may be the only suitable treatment option.

KEYWORDS

Ascites, cirrhosis, diagnosis, treatment

INTRODUCTION

Ascites is the most common complication in patients with cirrhosis of the liver, developing in more than 50% of the patients within ten years of the initial diagnosis.[1] Cirrhosis of the liver is the most common aetiology for ascites, responsible for 80% of all cases of ascites.[2] The onset of ascites marks a turning point in the prognosis of cirrhotic patients with a mortality rate of 50% within two to five years after its first appearance.[3-6]

In this article, we review the pathophysiology and management of ascites and the most common complications, including spontaneous bacterial peritonitis (SBP) and hepatorenal syndrome (HRS).

PATHOPHYSIOLOGY

The precise mechanism leading to the formation of ascites is not completely understood. The prevailing theory now is that portal hypertension, and specifically sinusoidal hypertension, is the central pathophysiological abnormality. Increased portal pressure causes splanchnic vasodilatation, mainly due to increased local production of nitric oxide, thereby creating a hyperdynamic circulation. This results in increased capillary pressure and permeability and a decreased effective arterial blood volume. An increase in plasma volume and cardiac output are accommodating mechanisms for this reduction in arterial blood volume.[7,8] Activation of the sympathetic nervous system and renin-angiotensin-aldosterone system (RAAS) lead to a compensatory sodium and water retention, thereby facilitating the formation of ascites.[4,5,9]

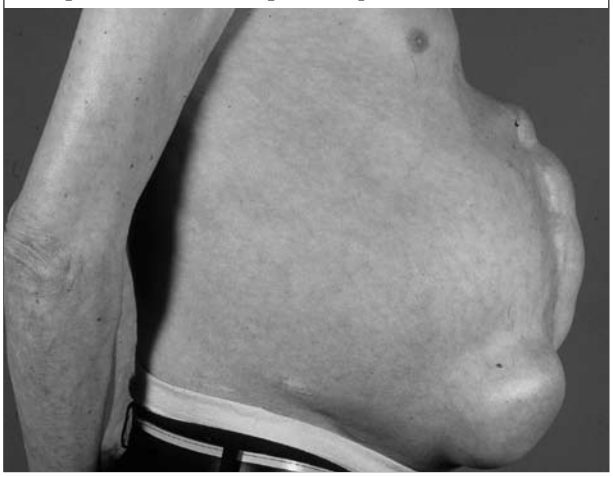
EVALUATION

Abdominal ultrasound is the gold standard for the evaluation of ascites and portal hypertension. Ultrasound examination can reliably detect amounts of peritoneal fluid as low as 100 ml that are not usually detected on

© 2007 Van Zuiden Communications B.V. All rights reserved.

physical examination. According to the quantity of ascites, physical examination may suggest the presence of ascites by shifting dullness or by demonstration of a fluid thrill or wave. Patients with ascites usually have additional stigmata of chronic liver disease such as cutaneous collaterals of the abdomen, vascular spiders, and splenomegaly. In patients with large amounts of ascites the nutritional status is often poor. Umbilical, inguinal, and incisional hernias are particularly frequent (*figure 1*). The hyperdynamic circulation and raised cardiac output are evidenced by a normal/low blood pressure and tachycardia; an ejection systolic murmur may be present. Leg oedema is variably found.

Figure 1. *Incisional hernia in patient with ascites and previous midline laparotomy*



Pleural effusions (hepatic hydrothorax), due to migration of ascites through micropores in the diaphragm, may also be present. In about 80% of cases the effusions are right-sided. It should be stressed that ascites may well be absent in patients with hepatic hydrothorax.[10]

When in doubt about the aetiology of ascites, diagnostic paracentesis is indicated. In recent years the transsudate-exudate concept has been replaced by a classification based on the serum ascites albumin gradient (SAAG).[4] A SAAG of ≥11 g/l is indicative for a hepatic cause of ascites (*table 1*). In addition to the albumin concentration in ascites, other useful laboratory investigations may be the determination of the number of (polymorphonuclear) leucocytes, amylase, triglyceride concentration, chylomicrons and in selected cases cytological and immunological examination.

In all patients with ascites who clinically show deterioration (e.g. renal dysfunction, encephalopathy, admission to hospital) or have signs of infection (e.g. fever, abdominal discomfort, increased C-reactive protein level), diagnostic paracentesis should be performed to rule out infection.

