The Management of Ascites in Cirrhosis: Report on the Consensus Conference of the International Ascites Club

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Ascites is a common complication of cirrhosis, and heralds a new phase of hepatic decompensation in the progression of the cirrhotic process. The development of ascites carries a significant worsening of the prognosis. It is important to diagnose noncirrhotic causes of ascites such as malignancy, tuberculosis, and pancreatic ascites since these occur with increased frequency in patients with liver disease. The International Ascites Club, representing the spectrum of clinical practice from North America to Europe, have developed guidelines by consensus in the management of cirrhotic ascites from the early ascitic stage to the stage of refractory ascites. Mild to moderate ascites should be managed by modest salt restriction and diuretic therapy with spironolactone or an equivalent in the first instance. Diuretics should be added in a stepwise fashion while maintaining sodium restriction. Gross ascites should be treated with therapeutic paracentesis followed by colloid volume expansion, and diuretic therapy. Refractory ascites is managed by repeated large volume paracentesis or insertion of a transjugular intrahepatic portosystemic stent shunt (TIPS). Successful placement of TIPS results in improved renal function, sodium excretion, and general well-being of the patient but without proven survival benefits. Clinicians caring for these patients should be aware of the potential complications of each treatment modality and be prepared to discontinue diuretics or not proceed with TIPS placement should complications or contraindications develop. Liver transplantation should be considered for all ascitic patients, and this should preferably be performed prior to the development of renal dysfunction to prevent further compromise of their prognosis. (HEPATOLOGY 2003;38:258-266.)

Ascites occurs in more than 50% of patients within 10 years of the diagnosis of cirrhosis. Cirrhotic ascites accounts for over 75% of patients who present with ascites, with the remaining 25% being due to malignancy (10%), cardiac failure (3%), pancreatitis (1%), tuberculosis (2%), or other rarer causes.[1] There have been several changes in the clinical management of ascites over recent years. The recommendations put forward in this document were agreed on by an International Ascites Club Consensus Meeting on the management of ascites. This meeting was supported by an unconditional educational grant from Searle, Spain. These recommendations have been updated in line with subsequent recent publications of controlled clinical studies.

Diagnosis and Investigation of Ascites

All patients need investigation of the causes of ascites, even when cirrhosis is suspected. Ascitic fluid should be sent for the determination of albumin or protein concentration. To diagnose spontaneous bacterial peritonitis (SBP), ascitic fluid should be examined by microscopy and inoculated directly into blood culture bottles. An ascitic fluid neutrophil count of ≥ 250 polymorphonuclear cells/mm^3 is diagnostic of SBP, but a Gram stain of the ascitic fluid is usually uninformative.[2] Ascitic fluid from patients with suspected malignant or pancreatic ascites should be sent for cytology or measurement of amylase.

The use of ascitic fluid protein in the differential diagnosis of the causes of ascites is overrated and misinterpreted. Conventionally, the type of ascites is divided into exudates and transudates in which the ascitic fluid protein concentration is ≥25 g/L or <25 g/L, respectively, to help in the differential diagnosis of the causes of ascites. However, many physicians assume that cardiac ascites will have a low ascitic protein, but this is rarely the case.[3] Moreover, ~15% of cases of cirrhotic ascites have an ascitic protein >25 g/L, and 20% of patients with malignancy have a low ascitic protein.[4] The serum-ascites albumin gradient (*i.e.*, serum albumin − ascitic fluid albumin concentration) is more specific and sensitive at distinguishing ascites due to portal (sinusoidal) hypertension (gradient ≥11 g/L) from that occurring as a result of different pathogenetic mechanisms, such as inflammation or peritoneal malignancy (gradient ≤11 g/L).[5,6] Thus, ascitic fluid protein classified the causes of ascites correctly in 55% of cases, whereas serum-ascitic albumin gradient assigns the causes correctly 97% of the time.[5]

Definitions

Uncomplicated Ascites. Uncomplicated ascites is ascites that is not infected and that is not associated with the development of the hepatorenal syndrome (HRS). *Grade 1 ascites* is mild ascites only detectable by ultrasound examination. *Grade 2 ascites* or moderate ascites is manifest by moderate symmetrical distension of abdomen. *Grade 3 ascites* is large or gross ascites with marked abdominal distension.

Refractory Ascites. In 1996 the International Ascites Club defined "refractory ascites" as ascites that cannot be mobilized or the early recurrence of which cannot be satisfactorily prevented by medical therapy.[7] It occurs in approximately 5% to 10% of all cases of ascites.[8] Two subgroups were identified as diuretic-resistant ascites and diuretic-intractable ascites.[7] Additional findings frequently include type II HRS, dilutional hyponatremia, and wasting. The diagnostic criteria for refractory ascites have been slightly revised and are shown in Table 1.

Prognosis of Cirrhosis With Ascites

The development of ascites in patients with cirrhosis indicates a poor prognosis. The probability of death in cirrhotic patients hospitalized with ascites is ~40% at 2 years.[8] The prognosis is worse for those with refractory ascites and those who develop SBP.[2]

Treatment of Ascites: An Evidenced Based Approach

The aim of treatment is to improve sodium balance or circulatory function until liver transplantation or until the disease runs its natural course. Patients with alcohol-induced cirrhosis who stop drinking may have a considerable improvement of liver function with resolution of ascites.

Table 1. Revised Diagnostic Criteria of Refractory Ascites

1. Treatment duration: Patients must be on intensive diuretic therapy (spironolactone 400 mg/d and furosemide 160 mg/d) for at least 1 week and on a salt-restricted diet of less than 90 mmoles or 5.2 g of salt/d.
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 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.

