Pathogenesis and Treatment of Hepatorenal Syndrome

Vicente Arroyo, M.D.,[1] Javier Fernandez, M.D.,[1] and Pere Ginès, M.D.[1]

ABSTRACT

Hepatorenal syndrome (HRS) is a functional renal failure that frequently develops in patients with advanced cirrhosis and severe impairment in systemic circulatory function. Traditionally it has been considered to be the consequence of a progression of the splanchnic arterial vasodilation occurring in these patients. However, recent data indicate that a reduction in cardiac output also plays a significant role. There are two different types of HRS. Type-2 HRS consists of a moderate and steady or slowly progressive renal failure. It represents the extreme expression of the circulatory dysfunction that spontaneously develops in patients with cirrhosis. The main clinical problem in these patients is refractory ascites. Type-1 HRS is a rapidly progressive acute renal failure that frequently develops in closed temporal relationship with a precipitating event, commonly spontaneous bacterial peritonitis. In addition to renal failure, patients with type-1 HRS present deterioration in the function of other organs, including the heart, brain, liver, and adrenal glands. Type-1 HRS is the complication of cirrhosis associated with the worst prognosis. However, effective treatments of HRS (vasoconstrictors associated with intravenous albumin, transjugular intrahepatic portacaval shunt, albumin dialysis) that can improve survival have recently been introduced.

KEYWORDS: Cirrhosis, type-1 HRS, type-2 HRS, pharmacological treatment, transjugular intrahepatic portacaval shunt, extracorporeal albumin dialysis

CONCEPT

Hepatorenal syndrome (HRS) is a common problem in patients with advanced cirrhosis and ascites. The annual incidence of HRS in patients with cirrhosis and ascites has been estimated as 8%. It is characterized by an intense renal vasoconstriction, which leads to very low renal perfusion and glomerular filtration rate (GRF). The renal ability to excrete sodium and free water is also severely reduced and most patients present dilutional hyponatremia.[1–3] Renal histology shows no lesions sufficient to justify the impairment in renal function. HRS occurs in the setting of a severe circulatory dysfunction characterized by arterial hypotension and intense stimulation of the renin-angiotensin system, sympathetic nervous system, and antidiuretic hormone. It has been classically considered to be the consequence of an arterial vasodilation in the splanchnic circulation (peripheral arterial vasodilation hypothesis). However, recent data indicate that a reduction in cardiac output also plays a significant role. Cirrhotic patients with ascites, increased activity of the renin-angiotensin and sympathetic nervous systems, and intense sodium retention and those with dilutional hyponatremia are predisposed to develop HRS. This syndrome may develop spontaneously or be

[1]Liver Unit, Institute of Digestive and Metabolic Diseases, CIBER-EHD, Hospital Clinic, University of Barcelona, Spain.

Address for correspondence and reprint requests: Vicente Arroyo, M.D., Liver Unit, Institute of Digestive and Metabolic Diseases, Hospital Clinic, University of Barcelona, Villarroel 170, 08036 Barcelona, Spain (e-mail: varroyo@clinic.ub.es).

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precipitated by factors that induce renal hypoperfusion. Bacterial infections, especially spontaneous bacterial peritonitis (SBP), are by far the most frequent precipitating causes of HRS. Due to the functional nature of renal failure, there is no specific diagnostic marker for HRS.[2,4,5] Thus, diagnosis relies on the exclusion of other causes of renal insufficiency.[6]

There are two different types of HRS. Type-2 HRS consists of a moderate and steady functional renal failure. It represents the extreme expression of the circulatory dysfunction that spontaneously develops in patients with cirrhosis. The main clinical problem in these patients is refractory ascites. In contrast, type-1 HRS is a rapidly progressive acute renal failure that frequently develops in close temporal relationship with a precipitating event and occurs in the setting of deterioration in the function of other organs, including the heart, the brain, the liver, and possibly the adrenal glands. Type-1 HRS is the complication of cirrhosis associated with the worst prognosis and, for many years, it has been considered as a terminal event of the disease. However, effective treatments of type-1 HRS have been introduced recently. These treatments improve survival and make it possible for a significant number of patients to arrive to liver transplantation. The current article offers a review of the pathogenesis, clinical aspects, prevention, and treatment of type-1 and type-2 HRS. The reader interested in this topic should consult other reviews published recently,[7,8] as well as the reports of two consensus conferences on HRS organized by the International Ascitis Club in Chicago and San Francisco.[9,10]

