

REVIEW ARTICLE

CURRENT CONCEPTS

Management of Cirrhosis and Ascites

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N Engl J Med 2004;350:1646-54.
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CIRRHOSIS, MOST FREQUENTLY CAUSED BY HEPATITIS C OR ALCOHOLISM, was the 12th leading cause of death in the United States in 2000, accounting for more than 25,000 deaths.¹ Ascites is the most common complication of cirrhosis and is associated with a poor quality of life, increased risks of infections and renal failure, and a poor long-term outcome.^{2,3} In recent years, important advances have been made in the management of cirrhosis and ascites.

PATHOPHYSIOLOGY OF ASCITES

The chief factor contributing to ascites is splanchnic vasodilatation.⁴ Increased hepatic resistance to portal flow due to cirrhosis causes the gradual development of portal hypertension, collateral-vein formation, and shunting of blood to the systemic circulation. As portal hypertension develops, local production of vasodilators, mainly nitric oxide, increases, leading to splanchnic arterial vasodilatation.⁵ In the early stages of cirrhosis, splanchnic arterial vasodilatation is moderate and has only a small effect on the effective arterial blood volume, which is maintained within normal limits through increases in plasma volume and cardiac output.⁴ In the advanced stages of cirrhosis, splanchnic arterial vasodilatation is so pronounced that the effective arterial blood volume decreases markedly, and arterial pressure falls. As a consequence, arterial pressure is maintained by homeostatic activation of vasoconstrictor and antinatriuretic factors, resulting in sodium and fluid retention. The combination of portal hypertension and splanchnic arterial vasodilatation alters intestinal capillary pressure and permeability, facilitating the accumulation of retained fluid within the abdominal cavity. As the disease progresses, there is marked impairment in renal excretion of free water and renal vasoconstriction—changes that lead to dilutional hyponatremia and the hepatorenal syndrome, respectively^{4,6} (Fig. 1).

EVALUATION OF PATIENTS WITH ASCITES

GENERAL ASSESSMENT

The evaluation of patients with cirrhosis and ascites should include not only an assessment of liver function but also an assessment of renal and circulatory function (Table 1). Ideally, patients should be evaluated when they are not receiving diuretic agents, since some variables related to renal function may be altered by the administration of these medications. Ascitic fluid should be examined to rule out spontaneous bacterial peritonitis in patients with new-onset ascites, whether or not they are hospitalized, and especially in those who have signs of infection, abdominal pain, encephalopathy, or gastrointestinal bleeding.