Bed Rest

In patients with cirrhosis and ascites, upright posture activates sodium-retaining systems and impairs renal perfusion and sodium excretion. In one study, bed rest improved the response to diuretics.[9] However, no clinical trials have shown that bed rest actually improves the efficacy of medical treatment.

Sodium and Water Restriction

A negative sodium balance can be achieved by dietary salt restriction or by increasing renal sodium excretion. With dietary salt restriction, loss of ascites occurs in 10% to 15% of patients.[1] The use of low salt diets is almost universally recommended. However, this approach is not backed by the results of controlled clinical trials.

Trials on Sodium Restriction. Severe sodium restricted diets are unpalatable, leading to poor patient compliance and poor nutrition. Five studies have compared the efficacy of different dietary regimes.[10-14] Some societies readily adapt to a lower salt intake, whereas others are less compliant because of cultural differences. When severe dietary salt restriction (22 mmol/d) was compared with a less restricted diet, dietary salt restriction was associated with a shorter time for resolution of ascites but was associated with a higher incidence of diuretic-induced renal impairment and hyponatremia.[10-13] In one controlled study, a slightly reduced salt diet (120 mmoles/d) was equally effective in patients with ascites when compared with a low-salt diet (50 mmol/d).[14] There are no significant differences in survival between patients receiving salt-restricted or -unrestricted diets, al-

though the survival of patients with previous gastrointestinal bleeding was better in the low-salt group.[13] A limitation of all such studies is patient compliance and being able to verify compliance.

Water Restriction. Dilutional hyponatremia occurs in patients with decreased free water clearance, which is driven by nonosmotic baroceptor secretion of antidiuretic hormone secondary to effective central hypovolemia.[15] Treatment of dilutional hyponatremia classically consists of water restriction. However, there have been no clinical trials to assess the effects of water restriction in patients with cirrhosis and dilutional hyponatremia, and indeed this treatment may exacerbate the central hypovolemia.

Diuretics

Anti-Mineralocorticoids. Secondary hyperaldosteronism is a major factor promoting renal sodium retention[16] in the distal tubules and collecting ducts of the nephron. Both controlled and uncontrolled clinical trials have shown that spironolactone is the drug of choice for the initial treatment.[11-14,17,18] Spironolactone or canrenoate (not available in North America) achieves a better natriuresis more often than "loop" diuretics such as furosemide.[18,19] The recommended initial dose of spironolactone is 100 to 200 mg once daily. When severe hyperaldosteronism (*i.e.,* severe sodium retention) is present, the dosage may be increased to 400 mg/d.[18,20,21] A therapeutic response is observed in ~75% of patients. Gynecomastia is the main side effect of spironolactone, but metabolic acidosis with or without hyperkalemia may occur with renal impairment.[22]

Other Potassium-Sparing Diuretics. Amiloride and triamterene also act in the distal tubule. No controlled clinical trials on triamterene are available. Amiloride (20-60 mg/d) has been shown to be less effective than potassium canrenoate (150-500 mg/d).[19]

Loop Diuretics. Loop diuretics, such as furosemide, are frequently used as an adjunct to spironolactone therapy. The initial oral dose of furosemide is usually 20 to 40 mg/d, and is generally adjusted upward every few days up to a maximum of 160 mg/d. Furosemide may cause potassium depletion, metabolic hypochloremic alkalosis, and hyponatremia, as well as hypovolemia, leading to renal dysfunction.[23,24]

Assessing the Response to Diuretics. The mobilization of ascites is best assessed by daily weighing of the patient using accurate standardized weighing protocols. The rate of weight loss should not exceed >0.5 kg/d in the absence of edema, or >1 kg/d when edema is present.[24] Medical treatment based on sodium-restricted diets, anti-mineralocorticoids, and loop diuretics achieves

a response rate in up to 90% of patients without renal failure in controlled clinical trials.[14,18,20]

Paracentesis

Paracentesis is used to treat ascites that has not responded to medical therapy, to resolve large-volume ascites rapidly, to enable easier ultrasound examination in patients with massive ascites, and to periodically treat refractory ascites.

Trials of Paracentesis Versus Diuretics. There have been 5 randomized controlled trials comparing therapeutic paracentesis with diuretics in cirrhotic patients with ascites.[25-29] These studies compared repeated large volume paracentesis (5 L/d) with albumin infusion (6-8 g/L of ascites removed), and showed that paracentesis was more effective than diuretics in eliminating ascites and shortened the duration of hospitalization. Moreover, there were significantly fewer complications in the paracentesis-treated group compared with those treated with diuretics alone. These data have been confirmed by other studies.[30] The issue of whether paracentesis should be repeated daily with 5-liter paracentesis or a single total paracentesis has been resolved.[31,32] Titò et al.[31] showed that total paracentesis was as effective and as safe as repeated partial paracentesis. Paracentesis causes an acute increase of cardiac output and a lowering of systemic vascular resistance, leading to a modest reduction of blood pressure.[32] Pulmonary capillary wedge pressure decreases at ~6 hours postparacentesis, whereas the right atrial pressure falls acutely following the onset of paracentesis, secondary to a reduction of intrathoracic pressure.[32] Since postparacentesis effective hypovolemia (PPH) can occur hours or days after the procedure (see below), volume expansion should commence once the paracentesis has been completed. Total paracentesis shortens the period of hospitalization and can be done as an outpatient procedure. However, paracentesis does not obviate the need for diuretics. In one study, ascites recurred within 4 weeks postparacentesis in 18% of patients receiving diuretics immediately postparacentesis, compared with 93% in patients receiving a placebo.[33]

Controversy of Volume Expansion. There is only one controlled trial comparing therapeutic paracentesis with and without volume expansion with follow-up over a few weeks. In this study, Gines et al. randomized patients to receive repeated paracentesis (~5 L/d) plus albumin or to repeated paracentesis alone.[30] Side effects occurred in 30% of patients treated with paracentesis without albumin compared with 16% in those treated with albumin. Complications included a high incidence of renal impairment and hyponatremia and a marked elevation of plasma renin and aldosterone concentrations.