CLINICAL ASPECTS

Diagnosis of Renal Failure in Cirrhosis

The first step in the diagnosis of HRS is the demonstration of a reduced GFR, and this is not easy in advanced cirrhosis. The muscle mass, and therefore, the release of creatinine, is reduced in these patients and they may present normal or only moderately increased serum creatinine concentration in the setting of a very low GFR. Similarly, urea is synthesized by the liver and may be reduced as a consequence of hepatic insufficiency. Therefore, false-negative diagnosis of HRS is relatively common.[11–13] There is consensus to establish the diagnosis of HRS when serum creatinine has risen above 1.5 mg/dL.[9,10] A creatinine clearance of less than 40 mL/min, which was also a criteria for the diagnosis of renal failure in cirrhosis (Table 1),[9] has been excluded because errors in the urine collection may lead to high rate of false-positive diagnosis. The second step is the differentiation of HRS from other types of renal failure. For many years this was based on the traditional parameters used to differentiate functional renal failure from acute tubular necrosis (urine volume, urine sodium concentration, and urine-to-plasma osmolality ratio). However, acute tubular necrosis in patients with cirrhosis and ascites usually courses with oliguria, low urine sodium concentration, and urine osmolality greater than plasma osmolality.[14] On the contrary, relatively high urinary sodium concentration has been observed in patients with HRS and high serum bilirubin.[15] Based on these data, these parameters have been removed from the diagnostic criteria of HRS (Table 2).[10]

Table 1 International Ascites Club's Diagnostic Criteria of HRS*

Major criteria

- Chronic or acute liver disease with advanced hepatic failure and portal hypertension
- Low glomerular filtration rate, as indicated by serum creatinine of > 1.5 mg/dL or 24-hr creatinine clearance < 40 mL/min
- Absence of shock, ongoing bacterial infection, and current or recent treatment with nephrotoxic drugs; absence of gastrointestinal fluid losses (repeated vomiting or intense diarrhea) or renal fluid losses (weight loss > 500 g/day for several days in patients with ascites without peripheral edema or 1000 g/day in patients with peripheral edema)
- No sustained improvement in renal function (decrease in serum creatinine to 1.5 mg/dL or less or increase in creatinine clearance to 40 mL/min or more) following diuretic withdrawal and expansion of plasma volume with 1.5 L of isotonic saline
- Proteinuria < 500 mg/day and no ultrasonographic evidence of obstructive uropathy or parenchymal renal disease

Additional criteria

- Urine volume < 500 mL/day
- Urine sodium < 10 mEq/L
- Urine osmolality greater than plasma osmolality
- Urine red blood cells < 50 per high-power field
- Serum sodium concentration < 130 mEq/L

*Arroyo V, Ginès P, Gerbes A, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. Hepatology 1996;23:164–176.

Because of the lack of specific tests, diagnosis of HRS is based on the exclusion of other disorders that can cause renal failure in cirrhosis (Tables 1 and 2).[9,10] Acute renal failure of pre-renal origin due to renal (diuretics) or extrarenal fluid losses should be investigated. If renal failure is secondary to volume depletion, renal function improves rapidly after volume expansion, whereas no improvement occurs in HRS. Even if there is no history of fluid losses, renal function should be assessed after diuretic withdrawal and volume expansion to rule out any subtle reduction in plasma volume as the cause of renal failure. The diagnostic criteria of HRS proposed by the International Ascites Club in San Francisco in 2005 consider that volume replacement should be performed with I.V. albumin (1 g/kg body weight up to a maximum of 100 g), rather than with saline.[10] This proposal is

Table 2 New Diagnostic Criteria of Hepatorenal Syndrome in Cirrhosis*

- Cirrhosis with ascites
- Serum creatinine > 133 μmol/L (1.5 mg/dL)
- No improvement of serum creatinine (decrease to a level of ≤ 133 μmol/L) after at least 2 days with diuretic withdrawal and volume expansion with albumin; the recommended dose of albumin is 1 g/kg of body weight per day up to a maximum of 100 g/day
- Absence of shock
- No current or recent treatment with nephrotoxic drugs
- Absence of parenchymal kidney disease as indicated by proteinuria > 500 mg/day, microhematuria (> 50 red blood cells per high-power field), and/or abnormal renal ultrasonography

*Salerno F, Gerbes A, Ginès P, Wong F, Arroyo V. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. Gut 2007;56:1310–1318.