Table 1. *Aetiology according to the serum ascites albumin gradient*

<11 g/l	Infection
	Nephrotic syndrome
	Malignancy
	Pancreatitis
≥11 g/l	Cirrhosis
	Budd-Chiari syndrome
	Veno-occlusive disease
	Alcoholic hepatitis
	Congestive heart failure

TREATMENT

The management of ascites should be dictated by the severity of symptoms. The mere presence of ascites does not merit active treatment and cosmetic reasons are only relative. Overtreatment, especially with diuretics, may easily lead to serious complications including hyponatraemia, renal failure, and encephalopathy. Therefore, the key management rule is that it is better to have a patient 'wet and wise' than 'dry and demented'. Primary focus for treatment should be the underlying liver disease. For instance, abstinence of alcohol in alcoholic liver disease and immunosuppressive treatment in autoimmune hepatitis may result in disappearance of ascites that had been difficult to manage.

Besides treating the underlying liver disease, the aim of the treatment should be aimed at achieving a negative sodium balance in order to diminish the ascites. In symptomatic patients the first therapeutic step is dietary sodium restriction to 60 to 90 mmol/day. Trials comparing low *vs* marked sodium restriction have shown comparable efficacy but better compliance with the more liberal diet.[5,11] To verify compliance to sodium restriction or in difficult-to-treat patients quantification of urinary sodium excretion can be used as a diagnostic tool.

Diuretic treatment

Most patients with symptomatic ascites do not respond sufficiently to sodium restriction alone and require additional diuretic treatment. In general, the preferred regimen is to start with spironolactone, an aldosterone antagonist, and to add a loop diuretic if necessary. The usual initial dose of spironolactone for moderate ascites is 50 to 100 mg/day; the maximal daily dose is 400 mg. Commonly experienced side effects are (painful) gynaecomastia and hyperkalaemia. Most patients show a significant decrease in ascitic fluid when spironolactone is given alone, usually in doses of up to 200 to 300 mg/day.[12] When the response is insufficient, combination therapy with furosemide, starting with doses of 20 to 40 mg/day, is recommended.[13,14] The American Association for the

Study of Liver Diseases (AASLD) guidelines have advised starting this combination therapy immediately so that side effects due to the spironolactone, i.e. hyperkalaemia, can be prevented.[12]

Especially during the phase of ascites mobilisation, regular monitoring of body weight, renal function and electrolytes is mandatory. As a rule of thumb, the daily weight loss should not exceed 1 kg for those patients with ascites and peripheral oedema, and 0.5 kg for those patients without oedema.[11]

New alternatives in the treatment of ascites are the aquaretics, selective V2 receptor antagonists. These agents improve urinary output and free water clearance by blocking the action of the antidiuretic hormone in the collecting tubuli and may be particularly helpful in the management of hyponatraemia.[15,16] Thus far aquaretics have only been used in the context of clinical studies. Before implementing aquaretics in clinical practice, further research on dosage and side effects is necessary.[17]

Paracentesis

In about 90% of the patients, ascites diminishes adequately with sodium restriction and diuretic treatment.[18] In patients where ascites does not diminish sufficiently in response to maximal diuretic treatment, or when severe side effects occur due to diuretic treatment, such as renal impairment, ascites is considered to be refractory. For patients with refractory ascites several therapeutic options remain available. The least invasive procedure is (repeated) large volume paracentesis (LVP) with removal of >5 litres of ascitic fluid. This can be done as an outpatient procedure and it is safe to remove all the ascites within one to three hours. Obviously, LVP is a symptom-relieving treatment and does not influence the mechanisms leading to the formation of ascites. LVP can be complicated by paracentesis-induced circulatory dysfunction (PICD). This is defined as an increase in plasma renin concentration >50% of the baseline value on day 6.[19] PICD is triggered by a decrease in systemic vascular resistance (SVR). The decrease in SVR is predominantly caused by an accentuation of the arterial vasodilatation already present. The mechanism as to how paracentesis induces an additional arterial vasodilatation is not yet understood. PICD induces compensatory activation of the RAAS, facilitating the development of notorious complications, such as HRS.[19-21] Studies have shown that PICD can be prevented by intravascular plasma expansion during or directly after paracentesis when ≥5 litres of ascites are removed. The preferred substitution is albumin, given intravenously in a dosage of 8 g per litre of ascites removed. Other plasma volume expanders, such as saline, dextran, and polygeline, have been compared with albumin, but none have shown to be superior or safer in the prevention of PICD.[22-25] Recent studies have explored the use of vasoconstrictors to prevent PICD.[26-29] Terlipressin, a vasopressin prodrug, administered as two to three bolus injections of 1 to 2 mg during and after paracentesis, appears to be as effective as albumin.[26,29] Larger studies are ongoing to see whether terlipressin can be considered a definite alternative for intravenous albumin administration.