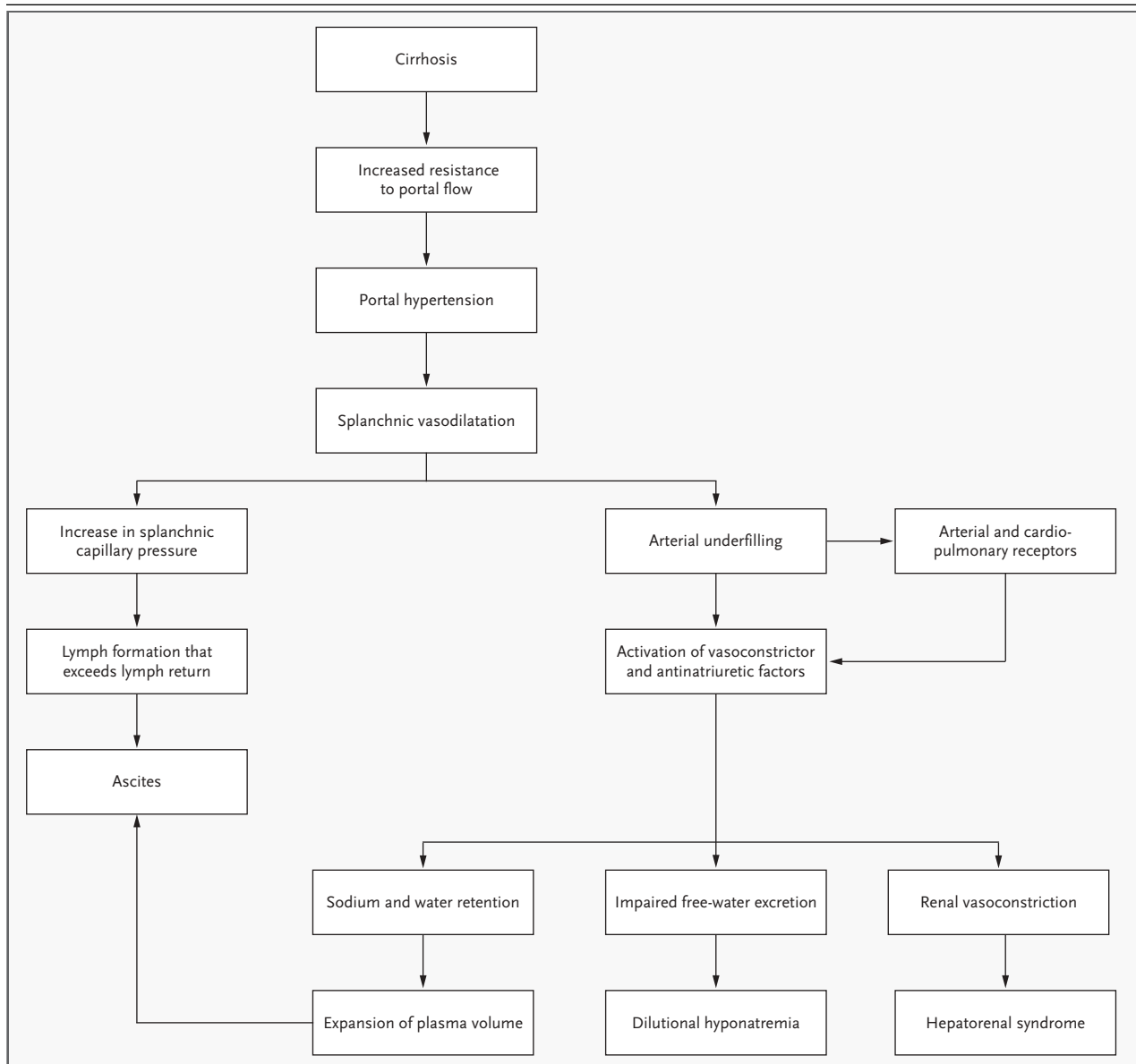


Figure 1. Pathogenesis of Ascites.

Vasoconstrictor and antinatriuretic factors include norepinephrine, angiotensin II, aldosterone, and antidiuretic hormone.

EVALUATION FOR LIVER TRANSPLANTATION

All patients with ascites should be evaluated for transplantation, since the presence of ascites is associated with poor long-term survival (survival rate at five years, 30 to 40 percent, vs. 70 to 80 percent among patients who have undergone transplantation).^{3,8} The prognosis is not uniform among patients with ascites, but there is no widely accepted model for determining the prognosis for these patients.^{3,9-11} In clinical practice, the best meth-

od of identifying patients who may have a poor outcome is to recognize conditions associated with severe impairment of renal or circulatory function, such as refractory ascites, spontaneous bacterial peritonitis, or the hepatorenal syndrome (Fig. 2). Transplantation in patients with any of these three conditions should be given priority. In the United States, priority is assigned on the basis of the Model for End-Stage Liver Disease score,¹² a quantitative index obtained with the use of a for-

mula that incorporates the serum bilirubin and creatinine concentrations and the international normalized ratio. This system has not been validated specifically for patients with ascites.