based on a randomized study showing that albumin is more effective as plasma expander than a saline solution of hydroxyethyl starch in patients with SBP.[16] The presence of shock before the onset of renal failure points toward the diagnosis of acute tubular necrosis. On the other hand, cirrhotic patients with infections may develop transient renal failure, which resolves after resolution of the infection. This occurs in approximately one third of patients.[17,18] Therefore, HRS in cirrhotic patients with bacterial infections should be diagnosed in patients without septic shock and only if renal failure does not improve following antibiotic administration. Complete resolution of the infection, which was required for the diagnosis of HRS in the initial proposal by the International Ascites Club in 1996 (Table 1),[9] is no longer accepted because it may delay the initiation of treatment with vasoconstrictors and albumin.[10] Cirrhotic patients are predisposed to develop renal failure in the setting of treatments with aminoglycosides,[19] nonsteroidal anti-inflammatory drugs,[20] and vasodilators (renin-angiotensin system inhibitors, prazosin, nitrates).[21] Therefore, treatment with these drugs in the days preceding the diagnosis of renal failure should be ruled out. Finally, patients with cirrhosis can develop renal failure due to intrinsic renal diseases, particularly glomerulonephritis in patients with hepatitis B or C (deposition of immunocomplexes) or with alcoholic cirrhosis (deposition of IgA). These cases can be recognized by the presence of proteinuria, hematuria or both, or abnormal renal ultrasonography (small irregular kidneys with abnormal echostructure).

Type-1 and Type-2 HRS: Clinical Characteristics and Prognosis

As indicated previously, there are two types of HRS.[9,10] Type-1 HRS consists of a severe and rapidly progressive renal failure, which has been defined as doubling of serum creatinine reaching a level greater than 2.5 mg/dL in less than 2 weeks. Although type-1 HRS may arise spontaneously, it frequently occurs in close relationship with a precipitating factor, such as severe bacterial infection, mainly SBP, gastrointestinal hemorrhage, major surgical procedure, or acute hepatitis superimposed to cirrhosis. The association of HRS, SBP, and other bacterial infections has been carefully investigated.[17,18,22–24] Type-1 HRS develops in ~25% of patients with SBP despite a rapid resolution of the infection with non-nephrotoxic antibiotics. Patients with severe circulatory dysfunction prior to infection or intense inflammatory response (high concentration of polymorphonuclear leukocytes in ascitic fluid and high cytokine levels in plasma and ascitic fluid) are prone to develop type-1 HRS after the infection. In addition to renal failure, patients with type-1 HRS induced by SBP show signs and symptoms of rapid and severe deterioration of liver function (jaundice, coagulopathy, and hepatic encephalopathy) and circulatory function (arterial hypotension, very high plasma levels of renin and norepinephrine).[22–24] It is interesting to note that in contrast to SBP, sepsis related to other types of infection in patients with cirrhosis is rarely associated with type-1 HRS. In one study, sepsis unrelated to SBP induced type-1 HRS only in the setting of lack of response to antibiotics.[17] In most patients with sepsis unrelated to SBP responding to antibiotics, renal impairment, which was also a frequent event, was reversible. In a second study,[18] the prevalence of HRS was of 30% in patients with SBP, of 19% in patients with severe acute urinary tract infection, and of only 4% in patients with sepsis of other origin. Interestingly enough, as in SBP, some patients with severe urinary tract infection developed type-1 HRS despite the resolution of the infection. The mechanism for the higher frequency of HRS in SBP as compared with other bacterial infections is unknown. Without treatment, type-1 HRS is the complication of cirrhosis with the poorest prognosis with a median survival time after the onset of renal failure of only 2 weeks (Fig. 1).[3]

Type-2 HRS is characterized by a moderate and slowly progressive renal failure (serum creatinine lower than 2.5 mg/dL). Patients with type-2 HRS show signs of liver failure and arterial hypotension but to a lesser extent than patients with type-1 HRS. The dominant clinical feature is severe ascites with poor or no response to diuretics (a condition known as refractory ascites). Patients with type-2 HRS are predisposed to develop type-1 HRS following infections or other precipitating events.[22–24] Median survival of patients with type-2 HRS (6 months) is worse than that of patients with nonazotemic cirrhosis with ascites (Fig. 1).[25]