Transjugular intrahepatic portosystemic shunt

Transjugular intrahepatic portosystemic shunt (TIPS) is another treatment modality for refractory ascites, especially when patients frequently require, or poorly tolerate, LVP.[14] TIPS reduces portal pressure; when this pressure is <12 mmHg, ascites is less likely to develop in cirrhotic patients.[30] Placement of TIPS leads to an increase in urinary sodium excretion 7 to 30 days after stent placement.[31-33] This is correlated with reduced activity of the RAAS and improvement of effective arterial blood volume.

In approximately 70% of patients TIPS is effective, although in most patients (low-dose) diuretic treatment must be continued.[33]

A main disadvantage of TIPS placement is the risk of new onset or worsening of pre-existent encephalopathy, a complication that occurs in about one-third of patients.[34] Risk factors are the presence of pre-TIPS hepatic encephalopathy, age >65 years, a low post-TIPS portosystemic pressure gradient and serum creatinine level.[35] The vast majority of patients developing encephalopathy respond well to standard treatment with lactulose; only 3 to 10% require narrowing or obliteration of the shunt.[33,36]

TIPS has shown to be better in preventing recurrence of ascites than paracentesis (48 *vs* 84%), but is associated with a higher incidence of hepatic encephalopathy (42 *vs* 23%) while mortality rates of the two treatment modalities are comparable.[33]

In most studies performed thus far uncovered stents were used. These stents are prone to occlude and in >50% of cases treated with TIPS, revision of the stent is required within one year. A newer stent, coated with polytetrafluoroethylene, is less prone to occlude. TIPS is probably more effective in controlling ascites when these covered stents are used.[37,38]

Eligibility for TIPS placement depends on several factors. Generally, established contraindications for TIPS placement are age >70 years, pulmonary hypertension, pre-existing cardiac dysfunction, renal failure due to organic kidney disease, hepatic malignancy and a Child Pugh score >11.[33,37]

Peritoneovenous (LeVeen; Denver) shunts have not been shown to be more efficacious than repeated paracenteses and complications, including occlusion, infection, and disseminated intravascular coagulation, are frequent.[39] These devices are nowadays rarely used in the treatment of refractory ascites.

Liver transplantation

The onset of ascites in patients with cirrhosis is associated with a markedly decreased survival. In patients with ascites, evaluation for liver transplantation should therefore always be considered, preferably before complications as SBP and HRS occur.

COMPLICATIONS

Spontaneous bacterial peritonitis

SBP, with a lifetime incidence of 10 to 30%, is the most common infection in patients with cirrhosis, primarily seen in hospitalised patients.[11,40] SBP is defined as an infection of ascitic fluid with an ascitic polymorphonuclear leucocyte count (PMN count) of ≥0.25 x 10^9/l, in the absence of an identifiable focal source of infection.[40]

Factors currently implicated in the pathogenesis of SBP are intestinal bacterial overgrowth, combined with a delayed intestinal transit time and increased permeability of the intestinal wall. Local intestinal immunodeficiency, such as decreased levels of mucosal IgA, may also play a role. These factors facilitate translocation of bacteria through the mucosal barrier. Intestinal bacteria may then migrate via the mesenteric lymph nodes and the systemic circulation and subsequently may lead to infection of the ascitic fluid. Low ascitic protein and complement levels are probable contributory factors.[41,42]

Diagnostic paracentesis should be performed in all patients with ascites who require hospitalisation to rule out SBP. A large proportion of patients with SBP are asymptomatic, while others show signs of fever, abdominal pain, nausea, encephalopathy or a deterioration in renal function. In approximately half of the cases encephalopathy develops or progresses at the time of SBP.