If volume expansion is not given following paracentesis, patients may develop postparacentesis hypovolemia, leading to hyponatremia and renal impairment. Postparacentesis volume expansion is recommended in patients with cirrhosis and ascites. The choice of fluid is, however, controversial. Human albumin solution is expensive and carries the risk of infection with noneradicated viruses or prion-related diseases. The use of albumin has been contested by the Practice Guidelines Committee of the American Association for the Study of Liver Diseases.[34] There have been 5 randomized controlled trials comparing volume expansion with albumin with other forms of plasma expanders, including dextrans, collagen-based colloids, and hydroxyethyl starch.[35-39] All studies have shown that synthetic plasma expanders are as effective as albumin at preventing the clinical complications of paracentesis, namely hyponatremia or renal impairment. However, Gines et al. showed that PPH, as defined by an increase in plasma renin activity or aldosterone concentrations, was prevented more effectively by albumin than synthetic plasma expanders.[35]

Contraindications and Complications of Paracentesis. Depite the fact that all published studies on paracentesis have excluded patients with SBP, renal failure, severe hepatic encephalopathy, thrombocytopenia, low blood pressure, or severe jaundice, there is no evidence that these complications should be considered as contraindications for paracentesis in clinical practice. Thus, some physicians carry out a total paracentesis in patients with SBP to remove the infected fluid. However, there are no data to support this approach, and controlled studies are needed. There are no data to support the correction of mild coagulopathy with blood products prior to therapeutic paracentesis,[40] but caution is needed when severe thrombocytopenia is present. Acute complications following paracentesis are sporadic. Bleeding occasionally occurs and may be fatal. Leakage of ascitic fluid should be managed by placing a purse-string suture around the opening and instructing the patient to lie with the puncture site uppermost. The most common complication is PPH and renal impairment. To date, there are no studies identifying factors that predict the development of postparacentesis hypovolemia and renal impairment.

Transjugular Intrahepatic Portosystemic Shunt (TIPS)

Short-Term and Long-Term Effects of TIPS on Circulatory Function and Renal Function. TIPS, in which a self-expanding shunt is inserted to create a shunt between the hepatic vein (low pressure) and portal vein (high pressure), can lead to an improvement of renal function and sodium excretion and the resolution of ascites.[41]

In the longer term it can also improve nitrogen balance and patient well being.[42-44] It has largely replaced the use of surgically placed shunts. Insertion of a TIPS shunt leads to a marked increase of cardiac output, right atrial pressure, and pulmonary artery pressure,[45] with a secondary decrease of systemic vascular resistance and an increase in pulmonary vascular resistance and effective arterial blood volume. Sodium excretion and renal function improve over 4 weeks.[46] Thus, serum creatinine decreased from 1.5 to 0.9 mg/dL in patients with refractory ascites post-TIPS.[47]

Complications. Immediate complications include capsule puncture and intra-abdominal bleeding. Late but common complications include shunt thrombosis and stenosis. The development of hepatic encephalopathy occurs in ~30% of patients post-TIPS, but the incidence is higher in those patients with pre-TIPS encephalopathy and in those greater than 60 years old.[48] TIPS increases the cardiac preload[45] and may precipitate cardiac failure in patients with cardiac disease. Liver function can also deteriorate significantly in the post-TIPS period, possibly secondary to shunting of blood away from the liver. The efficacy of TIPS to improve sodium excretion is dependent on the pre-TIPS renal function and age being less effective in those greater than 60 years old or those with creatinine clearance <40 mL/min.[47-49]

Controlled Trials Comparing TIPS With Paracentesis. There have been 4 randomized controlled trials comparing TIPS versus large-volume paracentesis as a treatment for refractory ascites.[50-53] In the first study, none of the Child-Pugh class C patients eliminated their ascites, and their overall survival was significantly worse in the TIPS group.[50] Thus, TIPS is generally considered to be contraindicated in Child-Pugh class C patients. In a larger study involving 60 patients with refractory or recurrent ascites, patients were randomized to repeated paracentesis or TIPS.[51] However, albumin was not systematically given postparacentesis. In the TIPS group there were 15 patient deaths and 1 underwent liver transplantation during follow-up compared with 23 deaths and 2 patients undergoing liver transplantation in the paracentesis group over ~4 years. The probability of survival without liver transplantation was 69% at 1 year and 58% at 2 years in the shunt group, as compared with 52% and 32% in the paracentesis group ($P = .11$). In a multivariate analysis, treatment with TIPS was independently associated with survival without the need for transplantation ($P = .02$). At 3 months, 61% of the patients in the shunt group and 18% of those in the paracentesis group had no ascites ($P = .006$). The frequency of hepatic encephalopathy was similar in the two groups.[51] In the third study, 49% of patients who received TIPS had recurrent

ascites compared with 83% of those treated by repeated large-volume paracentesis ($P = .003$).[52] Furthermore, the TIPS patients had a significantly lower risk of developing HRS ($P = .04$). However, the risk of severe hepatic encephalopathy and the cost of therapy were higher in the TIPS group, while the survival rate was no different.[52] Finally, in the North American multicenter randomized controlled trial involving 109 patients, TIPS was clearly superior to large-volume paracentesis in the control of ascites. The mean survival was identical in both groups. There was no difference in the frequency of adverse events, apart from a trend towards more severe encephalopathy in the TIPS arm ($P = .058$). There was no difference in the quality of life between the 2 treatment modalities (see Table 2).[53]

Peritoneovenous Shunts

There is little role for the use of peritoneovenous shunting in the treatment of refractory ascites. Peritoneovenous shunting may be useful in patients who are not candidates for liver transplantation, TIPS placement, or repeated large-volume paracentesis.