MANAGEMENT OF ASCITES

GENERAL MEASURES

Reduction of sodium intake is beneficial in patients with ascites, particularly those with severe sodium retention that does not respond or responds only minimally to diuretics.¹³ A low-sodium diet (60 to 90 mEq per day, equivalent to approximately 1500 to 2000 mg of salt per day) may facilitate the elimination of ascites and delay the reaccumulation of fluid.^{13,14} More stringent restriction is not recommended because it is poorly tolerated.¹⁴ Fluid intake should be restricted (to approximately 1000 ml per day) only in patients with dilutional hyponatremia, a condition characterized by a serum sodium concentration of less than 130 mmol per liter in the presence of ascites, edema, or both.¹⁵ Dilutional hyponatremia results from impaired renal excretion of free water due to inappropriately high concentrations of antidiuretic hormone.¹⁵

PREVENTION OF OTHER COMPLICATIONS OF CIRRHOSIS

Patients with cirrhosis and ascites are at high risk for other complications of cirrhosis. Thus, preventive measures should be undertaken with the aim of reducing morbidity and improving survival. Complications that can be effectively prevented include gastrointestinal bleeding due to gastroesophageal varices,¹⁶ spontaneous bacterial peritonitis, and the hepatorenal syndrome (Table 2).

SPECIFIC MEASURES

Moderate-Volume Ascites

In some patients, the amount of fluid in the peritoneal cavity is sufficient to cause moderate discomfort. Renal sodium excretion is not severely impaired in most of these patients, but they have a positive sodium balance because sodium excretion is low relative to sodium intake. The rate of accumulation of ascitic fluid is usually low, so large-volume ascites typically does not develop unless the sodium intake is high or there is a delay before medical assistance is sought. Renal free-water excretion and the glomerular filtration rate are normal in most cases; therefore, the serum sodium and creatinine concentrations are within normal limits.

Patients with moderate-volume ascites can be treated as outpatients and do not require hospitalization unless they have other complications of cirrhosis. In most cases, a negative sodium balance and loss of ascitic fluid are quickly achieved with low doses of diuretics.^{14,19,20} The diuretic of choice is either spironolactone (50 to 200 mg per day) or amiloride (5 to 10 mg per day). Low doses of furosemide (20 to 40 mg per day) may be added during the first few days to increase natriuresis, especially when peripheral edema is present. Furosemide should be used with caution because of the risk of excessive diuresis, which may lead to renal failure of prerenal origin. The recommended weight loss to prevent renal failure of prerenal origin is 300 to 500 g per day in patients without peripheral edema and 800 to 1000 g per day in those with peripheral edema.²¹ The response to diuretics can be evaluated on the basis of changes in body weight and by physical examination. Routine measurement of urinary sodium during diuretic therapy is not necessary, except in patients in whom there is no weight loss. In that situation, measurement of urinary sodium provides an exact assessment of the response to diuretics and may help in the decision whether to increase the dose of diuretics.

Table 1. Evaluation of Patients with Cirrhosis and Ascites.

Evaluation of liver disease
Liver-function and coagulation tests
Standard hematologic tests
Abdominal ultrasonography or computed tomography
Endoscopy of the upper gastrointestinal tract*
Liver biopsy in selected patients†
Evaluation of renal and circulatory function
Measurement of serum creatinine and electrolytes
Measurement of urinary sodium (preferably from a 24-hour urine collection)
Measurement of urinary protein (from a 24-hr urine collection)
Arterial blood pressure
Evaluation of ascitic fluid
Cell count
Bacterial culture
Measurement of total protein
Other tests (measurement of albumin, glucose, lactate dehydrogenase, amylase, and triglycerides; an acid-fast smear; and cytologic examination)‡

* Endoscopy allows assessment of the presence and characteristics of gastroesophageal varices.

† Liver biopsy is warranted in patients who present with ascites and liver disease of unclear type or cause.

‡ For the measurement of albumin, a gradient of serum albumin to ascitic fluid albumin that is greater than or equal to 1.1 g per deciliter suggests that the ascites is related to portal hypertension (which is indicative of cirrhosis in most cases), whereas a gradient of less than 1.1 g per deciliter suggests that the ascites has another cause, such as peritoneal carcinomatosis, tuberculous peritonitis, or pancreatitis.⁷

Large-Volume Ascites

Large-volume ascites — that is, ascites in an amount large enough to cause marked abdominal discomfort, which interferes with regular daily activities — can be treated on an outpatient basis unless there are associated complications. Patients with large-volume ascites usually present with severe sodium retention (urinary sodium concentration, less than 10 mmol per liter), so that ascitic fluid accumulates rapidly, even when sodium intake is restricted. Most patients with large-volume ascites have normal renal free-water excretion and a normal serum sodium concentration. In some, however, free-water excretion is impaired and dilutional hyponatremia may develop, either spontaneously or when fluid intake is increased. The serum creatinine concentration is normal or only moderately higher than normal, indicating that the glomerular filtration rate is normal or only moderately reduced.