In the diagnostic work-up for SBP the ascitic PMN count should be determined. At least 10 ml ascitic fluid per bottle should also be inoculated into aerobic/anaerobic blood culture bottles. This should be done immediately, at the bedside, to increase the sensitivity of this method. Even with this method cultures of ascitic fluid at the time of SBP remain negative in up to 60%.[43]

SBP is typically monobacterial and caused predominantly by gram-negative bacteria, especially *E. coli* and *Klebsiella* species. With the increased use of prophylactic antibiotics in cirrhotic patients, gram-positive bacteria are becoming increasingly common.[43,44] More than one bacterial species suggests the possibility of secondary bacterial peritonitis and possible causes, including appendicitis, diverticulitis and cholecystitis, should be evaluated.

After the diagnosis of SBP has been established by means of the PMN count, treatment should be started immediately. At present, third-generation cephalosporins are generally considered the gold standard in the treatment of SBP.[45] Especially cefotaxim 2 g/12 hours intravenously during at least five days has been extensively studied and found to be an effective regimen.[46,47] Reports on the use of amoxicillin/clavulanic acid, 1.2 g intravenously, four times daily, have shown comparable results with considerably lower costs, making them a safe alternative treatment regimen.[48]

Two randomised controlled trials have demonstrated that the intravenous administration of albumin may reduce the incidence of renal impairment and improve short-term survival in patients with SBP. The beneficial effect was obtained by the additional administration of albumin at a dose of 1.5 g/ kg body weight at the day of diagnosis of SBP followed by a dosage of 1 g/kg body weight at day 3.[49,50] The remaining question is whether albumin treatment should be limited to, for example, Child's stage C patients, while there is also room for more studies with respect to the optimal dosage regimen.

The long-term prognosis of cirrhotic patients with SBP is extremely poor, with reported mortality rates of 50 to 70% and 70 to 75% after one and two years, respectively.[40,51] This is largely attributable to the advanced stage of liver cirrhosis that is nearly always present in patients who acquire SBP. Septic shock, progressive renal and multiorgan failure, and variceal bleeding are frequent complications of SBP and account for significant in-hospital mortality.[11] Considering the poor prognosis, patients who overcome an episode of SBP should be evaluated for liver transplantation.

Given the high risk of recurrence of SBP of up to 70% within one year, there is consensus that patients who have recovered from an episode of SBP should receive secondary antibiotic prophylaxis. Certain groups at risk for SBP should also be considered for primary antibiotic prophylaxis, in particular cirrhotic patients with gastrointestinal bleeding. *Table 2* summarises the current recommendations for antibiotic prophylaxis.

Table 2. *Cirrhotic patients eligible for spontaneous bacterial peritonitis (SBP) prophylaxis*

Short-term prophylaxis	Long-term prophylaxis
Norfloxacin 400 mg twice daily for 7 days	Norfloxacin 400 mg daily
Patients with gastrointestinal bleeding	Patients recovered from episode of SBP
	Patients with ascites and low ascitic fluid protein count (<10g/l) (no consensus)

HEPATORENAL SYNDROME

HRS is a severe complication, occurring in ~10% of the patients with cirrhosis and ascites.[11] It is characterised by renal vasoconstriction leading to renal failure. The renal vasoconstriction is a compensatory effect of the

renin-angiotensin-aldosterone system and antidiuretic hormone, triggered by an extreme underfilling in the arterial circulation.[52]

The diagnosis of HRS is based on several criteria, of which the major criteria are necessary to establish the diagnosis of HRS (*table 3*).[18] Minor criteria for the diagnosis of HRS can be used as an additional tool to strengthen the diagnosis, but have recently been abandoned by the International Ascites Club as official minor criteria for establishing the diagnosis.[53] The urinary sodium excretion may help differentiate between HRS and acute tubular necrosis (ATN). A sodium excretion of <10 mmol/l strengthens the diagnosis of HRS whereas a sodium excretion of >10 mmol/l is more likely to fit the diagnosis of ATN.

There are two subtypes of HRS. HRS type 1 is rapidly progressive, often precipitated by a triggering event such as SBP, and has a median survival of approximately two weeks when treatment is not started rapidly. HRS type 2 develops gradually, as a consequence of aggravation of end-stage liver disease and requires no additional treatment.