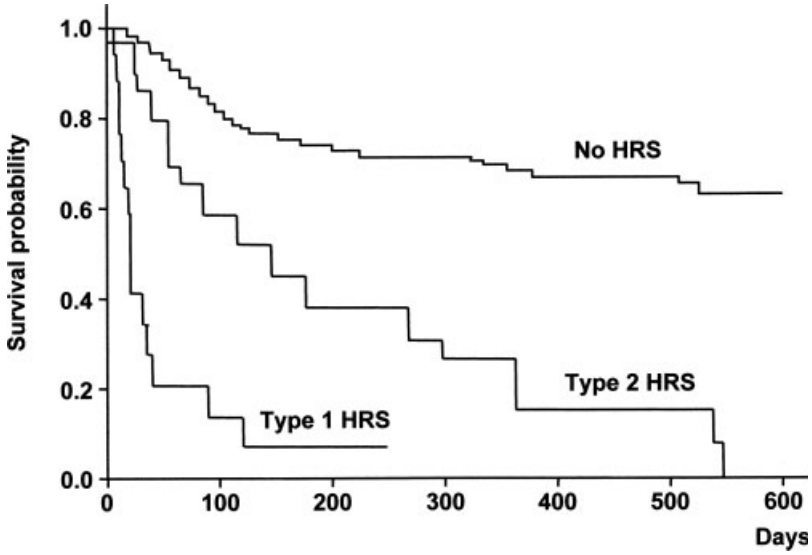

Figure 1 Survival of patients with cirrhosis after the diagnosis of type-1 or type-2 HRS. HRS, hepatorenal syndrome.

PATHOGENESIS OF HEPATORENAL SYNDROME IN CIRRHOSIS

Renal Dysfunction in Cirrhosis Is Related to Arterial Vasodilation: The "Classical Peripheral Arterial Vasodilation Hypothesis"

The development of portal hypertension in cirrhosis is associated with arterial vasodilation in the splanchnic circulation due to the local release of nitric oxide and other vasodilatory substances.[26–29] According to the "peripheral arterial vasodilation hypothesis" (Fig. 2), HRS would be the extreme expression of this splanchnic arterial vasodilation, which would increase steadily with the progression of the disease.[30] In the initial phases of cirrhosis, the decrease in systemic vascular resistance is compensated by the development of a hyperdynamic circulation (increased heart rate and cardiac output).[31–33] However, as the disease progresses and arterial vasodilation increases, the hyperdynamic circulation is insufficient to correct the effective arterial hypovolemia (Fig. 2).[30] Arterial hypotension develops, leading to the activation of high-pressure baroreceptors, reflex stimulation of the renin-angiotensin and sympathetic nervous systems, increase in arterial pressure to normal or near-normal levels, sodium and water retention, and ascites formation. The stimulation of antidiuretic hormone occurs later during the course of the disease. Patients then develop solute-free water retention and dilutional hyponatremia. At this stage of the disease, the renin-angiotensin and sympathetic nervous systems are markedly stimulated and arterial pressure is critically dependent on the vascular effect of the sympathetic nervous activity, angiotensin-II, and antidiuretic hormone (vasopressin). Since the splanchnic circulation is resistant to the effect of angiotensin-II, noradrenaline, and vasopressin due to the local release of nitric oxide and other vasodilators,[34,35] the maintenance of arterial pressure is due to vasoconstriction in extrasplanchnic vascular territories such as the kidneys, muscle, skin, and brain.[36–39] HRS develops in the final phase of the disease when there is an extreme deterioration in effective arterial blood volume and severe arterial hypotension. The homeostatic stimulation of the renin-angiotensin system, the sympathetic nervous system, and antidiuretic hormone is very intense leading to renal vasoconstriction and marked decrease in renal perfusion and GFR, azotemia, and increased serum creatinine concentration.

Cardiac Dysfunction Is Also Important: The "Revised Peripheral Arterial Vasodilation Hypothesis"

Most hemodynamic studies in cirrhosis have been performed in nonazotemic patients with and without ascites, and their findings have been extended to the entire population of decompensated cirrhosis. Based on these studies, it has been assumed that HRS develops in the setting of a hyperdynamic circulation, with low peripheral vascular resistance due to the splanchnic arterial vasodilation and high cardiac output. However, in the few studies assessing cardiovascular function in patients with HRS or refractory ascites (most of them with type-2 HRS), cardiac output was found to be significantly reduced compared with patients without HRS.[40,41] In some cases cardiac output was even lower than in normal subjects, suggesting that circulatory dysfunction associated with HRS is due not only to arterial vasodilation but also to a decrease in cardiac function. Two studies by Ruiz-del-Arbol et al support this idea.[42,43]