Liver Transplantation

Any patient with cirrhosis who develops ascites should be considered as a potential candidate for liver transplantation, because the long-term prognosis of patients with ascites is poor. The success of liver transplantation has resulted in a rapid growth in numbers of patients waiting for the procedure, out of proportion to the number of available donors. The mean waiting time for liver transplantation in the United States is estimated to be about 500 days, but this is considerably shortened in Europe with an average wait in the United Kingdom of 120 days and in Spain of 180 days. The long waiting time in the United States limits the options for timing the work-up and listing for liver transplantation. Given these limitations, some liver centers adopt the philosophy of placing every patient on the active waiting list as soon as ascites develops in order to successfully compete for an organ when necessary.

Consensus Proposals for the Treatment of Ascites

Treatment of Uncomplicated Ascites

Grade 1 Ascites. Grade 1 ascites does not require specific treatment, but the patient should be followed up carefully and advised to reduce their sodium intake, since these patients usually progress to the development of grade 2 ascites.

Grade 2 Ascites. *Bed rest.* Bed rest is probably of no benefit in patients with preserved renal function and a

Table 2. The Effects of TIPS on the Management of Ascites, Summary of Published Randomized Controlled Trials

	n	Child-Pugh Score	Control of Ascites	Survival
Lebrec et al.[50]				
LVP	12	9.3 ± 0.6	1/12 (1 y)	60 ± 16% (2 y)
TIPS	13	9.2 ± 0.6	3/13 (1 y)	29 ± 13% (2 y)*
				42 ± 17% (C-P B patients)
				0% (C-P C patients)
Rossle et al.[51]				
LVP	31	8.7 ± 1.2	6/31 (6M)	32% (2 y)
TIPS	29	9.1 ± 1.9	16/29 (6M)*	58% (2 y)
Gines et al.[52]				
LVP	35	9.2 ± 0.3	6/35 (1 y)	30% (2 y)
TIPS	35	9.3 ± 0.2	18/35 (1 y)*	26% (2 y)
Sanyal et al.[53]				
LVP	57	9.3 ± 1.3	9/57 (1 y)	12.4 mo (median)
TIPS	52	9.2 ± 1.2	30/52 (1 y)*	19.6 mo (median)

Abbreviations: LVP, large-volume paracentesis; C-P, Child-Pugh class.
*$P < .05$.

good initial response to diuretics. However, there are data to suggest that it may be beneficial in those with a poor response to diuretics, but further studies are required.

Dietary sodium restriction. Dietary salt should be moderately restricted to 5.2 g/d (90 mmol) and should be continued unless there is normalization of the renal ability to excrete sodium. In selected cases, it may be necessary to restrict sodium intake further. There is no role for the prophylactic use of sodium restriction in patients who have never had ascites.

Use of diuretics. Treatment of grade 2 ascites should initially include both salt restriction (5.2 g or 90 mmol salt/d) and administration of diuretics. A positive response to diet alone is slow and rare. The aim of diuretic treatment is to achieve a negative sodium balance such that ascites resolves completely. The core diuretic should be spironolactone (or canrenoate, not available in North America), which should initially be given alone once per day with food (*e.g.*, 100-200 mg spironolactone/d). The clinical response to diuretics should be monitored by daily weighing of the patient, and the rate of weight loss should not exceed 0.5 kg/d in those without peripheral edema and 1 kg/d in those with edema. Daily weights can be recorded by patients who are at home. The development of electrolyte or renal abnormalities should be monitored by measurement of serum electrolytes, urea, and creatinine. The initial response to diuretics is slow, and therefore diuretic dosage should be increased stepwise if there is insufficient diuretic response as defined by a weight loss of less than 1 kg in the first 7 days, and 2 kg every 7 days thereafter until ascites is adequately mobilized. A loop diuretic (furosemide 20-40 mg/d) may be added if a patient fails to respond to the equivalent of 200

mg spironolactone per day after the first 2 to 3 weeks. The dose of spironolactone or furosemide should be doubled to a maximum of 400 or 160 mg/d, respectively, for those that fail to respond. Urinary sodium excretion should be determined in nonresponders to identify noncompliance with sodium restriction. Patients who excrete greater than 90 mmol of sodium per day, and who fail to lose ascites are not compliant with their diet. Amiloride (5-30 mg/d) or canrenoate may be used as an alternative diuretic in those patients who develop gynecomastia on spironolo-actone. Amiloride is particularly effective in those patients with a nonactivated renin-angiotensin-aldosterone system. Loop diuretics other than furosemide may be equally efficacious.