There are two therapeutic strategies for large-volume ascites: large-volume paracentesis and the administration of diuretics at increasing doses (maximal doses, 400 mg of spironolactone per day and 160 mg of furosemide per day) until loss of ascitic fluid is achieved. The results of randomized trials comparing these two approaches support paracentesis as the method of choice.^{22,23} Although there is no difference between the two strategies with respect to long-term mortality, large-volume paracentesis is faster, is more effective, and is associated with fewer adverse events than diuretic therapy. Regardless of the strategy used, diuretics should be given as maintenance therapy to prevent recurrence of ascites.²⁴

Removal of large amounts of ascitic fluid by paracentesis without the use of plasma expanders is associated with a derangement in circulatory function, characterized by a reduction of effective arterial-blood volume and activation of vasoconstrictor and antinatriuretic factors.²⁵⁻²⁷ Circulatory dysfunction after large-volume paracentesis is associated with a high rate of recurrence of ascites, development of the hepatorenal syndrome or dilutional hyponatremia in 20 percent of cases, and shortened survival.^{25,28-30} Plasma expanders are effective in preventing this complication.^{25,28} Albumin is superior to dextran 70 and polygeline in preventing circulatory dysfunction after paracentesis involving the removal of more than 5 liters of fluid, but randomized studies show no significant difference in survival between patients treated with albumin and those treated with other plasma expanders, probably be-

cause of the studies' sample sizes.^{28,31,32} Although the use of albumin in this setting remains controversial because of its high cost and the lack of a documented survival benefit, albumin has a greater protective effect on the circulatory system than other expanders, a feature that supports its use in patients treated with large-volume paracentesis.

Severe local complications related to paracentesis, such as infection or intestinal perforation, are exceedingly rare if the procedure is performed with an appropriate technique and with an appropriate needle.^{14,22,23,25-33} The incidence of clinically significant bleeding at the puncture site or hemoperitoneum is also extremely low, but most clinical trials have excluded patients with an elevated prothrombin time (more than 21 seconds), an international normalized ratio that exceeds 1.6, or a platelet count below 50,000 per cubic millimeter. The risk of bleeding complications in patients with more severe coagulopathy is unknown and warrants investigation.

Refractory Ascites

Refractory ascites, which occurs in 5 to 10 percent of patients with ascites, is defined as a lack of response to high doses of diuretics (400 mg of spironolac-

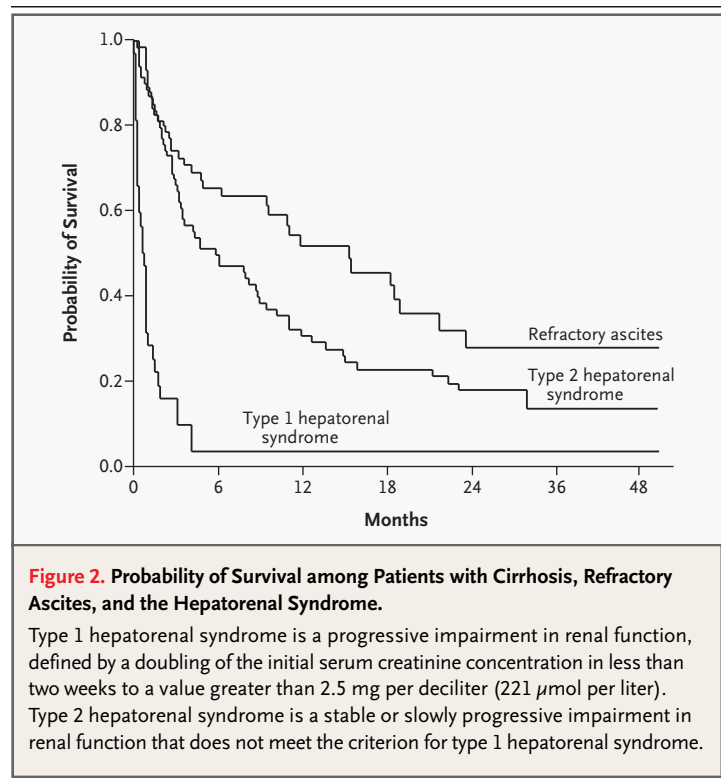


Table 2. Effective Interventions for Preventing Complications in Patients with Cirrhosis and Ascites.