Table 3. *Major criteria for diagnosing the hepatorenal syndrome*

Serum creatinine >130 μmol/l
No shock, ongoing bacterial infection, volume depletion, or treatment with nephrotoxic drugs
No improvement after cessation of diuretics or fluid challenge (1.5 litre saline infusion or albumin infusion 1 g/kg body weight, max 100 g albumin)
No proteinuria (<500 mg/day) or evidence of parenchymal renal disease or obstructive uropathy by ultrasound

General management of patients with HRS type 1 consists of close monitoring of vital signs, electrolytes, and fluid balance. A fluid restriction of 1 litre a day is only advised in patients with a dilutional hyponatraemia (<125 mmol/l). To retain renal function and prevent electrolyte dysbalance cessation of diuretic treatment is necessary. Since 30% of the episodes of HRS are precipitated by SBP a diagnostic puncture of ascitic fluid should always be performed to rule out infection. Until now no consensus has been reached as to whether it is safe to perform LVP in patients with HRS type 1. LVP with adequate suppletion of albumin may provide comfort to the patient, but it may also attenuate the arterial underfilling already present, thereby worsening renal dysfunction.

Most important in patients with HRS type 1 is pharmacological treatment. Treatment consists of a combination of a plasma expander and a vasoconstrictor. The preferred plasma expander is albumin intravenously in a dosage of 1 g/kg body weight on the first day followed by 20 to 40 g/day for the remainder of treatment. The first choice for vasoconstrictor therapy is vasopressin analogues, for which the best results have been obtained with terlipressin.[18,27] Terlipressin has its primary action in the splanchnic area. The drug is administered in a stepwise schedule with a starting dosage of 0.5 mg/4 hours. The dosage can be increased stepwise every two to three days to 1 to 2 mg/4 hours, according to the effect of treatment. The effect of therapy is measured by a decrease in serum creatinine level; the goal is to obtain a serum creatinine of <130 μmol/l.

There are alternative vasoconstrictor treatments, such as combinations of noradrenaline or midodrine and octreotide, but their effect has been less thoroughly studied.[27]

Patients with HRS type 2 can be monitored in an outpatient setting. Caution should be applied in dosing diuretics to preserve renal function. Special attention should be given to prevention of triggers that lead to a deterioration into HRS type 1; in specific SBP, variceal bleeding, or no adequate substitution during LVP.

REFERENCES

1. Gines P, Quintero E, Arroyo V, et al. Compensated cirrhosis: natural history and prognostic factors. Hepatology 1987;7(1):122-8.
2. Runyon BA, Montano AA, Akriviadis EA, Antillon MR, Irving MA, McHutchison JG. The serum-ascites albumin gradient is superior to the exudate-transudate concept in the differential diagnosis of ascites. Ann Intern Med 1992;117(3):215-20.
3. Fattovich G, Giustina G, Degos F, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. Gastroenterology 1997;112(2):463-72.
4. Gines P, Arroyo V, Rodes J, Schrier RW. Ascites and renal dysfunction in liver disease. 2nd ed. Malden, MA: Blackwell Publishing Ltd, 2005.
5. Saadeh S, Davis GL. Management of ascites in patients with end-stage liver disease. Rev Gastroenterol Disord 2004;4(4):175-85.
6. D'Amico G, Morabito A, Pagliaro L, Marubini E. Survival and prognostic indicators in compensated and decompensated cirrhosis. Dig Dis Sci 1986;31(5):468-75.
7. Arroyo V, Jimenez W. Complications of cirrhosis. II. Renal and circulatory dysfunction. Lights and shadows in an important clinical problem. J Hepatol 2000;32(1 Suppl):157-70.
8. Gentilini P, Vizzutti F, Gentilini A, Zipoli M, Foschi M, Romanelli RG. Update on ascites and hepatorenal syndrome. Dig Liver Dis 2002;34(8):592-605.
9. Heneghan MA, Harrison PM. Pathogenesis of ascites in cirrhosis and portal hypertension. Med Sci Monit 2000;6(4):807-16.
10. Kuiper JJ, de Man RA, van Buuren HR. Hepatic hydrothorax. Ned Tijdschr Geneeskd 2006;150(21):1157-61.
11. Gines P, Cardenas A, Arroyo V, Rodes J. Management of cirrhosis and ascites. N Engl J Med 2004;350(16):1646-54.
12. Runyon BA. Management of adult patients with ascites due to cirrhosis. Hepatology 2004;39(3):841-56.
13. Santos J, Planas R, Pardo A, et al. Spironolactone alone or in combination with furosemide in the treatment of moderate ascites in nonazotemic cirrhosis. A randomized comparative study of efficacy and safety. J Hepatol 2003;39(2):187-92.
14. Moore KP, Wong F, Gines P, et al. The management of ascites in cirrhosis: report on the consensus conference of the International Ascites Club. Hepatology 2003;38(1):258-66.