Complications of diuretic therapy. The common complications of diuretic therapy are hyponatremia, renal impairment, hepatic encephalopathy, and muscle cramps. Patients on diuretic therapy should be monitored for the development of renal impairment, which is usually reversible after discontinuation of treatment and correction of hypovolemia. Specific complications include the development of hyperkalemia, metabolic acidosis, or gynecomastia with spironolactone, and hypokalemia when furosemide is used alone. Hyperkalemia usually occurs in those patients with refractory ascites and impaired renal function requiring high doses of diuretics. In patients developing hyperkalemia, the dose of spironolactone should be decreased or stopped when the serum potassium is >5.5 mmol/L or 6 mmol/L, respectively. For those that develop hypokalemia secondary to the use of loop diuretics, furosemide should be stopped or decreased if serum potassium is less than 3.5 mmol/L. Diuretics may cause hepatic encephalopathy. In cases of mild hepatic encephalopathy (grade 1), diuretics may be continued and hepatic encephalopathy treated conventionally. For those with more severe hepatic encephalopathy, diuretics should be stopped temporarily and their use reassessed. Diuretic therapy is often associated with the development of muscle cramps.[54] Muscle cramps in patients with ascites are frequently due to effective hypovolemia. For those with severe incapacitating muscle cramps, diuretics should be decreased or stopped. Therapies that have been shown to be effective in muscle cramps include albumin,[54] quinidine,[55] quinine,[56] and possibly zinc sulfate.[57]

Contraindications of diuretic therapy. Diuretics are relatively contraindicated in patients with severe hyponatremia, renal dysfunction (serum creatinine >150 μmoles/L or 1.75 mg/dL), or active bacterial infection. With respect to the use of diuretics in patients with renal impairment, there are no data to support the withholding of diuretics in patients with a primary renal abnormality, *e.g.*, diabetic nephropathy, although it is agreed that diuretics should be withheld from patients in whom the renal impairment is secondary to their liver disease or hypovolemia. There are no data on the level of serum sodium at which diuretics should be stopped. It was agreed that diuretics should be stopped temporarily when the serum sodium is less than 120 mmoles/L. Patients with type 2 HRS usually have a poor response to diuretics.

Grade 3 Ascites. *Paracentesis.* Paracentesis is the treatment of choice in grade 3 ascites and should be followed by diuretic therapy and sodium restriction. Total paracentesis should be carried out as a single procedure, and it is safe to remove all of the ascitic fluid in a single session, even when a large amount of ascites is present. Plasma volume expansion is recommended in all patients, including those with peripheral edema, to prevent renal complications. Following total paracentesis, a synthetic plasma substitute may be used if the volume of ascites removed is less than 5 L.[58] For those in whom greater than 5 L ascites is removed, it is generally recommended that albumin is used at a dose of 8 g/L of ascites removed. There are no data on whether smaller or larger amounts of albumin have differing degrees of efficacy. Further large randomized controlled trials are needed to determine whether giving smaller amounts of albumin or whether synthetic plasma expanders are equally safe in terms of mortality or morbidity.

Complications and contraindications to paracentesis. It is generally agreed that there are no contraindications to paracentesis. Some clinicians have concerns about carrying out paracentesis in patients with severe coagulopathy or marked thrombocytopenia in case of localized bleeding complications, but there are no published data to support this. Many clinicians correct severe thrombocytopenia (platelet count <50 000/mm³) to minimize the risk of bleeding, since this is logical and there are no data to support or refute this approach. Second, patients who have undergone previous surgery and who have peritoneal adhesions have an increased risk of bowel perforation, and paracentesis should be carried out with care or avoided altogether. These, and other patients may also have loculated ascites, which is not amenable to total or effective drainage.

Treatment of Refractory Ascites

Paracentesis. The first-line treatment of refractory ascites is repeated total paracentesis. To reduce the frequency of repeated paracentesis, patients may continue to receive diuretics as tolerated. Diuretics should be stopped if there are significant complications or if urine sodium is less than 30 mmoles/d. Some patients may require very frequent paracenteses, which becomes intolerable to the

patient. In this instance, the use of TIPS should be considered.

TIPS. TIPS is an effective treatment for refractory ascites. The main indication for insertion of a TIPS for the treatment of refractory ascites is the frequency of repeated paracentesis. It is generally agreed on that when the frequency of paracentesis is greater than 3 times per month, TIPS insertion should be considered, but this decision will depend on practical and patient issues and informed discussion about the risks of encephalopathy and consent with the patient. TIPS may be indicated in any patient that does not tolerate paracentesis or in whom paracentesis is contraindicated or ineffective, such as multiple adhesions or loculated ascites. Although there are no randomized studies available, TIPS should be considered for the treatment of recurrent massive hepatic hydrothorax, because it results in resolution of hepatic hydrothorax in ~70% of patients.[59]

Complications and contraindications of TIPS. TIPS is associated with a 30% incidence of hepatic encephalopathy. Shunt stenosis or obstruction occurs in 70% by 1 year,[53] although recent studies have suggested that polytetrafluoroethylene-coated TIPS stents may have a lower rate of occlusion.[60] Other important complications include cardiopulmonary disease or hemolytic anemia. There are data to suggest that TIPS-associated mortality in Child class C patients may be increased. The main contraindications are pre-existing hepatic encephalopathy, age greater than 70 years, pre-existing cardiac dysfunction, and Child-Pugh Score greater than 12. Although there are no studies to date assessing the level of cardiac function that contraindicates TIPS placement, it is generally accepted that patients need to have a normal ejection fraction of greater than 55% in order to cope with the volume returned from the splanchnic circulation immediately after TIPS insertion.

Treatment of Dilutional Hyponatremia

Dilutional hyponatremia is a problem in terms of management, since there are no published controlled trials. There is general agreement that water restriction is ineffective at increasing serum sodium concentration in patients with dilutional hyponatremia in liver disease. Water restriction may cause a further decline of renal function. Since the nonosmotic secretion of antidiuretic hormone due to a decreased effective arterial blood volume is a prime mover in the development of dilutional hyponatremia, many experts in the field use volume expansion with colloids (which are usually saline based) to try to improve renal function. There are data emerging that support the use of specific vasopressin-2 receptor antagonists in the treatment of dilutional hyponatremia,[61,62] but whether this improves overall morbidity and mortality is not yet known.