Complication and Setting	Intervention	Comments	Reference
Gastrointestinal bleeding due to gastroesophageal varices	Propranolol or nadolol (stepwise increase in dose until the heart rate decreases by 25% or to 55–60 beats/min)	Reduces the risk of variceal bleeding and improves survival	Bosch et al. ¹⁶
Spontaneous bacterial peritonitis			
In patients with acute variceal bleeding	Oral norfloxacin (400 mg twice daily for 7 days), intravenous ofloxacin (400 mg daily for 7 days), or intravenous ciprofloxacin (200 mg daily) plus oral amoxicillin–clavulanic acid (1 g and 200 mg, respectively, three times daily) for 7 days	Reduces the risk of spontaneous bacterial peritonitis and improves survival	Rimola et al. ¹⁷
In patients with ascitic-fluid protein concentration <15 g/liter	Oral norfloxacin (400 mg daily, indefinitely); oral ciprofloxacin (750 mg weekly, indefinitely); or oral trimethoprim–sulfamethoxazole (160 mg and 800 mg, respectively, five days per week, indefinitely)	Reduces the risk of a first episode of spontaneous bacterial peritonitis; use of antibiotics is controversial because a beneficial effect on survival has not been demonstrated and because there is an increased risk of infections with resistant organisms	Rimola et al. ¹⁷
Hepatorenal syndrome in patients with spontaneous bacterial peritonitis	Intravenous albumin (1.5 g/kg of body weight on diagnosis of the infection and 1 g/kg after 2 days)	Reduces the risk of the hepatorenal syndrome and improves survival	Sort et al. ¹⁸

tone per day plus 160 mg of furosemide per day).⁶ Patients in whom there are recurrent side effects (e.g., hepatic encephalopathy, hyponatremia, hyperkalemia, or azotemia) when lower doses are given are also considered to have refractory ascites.⁶ The main clinical features include frequent recurrence of ascites after paracentesis, an increased risk of type 1 hepatorenal syndrome (which is characterized by progressive oliguria and a rapid increase in the serum creatinine concentration), and a poor prognosis (Fig. 2). Current therapeutic strategies include repeated large-volume paracentesis with the use of plasma expanders and transjugular intrahepatic portosystemic shunts. The use of peritoneovenous shunts was abandoned because of significant rates of complications.³³ Repeated large-volume paracentesis plus albumin administration is the most widely accepted therapy for refractory ascites. Patients generally require paracentesis every two to four weeks, and the procedure can be performed in an outpatient setting. The main drawback is early recurrence of ascites, because paracentesis does not affect the mechanisms responsible for the accumulation of ascitic fluid.

In contrast to paracentesis, the use of a transjugular intrahepatic portosystemic shunt, which consists of an intrahepatic stent inserted between one

hepatic vein and the portal vein by a transjugular approach, is effective in preventing recurrence in patients with refractory ascites.³⁴ Transjugular intrahepatic portosystemic shunting decreases the activity of sodium-retaining mechanisms and improves the renal response to diuretics.³⁵ The main disadvantages of this technique include a high rate of shunt stenosis (up to 75 percent after 6 to 12 months), which can lead to recurrence of ascites; hepatic encephalopathy; a high cost; and lack of availability in some centers.^{35–37}

Although it has been claimed that transjugular intrahepatic portosystemic shunting, as compared with large-volume paracentesis, improves survival in patients with refractory ascites,³⁸ this finding was not confirmed in two recent, randomized studies.^{39,40} Therefore, the use of a transjugular intrahepatic portosystemic shunt should not be recommended as the treatment of choice for refractory ascites. This method should probably be reserved for patients without severe liver failure or encephalopathy who have loculated fluid that cannot be treated with paracentesis and for those who are unwilling to undergo repeated paracentesis. There is no evidence that transjugular intrahepatic portosystemic shunting improves either the likelihood of survival until liver transplantation or the outcome

after transplantation. The presence of a transjugular intrahepatic portosystemic shunt may increase the technical difficulties of transplantation in some patients,^{41,42} although such difficulties are uncommon in experienced centers.