15. Schrier RW, Gross P, Gheorghiade M, et al. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. N Engl J Med 2006;355(20):2099-112.

16. Thuluvath PJ, Maheshwari A, Wong F, et al. Oral V2 receptor antagonist (RWJ-351647) in patients with cirrhosis and ascites: a randomized, double-blind, placebo-controlled, single ascending dose study. Aliment Pharmacol Ther 2006;24(6):973-82.

17. Yeates KE, Morton AR. Vasopressin antagonists: role in the management of hyponatremia. Am J Nephrol 2006;26(4):348-55.

18. Arroyo V, Gines P, Gerbes AL, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. International Ascites Club. Hepatology 1996;23(1):164-76.

19. Ruiz-del-Arbol L, Monescillo A, Jimenez W, Garcia-Plaza A, Arroyo V, Rodes J. Paracentesis-induced circulatory dysfunction: mechanism and effect on hepatic hemodynamics in cirrhosis. Gastroenterology 1997;113(2):579-86.

20. Coll S, Vila MC, Molina L, Gimenez MD, Guarner C, Sola R. Mechanisms of early decrease in systemic vascular resistance after total paracentesis: influence of flow rate of ascites extraction. Eur J Gastroenterol Hepatol 2004;16(3):347-53.

21. Vila MC, Sola R, Molina L, et al. Hemodynamic changes in patients developing effective hypovolemia after total paracentesis. J Hepatol 1998;28(4):639-45.

22. Garcia-Compean D, Blanc P, Larrey D, et al. Treatment of cirrhotic tense ascites with Dextran-40 versus albumin associated with large volume paracentesis: a randomized controlled trial. Ann Hepatol 2002;1(1):29-35.

23. Gines A, Fernandez-Esparrach G, Monescillo A, et al. Randomized trial comparing albumin, dextran 70, and polygeline in cirrhotic patients with ascites treated by paracentesis. Gastroenterology 1996 ;111(4):1002-10.

24. Sola-Vera J, Minana J, Ricart E, et al. Randomized trial comparing albumin and saline in the prevention of paracentesis-induced circulatory dysfunction in cirrhotic patients with ascites. Hepatology 2003;37(5):1147-53.

25. Moreau R, Valla DC, Durand-Zaleski I, et al. Comparison of outcome in patients with cirrhosis and ascites following treatment with albumin or a synthetic colloid: a randomised controlled pilot trial. Liver Int 2006;26(1):46-54.

26. Moreau R, Asselah T, Condat B, et al. Comparison of the effect of terlipressin and albumin on arterial blood volume in patients with cirrhosis and tense ascites treated by paracentesis: a randomised pilot study. Gut 2002;50(1):90-4.

27. Moreau R, Lebrec D. The use of vasoconstrictors in patients with cirrhosis: type 1 HRS and beyond. Hepatology 2006;43(3):385-94.

28. Singh V, Kumar B, Nain CK, et al. Noradrenaline and albumin in paracentesis-induced circulatory dysfunction in cirrhosis: a randomized pilot study. J Intern Med 2006;260(1):62-8.

29. Singh V, Kumar R, Nain CK, Singh B, Sharma AK. Terlipressin versus albumin in paracentesis-induced circulatory dysfunction in cirrhosis: a randomized study. J Gastroenterol Hepatol 2006;21(1 Pt 2):303-7.

30. Abraldes JG, Tarantino I, Turnes J, Garcia-Pagan JC, Rodes J, Bosch J. Hemodynamic response to pharmacological treatment of portal hypertension and long-term prognosis of cirrhosis. Hepatology 2003;37(4):902-8.

31. Quiroga J, Sangro B, Nunez M, et al. Transjugular intrahepatic portal-systemic shunt in the treatment of refractory ascites: effect on clinical, renal, humoral, and hemodynamic parameters. Hepatology 1995;21(4):986-94.

32. Wong W, Liu P, Blendis L, Wong F. Long-term renal sodium handling in patients with cirrhosis treated with transjugular intrahepatic portosystemic shunts for refractory ascites. Am J Med 1999;106(3):315-22.