The Role of Liver Transplantation in Patients With Ascites

The prognosis of patients with ascites is poor, and especially so in those with complicated ascites. Since the overall 1-year survival rate is 85% in patients undergoing liver transplantation, all patients with ascites should be considered as potential candidates for liver transplantation. The policy for deciding the point at which a patient should be listed for liver transplantation largely depends on local factors such as organ availability and waiting time.

Summary

The development of ascites is a major event in the natural history of cirrhosis and is associated with a significant deterioration in prognosis. With better understanding of the pathophysiology of ascites formation, the management of ascites has improved significantly in recent years. The mainstay of treatment of responsive ascites remains sodium restriction and judicious use of diuretic therapy together with paracentesis for gross ascites. Ascites that is refractory to diuretic therapy requires either repeated large-volume or total paracentesis. In selected patients, TIPS insertion has provided satisfactory control of ascites. Liver transplantation should be considered for all cirrhotic patients with ascites.

References

1. Reynolds TB. Ascites. Clin Liver Dis 2000;4:151-168.
2. Rimola A, Garcia-Tsao G, Navasa M, Piddock LJ, Planas R, Bernard B, Inadomi JM. Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: a consensus document. International Ascites Club. J Hepatol 2000;32:142-153.
3. Runyon BA. Cardiac ascites: a characterization. J Clin Gastroenterol 1988; 10:410-412.
4. Alexandrakis MG, Moschandrea JA, Koulocheri SA, Kouroumalis E, Eliopoulos GD. Discrimination between malignant and nonmalignant ascites using serum and ascitic fluid proteins in a multivariate analysis model. Dig Dis Sci 2000;45:500-508.
5. 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;117:215-220.
6. Pare P, Talbot J, Hoefs JC. Serum-ascites albumin concentration gradient: a physiologic approach to the differential diagnosis of ascites. Gastroenterology 1983;85:240-244.
7. Arroyo V, Gines P, Gerbes AL, Dudley FJ, Gentilini P, Laffi G, Reynolds TB, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. International Ascites Club. HEPATOLOGY 1996;23:164-176.
8. Salerno F, Borroni G, Moser P, Badalamenti S, Cassara L, Maggi A, Fusini M, et al. Survival and prognostic factors of cirrhotic patients with ascites: a study of 134 outpatients. Am J Gastroenterol 1993;88:514-519.
9. Ring-Larsen H, Henriksen JH, Wilken C, Clausen J, Pals H, Christensen NJ. Diuretic treatment in decompensated cirrhosis and congestive heart failure: effect of posture. Br Med J 1986;292:1351-1353

10. Reynolds TB, Lieberman FL, Goldman AR. Advantages of treatment of ascites without sodium restriction and without complete removal of excess fluid. Gut 1978;19:549-553.

11. Descos L, Gauthier A, Levy VG, Michel H, Quinton A, Rueff B, Fermanian J, et al. Comparison of six treatments of ascites in patients with liver cirrhosis. A clinical trial. Hepatogastroenterology 1983;30:15-20.

12. Strauss E, De Sa MF, Lacet CM, Cartapattida da Silva E, Dos Santos RW. Padronizaçao de conduta terapeutica das ascites do hepatopata cronico. Estudo prospectivo de 100 casos. GED 1985;4:79-86.

13. Gauthier A, Levy VG, Quinton A, Michel H, Rueff B, Descos L, Durbec JP, et al. Salt or no salt in the treatment of cirrhotic ascites: a randomised study. Gut 1986;27:705-709.

14. Bernardi M, Laffi G, Salvagnini M, Azzena G, Bonato S, Marra F, Trevisani F, et al. Efficacy and safety of the stepped care medical treatment of ascites in liver cirrhosis: a randomized controlled clinical trial comparing two diets with different sodium content. Liver 1993;13:156-162.

15. Porcel A, Diaz F, Rendon P, Macias M, Martin-Herrera L, Giron-Gonzalez JA. Dilutional hyponatremia in patients with cirrhosis and ascites. Arch Intern Med 2002;162:323-328.

16. Wilkinson SP, Jowett TP, Slater JD, Arroyo V, Moodie H, Williams R. Renal sodium retention in cirrhosis: relation to aldosterone and nephron site. Clin Sci 1979;56:169-177.

17. Fogel MR, Sawhney VK, Neal EA, Miller RG, Knauer CM, Gregory PB. Diuresis in the ascitic patient: a randomized controlled trial of three regimens. J Clin Gastroenterol 1981;3(Suppl 1):73-80.

18. Pérez-Ayuso RM, Arroyo V, Planas R, Gaya J, Bory F, Rimola A, Rivera F, et al. Randomized comparative study of efficacy of furosemide versus spironolactone in patients with liver cirrhosis and ascites. Gastroenterology 1983;84:961-968.

19. Angeli P, Dalla Pria M, De Bei E, Albino G, Caregaro L, Merkel C, Ceolotto G, et al. Randomized clinical study of the efficacy of amiloride and potassium canrenoate in nonazotemic cirrhotic patients with ascites. HEPATOLOGY 1994;19:72-79.

20. Gatta A, Angeli P, Caregaro L, Menon F, Sacerdoti D, Merkel C. A pathophysiological interpretation of unresponsiveness to spironolactone in a stepped care approach to the diuretic treatment of ascites in nonazotemic cirrhotic patients with ascites. HEPATOLOGY 1991;14:231-236.