The Hepatorenal Syndrome

The hepatorenal syndrome is characterized by renal failure due to severe vasoconstriction of the renal circulation.^{6,43} Pathogenetically, the hepatorenal syndrome consists of renal failure of hemodynamic origin resulting from extreme underfilling of the arterial circulation.⁴ It occurs in up to 10 percent of patients with advanced cirrhosis and ascites and may follow either of two clinical patterns⁶ (Table 3). In some patients, there is progressive oliguria and a rapid rise of the serum creatinine concentration. This condition is known as type 1 hepatorenal syndrome. A common precipitating event that triggers the impairment in renal function is spontaneous bacterial peritonitis.⁴⁴ In other patients, most of whom have refractory ascites, the increase in the serum creatinine concentration is moderate and has no tendency to progress over time. This pattern is known as type 2 hepatorenal syndrome. The hepatorenal syndrome may be diagnosed after nonfunctional causes of renal failure are ruled out⁶ (Table 3). The prognosis is poor, particularly among patients with type 1 hepatorenal syndrome, who have a median survival of less than one month without therapy (Fig. 2).⁴⁵

Dopamine and prostaglandins are ineffective in treating patients with the hepatorenal syndrome.^{46,47} By contrast, vasoconstrictor drugs (vasopressin analogues or α -adrenergic agents), in combination with albumin, are effective in approximately two thirds of patients⁴⁸⁻⁵³ (Table 4). Octreotide is ineffective when administered alone,⁵⁴ yet it has been reported to be beneficial when given in combination with midodrine.⁴⁹ Whether octreotide improves the efficacy of midodrine is unknown. Recurrence of the hepatorenal syndrome is uncommon after the discontinuation of vasoconstrictors, although it is not currently known whether the recurrence rate differs between patients with type 1 hepatorenal syndrome and those with type 2. Patients who have a response to terlipressin have a higher rate of survival than patients who do not have a response.^{51,53} Therefore, treatment with vasoconstrictors may increase the likelihood that patients with the hepatorenal syndrome will survive long

Table 3. Criteria for Diagnosis of the Hepatorenal Syndrome.*

Presence of the hepatorenal syndrome
Serum creatinine concentration >1.5 mg/dl or 24-hr creatinine clearance <40 ml/min
Absence of shock, ongoing bacterial infection, and fluid loss, and no current treatment with nephrotoxic drugs
Absence of sustained improvement in renal function (decrease in serum creatinine to ≤ 1.5 mg/dl) after discontinuation of diuretics and a trial of plasma expansion
Absence of proteinuria (<500 mg/day) or hematuria (<50 red cells per high-power field)
Absence of ultrasonographic evidence of obstructive uropathy or parenchymal renal disease
Urinary sodium concentration <10 mmol/liter†
Type of hepatorenal syndrome
Type 1: progressive impairment in renal function as defined by a doubling of initial serum creatinine above 2.5 mg/dl in less than two weeks
Type 2: stable or slowly progressive impairment in renal function not meeting the above criteria

* To convert the values for creatinine to micromoles per liter, multiply by 88.4.

† Although the urinary sodium concentration is less than 10 mmol per liter in most patients with the hepatorenal syndrome, this finding is not considered a major diagnostic criterion because some patients with this syndrome may not have markedly low sodium excretion.⁶

Table 4. Recommendations for Treatment with Vasoconstrictors in Patients with the Hepatorenal Syndrome.