33. Garcia-Tsao G. The transjugular intrahepatic portosystemic shunt for the management of cirrhotic refractory ascites. Nat Clin Pract Gastroenterol Hepatol 2006;3(7):380-9.

34. Russo MW, Sood A, Jacobson IM, Brown RS Jr. Transjugular intrahepatic portosystemic shunt for refractory ascites: an analysis of the literature on efficacy, morbidity, and mortality. Am J Gastroenterol 2003;98(11):2521-7.

35. ter Borg PC, Hollemans M, van Buuren HR, et al. Transjugular intrahepatic portosystemic shunts: long-term patency and clinical results in a patient cohort observed for 3-9 years. Radiology 2004;231(2):537-45.

36. Kochar N, Tripathi D, Ireland H, Redhead DN, Hayes PC. Transjugular intrahepatic portosystemic stent shunt (TIPSS) modification in the management of post-TIPSS refractory hepatic encephalopathy. Gut 2006;55(11):1617-23.

37. Tripathi D, Ferguson J, Barkell H, et al. Improved clinical outcome with transjugular intrahepatic portosystemic stent-shunt utilizing polytetrafluoroethylene-covered stents. Eur J Gastroenterol Hepatol 2006;18(3):225-32.

38. Tripathi D, Redhead D. Transjugular intrahepatic portosystemic stent-shunt: technical factors and new developments. Eur J Gastroenterol Hepatol 2006;18(11):1127-33.

39. Gines P, Arroyo V, Vargas V, et al. Paracentesis with intravenous infusion of albumin as compared with peritoneovenous shunting in cirrhosis with refractory ascites. N Engl J Med 1991;325(12):829-35.

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

41. Guarner C, Soriano G. Bacterial translocation and its consequences in patients with cirrhosis. Eur J Gastroenterol Hepatol 2005;17(1):27-31.

42. Kalaitzakis E, Johansson JE, Bjarnason I, Bjornsson E. Intestinal permeability in cirrhotic patients with and without ascites. Scand J Gastroenterol 2006;41(3):326-30.

43. Fernandez J, Navasa M, Gomez J, et al. Bacterial infections in cirrhosis: epidemiological changes with invasive procedures and norfloxacin prophylaxis. Hepatology 2002;35(1):140-8.

44. Singh N, Wagener MM, Gayowski T. Changing epidemiology and predictors of mortality in patients with spontaneous bacterial peritonitis at a liver transplant unit. Clin Microbiol Infect 2003;9(6):531-7.

45. Portal hypertension IV: proceedings from the fourth Baveno International Consensus Workshop. Blackwell Publishing ltd; 2006.

46. Runyon BA, McHutchison JG, Antillon MR, Akriviadis EA, Montano AA. Short-course versus long-course antibiotic treatment of spontaneous bacterial peritonitis. A randomized controlled study of 100 patients. Gastroenterology 1991;100(6):1737-42.

47. Rimola A, Salmeron JM, Clemente G, et al. Two different dosages of cefotaxime in the treatment of spontaneous bacterial peritonitis in cirrhosis: results of a prospective, randomized, multicenter study. Hepatology 1995;21(3):674-9.

48. Ricart E, Soriano G, Novella MT, et al. Amoxicillin-clavulanic acid versus cefotaxime in the therapy of bacterial infections in cirrhotic patients. J Hepatol 2000;32(4):596-602.

49. Fernandez J, Monteagudo J, Bargallo X, et al. A randomized unblinded pilot study comparing albumin versus hydroxyethyl starch in spontaneous bacterial peritonitis. Hepatology 2005;42(3):627-34.

50. Sort P, Navasa M, Arroyo V, Aldeguer X, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. N Engl J Med 1999;341(6):403-9.

51. Kuiper JJ BvH, Man de RA Limited role for routine ascitic culture as a diagnostic tool for spontaneous bacterial peritonitis in the era of prophylactic antibiotics. J Hepatol 2007;46(suppl 1):S96.

52. Ruiz-del-Arbol L, Monescillo A, Arocena C, et al. Circulatory function and hepatorenal syndrome in cirrhosis. Hepatology 2005;42(2):439-47.

53. Salerno F, Gerbes A, Gines P, Wong F, Arroyo V. Diagnosis, prevention and treatment of the hepatorenal syndrome in cirrhosis. A consensus workshop of the international ascites club. Gut 2007; epub ahead of print.