21. Bernardi M, Servadei D, Trevisani F, Rusticali AG, Gasbarrini G. Importance of plasma aldosterone concentration on the natriuretic effect of spironolactone in patients with liver cirrhosis and ascites. Digestion 1985;31:189-193.

22. Gabow PA, Moore S, Schrier RW. Spironolactone-induced hyperchloremic acidosis in cirrhosis. Ann Intern Med 1979;90:338-340.

23. Bernardi M, De Palma R, Trevisani F, Santini C, Patrono D, Motta R, Servadei D, et al. Effects of a new loop diuretic (muzolimine) in cirrhosis with ascites: comparison with furosemide. HEPATOLOGY 1986;6:400-405.

24. Pockros PJ, Reynolds TB. Rapid diuresis in patients with ascites from chronic liver disease: the importance of peripheral edema. Gastroenterology 1986;90:1827-1833.

25. Ginès P, Arroyo V, Quintero E, Planas R, Bory F, Cabrera J, Rimola A, et al. Comparison of paracentesis and diuretics in the treatment of cirrhotics with tense ascites. Results of a randomized study. Gastroenterology 1987;93:234-341.

26. Salerno F, Badalamenti S, Incerti P, Tempini S, Restelli B, Bruno S, Bellati G, et al. Repeated paracentesis and iv albumin infusion to treat tense ascites in cirrhotic patients. A safe alternative therapy. J Hepatol 1987;5:102-108.

27. Sola R, Vila MC, Andreu M, Oliver MI, Coll S, Gana J, Ledesma S, et al. Total paracentesis with dextran 40 vs diuretics in the treatment of ascites in cirrhosis: a randomized controlled study. J Hepatol 1994;20:282-288.

28. Cotrim HP, Garrido V, Parana R, Santana G, Dultra D, Pinto M, Lyra L. Paracentesis associated to dextran-70 in the treatment of ascites in patients with chronic liver diseases: a randomized therapeutic study. Arq Gastroenterol 1994;31:125-129.

29. Hagengue H, Ink O, Ducreux M, Pelletier G, Buffet C, Etienne JP [Treatment of ascites in patients with liver cirrhosis without neither hyponatremia nor renal insufficiency. Results of a randomized study comparing diuretics and punctures compensated by albumin]. Gastroenterol Clin Biol 1992;16:751-755.

30. Gines P, Tito L, Arroyo V, Planas R, Panes J, Viver J, Torres M, et al. Randomized comparative study of therapeutic paracentesis with and without intravenous albumin in cirrhosis. Gastroenterology 1988;94:1493-1502.

31. Titò L, Ginès P, Arroyo V, Planas R, Panes J, Rimola A, Llach J, et al. Total paracentesis associated with intravenous albumin management of patients with cirrhosis and ascites. Gastroenterology 1990;98:146-151.

32. Panos MZ, Moore K, Vlavianos P, Chambers JB, Anderson JV, Gimson AES, Slater JDH, et al. Single, total paracentesis for tense ascites: sequential hemodynamic changes and right atrial size. HEPATOLOGY 1990;11:662-667.

33. Fernandez-Esparrach G, Guevara M, Sort P, Pardo A, Jimenez W, Gines P, Planas R, Lebrec D, et al. Diuretic requirements after therapeutic paracentesis in non-azotemic patients with cirrhosis. A randomized double-blind trial of spironolactone versus placebo. J Hepatol 1997;26:614-620.

34. Runyon BA. Management of adult patients with ascites caused by cirrhosis. HEPATOLOGY 1998;27:264-272.

35. Ginès A, Fernandez-Esparrach G, Monescillo A, Villa C, Domenech E, Abecasis R, Angeli P, et al. Randomized trial comparing albumin, dextran 70, and polygeline in cirrhotic patients with ascites treated by paracentesis. Gastroenterology 1996;111:1002-1010.

36. Altman C, Bernard B, Roulot D, Vitte RL, Ink O. Randomized comparative multicenter study of hydroxyethyl starch versus albumin as a plasma expander in cirrhotic patients with tense ascites treated with paracentesis. Eur J Gastroenterol Hepatol 1998;10:5-10.

37. Planas R, Ginès P, Arroyo V, Llach J, Panes J, Vargas V, Salmeron JM, et al. Dextran-70 versus albumin as plasma expanders in cirrhotic patients with ascites treated with total paracentesis. Results of a randomized study. Gastroenterology 1990;99:1736-1744.

38. Salerno F, Badalamenti S, Lorenzano E, Moser P, Incerti P. Randomized comparative study of hemaccel vs albumin infusion after total paracentesis in cirrhotic patients with refractory ascites. HEPATOLOGY 1991;13:707-713.

39. Fassio E, Terg R, Landeira G, Abecasis R, Salemne M, Podesta A, Rodriguez P, et al. Paracentesis with dextran 70 vs paracentesis with albumin in cirrhosis with tense ascites. Results of a randomized study. J Hepatol 1992; 14:310-316.

40. McVay PA, Toy PT. Lack of increased bleeding after paracentesis and thoracentesis in patients with mild coagulation abnormalities. Transfusion 1991;31:164-171.

41. Wong F, Sniderman K, Liu P, Allidina Y, Sherman M, Blendis LM. The effects of transjugular intrahepatic portosystemic shunt on systemic and renal hemodynamics and sodium homeostasis in cirrhotic patients with refractory ascites. Ann Intern Med 1995;122:816-822.