Recommendation	Reference
Administration of one of the following drugs or drug combinations	
Norepinephrine (0.5–3.0 mg/hr intravenously)	Duvoux et al. ⁴⁸
Midodrine (7.5 mg orally three times daily, increased to 12.5 mg three times daily if needed) in combination with octreotide (100 μ g subcutaneously three times daily, increased to 200 μ g three times daily if needed)	Angeli et al. ⁴⁹
Terlipressin (0.5–2.0 mg intravenously every 4–12 hr)*	Uriz et al., ⁵⁰ Moreau et al., ⁵¹ Mulkay et al., ⁵² Ortega et al. ⁵³
Concomitant administration of albumin (1 g/kg intravenously on day 1, followed by 20–40 g daily)	Duvoux et al., ⁴⁸ Angeli et al., ⁴⁹ Uriz et al., ⁵⁰ Ortega et al. ⁵³
Duration of therapy: 5–15 days	
End point: reduction of serum creatinine concentration to <1.5 mg/dl†	

* Terlipressin is not available in some countries, including the United States.

† To convert the value for creatinine to micromoles per liter, multiply by 88.4.

enough to undergo liver transplantation. In addition, these agents offer the advantage of improving renal function before transplantation — a benefit that may reduce post-transplantation morbidity and mortality.⁵⁵⁻⁵⁷

Although emerging data on the use of vasocon-

strictors in patients with the hepatorenal syndrome are very promising, the available information is still limited and is based only on nonrandomized studies involving small numbers of patients. Transjugular intrahepatic portosystemic shunting also appears to be effective in treating the hepatorenal syndrome, but again, the available information is insufficient.^{58,59} More research is needed to establish the role of these therapies in the management of this syndrome.

Hemodialysis should not be used routinely in patients with the hepatorenal syndrome because it does not improve the outcome. However, it may have a role as a bridge to liver transplantation in patients who do not have a response to medical therapy.

Spontaneous Bacterial Peritonitis

Spontaneous bacterial peritonitis is characterized by the spontaneous infection of ascitic fluid in the absence of an intraabdominal source of infection. Its prevalence among patients with ascites ranges between 10 and 30 percent.¹⁷ The presence of at least 250 polymorphonuclear cells per cubic millimeter of ascitic fluid is diagnostic of this condition.¹⁷ Aerobic gram-negative bacteria, primarily *Escherichia coli*, are the most common isolates, although the frequency of episodes caused by gram-positive bacteria has recently increased.⁶⁰ Spontaneous bacterial peritonitis involves the translocation of bacteria from the intestinal lumen to the lymph nodes, with

subsequent bacteremia and infection of ascitic fluid.⁶¹ Third-generation cephalosporins are the treatment of choice.¹⁷

The most severe complication of spontaneous bacterial peritonitis is the hepatorenal syndrome, which occurs in up to 30 percent of patients and carries a high mortality rate.^{18,44} Intravenous albumin (1.5 g per kilogram of body weight at diagnosis and 1 g per kilogram 48 hours later) helps to prevent the hepatorenal syndrome and improves the probability of survival.¹⁸ This regimen is empirical, and no information exists on the efficacy of lower albumin doses or other plasma expanders. After resolution, spontaneous bacterial peritonitis frequently recurs, with an estimated 70 percent probability of recurrence at one year.^{62,63} Long-term antibiotic prophylaxis with quinolones (norfloxacin, 400 mg per day orally) reduces the rate of recurrence,^{17,63} but spontaneous bacterial peritonitis caused by quinolone-resistant bacteria is an emerging problem.⁶⁰ Trimethoprim-sulfamethoxazole may be an alternative to quinolones, but the information available with respect to its efficacy is very scarce.⁶⁴ Long-term antibiotic prophylaxis has a beneficial effect on patients' survival, probably because of the high mortality rate associated with spontaneous bacterial peritonitis. Nonetheless, this idea has not been specifically assessed in a clinical trial.

Supported in part by grants from Fondo de Investigaciones Sanitarias (FIS 00/0618 and 02/0701), Dirección General de Investigación Científica y Técnica (SAF 2001/0300), Instituto de Salud Carlos III (C03/2), and Marató Fundació TV3 (U-2000-TV2710).

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