42. Nazarian GK, Ferral H, Bjarnason H, Castaneda-Zuniga WR, Rank JM, Bemadas CA, Hunter DW. Effect of transjugular intrahepatic portosystemic shunt on quality of life. AJR 1996;167:963-969.

43. Trotter JF, Suhocki PV, Rockey DC. Transjugular intrahepatic portosystemic shunt (TIPS) in patients with refractory ascites: effect on body weight and Child-Pugh score. Am J Gastroenterol 1998;93:1891-1894.

44. Allard JP, J Chau, Sandokji AM, Blendis L, Wong F. Effects of transjugular intrahepatic portosystemic shunt (TIPS) on the nutritional status of cirrhotic patients with refractory ascites. Am J Gastroenterol 2001;96:2442-2447.

45. Huonker M, Schumacher YO, Ochs A, Sorichter S, Keul J, Rossle M. Cardiac function and haemodynamics in alcoholic cirrhosis and effects of the transjugular intrahepatic portosystemic stent shunt. Gut 1999;44:743-748.

46. Wong F, Sniderman K, Liu P, Blendis LM. The mechanism of the initial natriuresis after transjugular intrahepatic portosystemic shunt. Gastroenterology 1997;112:889-907.

47. Ochs A, Rossle M, Haag K, Hauenstein KH, Deibert P, Siegerstetter V, Huonker M, et al. Transjugular intrahepatic portosystemic stent shunt procedure for refractory ascites. N Engl J Med 1995;332:1192-1197.

48. Sanyal AJ, Freedman AM, Shiffman ML, Purdum PP 3rd, Luketic VA, Cheatham AK. Portosystemic encephalopathy after transjugular intrahepatic portosystemic shunt; results of a prospective controlled study. HEPATOLOGY 1994;20:46-55.

49. Deschenes M, Dufresne MP, Bui B, Fenyves D, Spahr L, Roy L, Lafortune M, et al. Predictors of clinical response to transjugular intrahepatic portosystemic shunt (TIPS) in cirrhotic patients with refractory ascites. Am J Gastroenterol 1999;94:1361-1365.

50. Lebrec D, Giuily N, Hadenque A, Vilgrain V, Moreau R, Poynard T, Gadano A, et al. Transjugular intrahepatic portosystemic shunt: comparison with paracentesis in patients with cirrhosis and refractory ascites: a randomized trial. J Hepatol 1996;25:135-144.

51. Rossle M, Ochs A, Gulberg V, Siegerstetter V, Holl J, Deibert P, Olschewski M, et al. A comparison of paracentesis and transjugular intrahepatic portosystemic shunting in patients with ascites. N Engl J Med 2000; 342:1701-1707.

52. Gines P, Uriz J, Calahorra B, Garcia-Tsao G, Kamath P, Ruiz del Arbol L, Planas R, et al. Transjugular intrahepatic portosystemic shunt versus paracentesis plus albumin for refractory ascites in cirrhosis. A multicenter randomized comparative study. Gastroenterology 2002;123:1839-1847.

53. Sanyal A, Gennings C, Reddy KR, Wong F, Kowdley K, Benner K, McCashland T, et al and the North American Study for Treatment of Refractory Ascites. A randomized controlled study of TIPS versus large volume paracentesis in the treatment of refractory ascites Gastroenterology 2003; 124:634-643.

54. Angeli P, Albino G, Carrarro P, Dalla Pria M, Merkel C, Caregaro L, De Bei E, et al. Cirrhosis and muscle cramps: evidence of a causal relationship. HEPATOLOGY 1996;23:264-273.

55. Lee FY, Lee SD, Tsai YT, Lai KH, Chao Y, Lin HC, Wang SS, Lo KJ. A randomized controlled trial of quinidine in the treatment of cirrhotic patients with muscle cramps. J Hepatol 1991;12:236-240.

56. Diener HC, Dethlefsen U, Dethlefsen-Gruber S, Verbeek P. Effectiveness of quinine in treating muscle cramps: a double-blind, placebo-controlled, parallel-group, multicentre trial. Int J Clin Pract 2002;56:243.

57. Kugelmas M. Preliminary observation: oral zinc sulfate replacement is effective in treating muscle cramps in cirrhotic patients. J Am Coll Nutr 2000;19:13-15.

58. Peltekian K, Wong F, Liu P, Allidina Y, Sherman M, Blendis LM. The effect of large volume paracentesis on total central blood volume, systemic and renal hemodynamics and renal sodium handling in cirrhosis. Am J Gastroenterol 1997;92:394-399.

59. Siegerstetter V, Deibert P, Ochs A, Olschewski M, Blum HE, Rossle M. Treatment of refractory hepatic hydrothorax with transjugular intrahepatic portosystemic shunt: longterm results in 40 patients. Eur J Gastroenterol Hepatol 2001;13:529-534.

60. Saxon RR, Timmermans HA, Uchida BT, Petersen BD, Benner KG, Rabkin J, Keller FS. Stent-grafts for revision of TIPS stenoses and occlusions: a clinical pilot study. J Vasc Interv Radiol 1997;8:539-548.

61. Gerbes AL, Gulberg V, Gines P, Decaux G, Gross P, Gandjini H, Djian J. Therapy of hyponatremia in cirrhosis with a vasopressin receptor antagonist: a randomized double-blind multicenter trial. Gastroenterology 2003; 124:933-939.

62. Wong F, Blei A, Blendis LM, Thuluvath PJ, and the North American VPA-985 Study Group. The effects of VPA-985, a vasopressin receptor antagonist, on water metabolism in patients with hyponatremia: a multicenter randomized placebo controlled trial. HEPATOLOGY 2003;37:182-191.