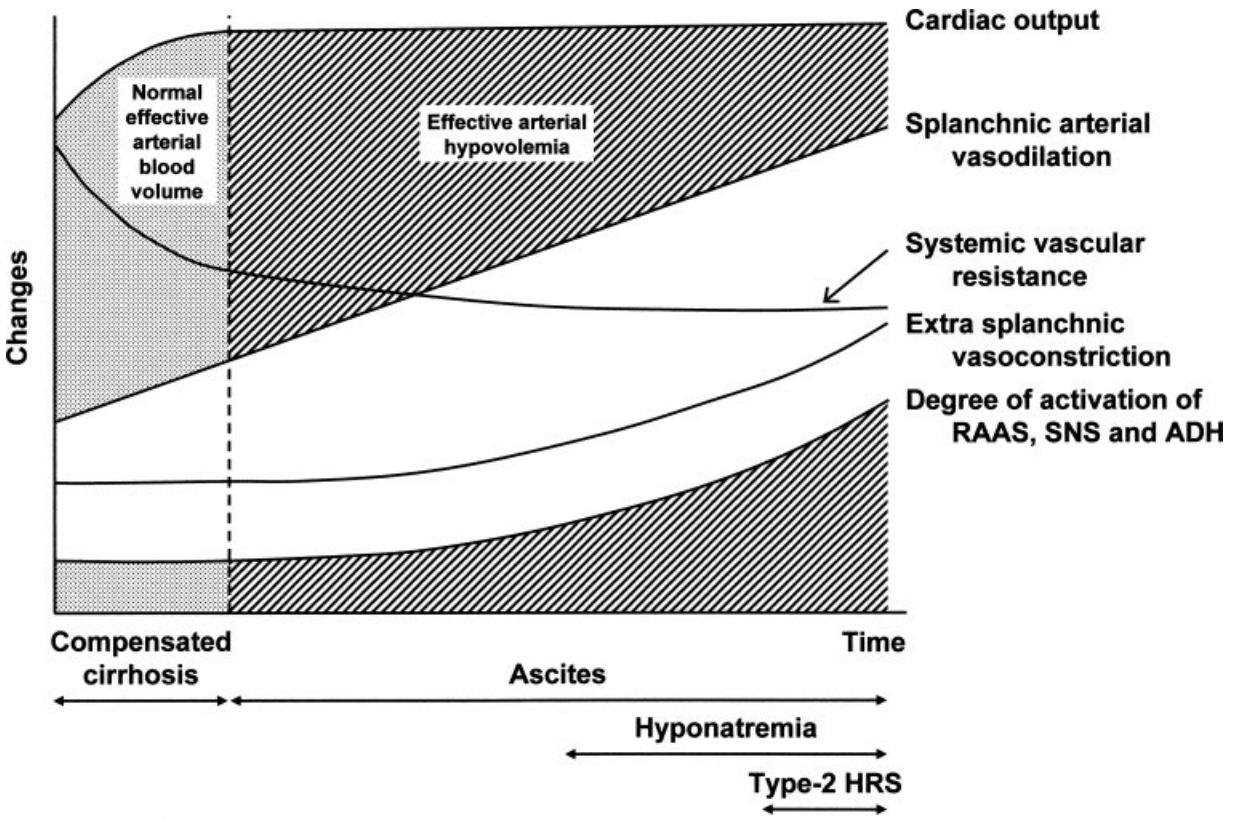

Figure 2 Peripheral arterial vasodilation hypothesis and renal dysfunction in cirrhosis. In initial phases, when cirrhosis is compensated, the increase in splanchnic arterial vasodilation is compensated by an increase in cardiac output (hyperdynamic circulation). The effective arterial blood volume and the activity of renin-angiotensin (RAAS), sympathetic nervous system (SNS), and plasma antidiuretic hormone (ADH) are normal despite a reduction in systemic vascular resistance. With the progression of liver disease, splanchnic arterial vasodilation increases but the cardiac output does not. An effective arterial hypovolemia therefore develops, leading to activation of the RAAS and SNS and ADH. Systemic vascular resistance does not decrease due to vasoconstriction of extrasplanchnic organs. Type-2 HRS could be the extreme expression of renal vasoconstriction.

In the first study,[42] systemic and hepatic hemodynamics and the endogenous vasoactive systems were measured in 23 cirrhotic patients with SBP at infection diagnosis and after SBP resolution. Eight patients developed type-1 HRS. The remaining 15 patients did not develop renal failure. Development of type-1 HRS was associated with a significant decrease in mean arterial pressure and a marked stimulation of the renin-angiotensin and sympathetic nervous systems, indicating a severe impairment in effective arterial blood volume. Peripheral vascular resistance did not change despite the intense stimulation of these endogenous vasoconstrictor systems, which is consistent with a progression of the arterial vasodilation already present in these patients. The most important result of the study, however, was the observation of a marked decrease in cardiac output in all cases. These changes were not observed in patients not developing renal failure. Impairment in systemic hemodynamics and type-1 HRS associated with SBP was, therefore, clearly related to the simultaneous occurrence of a decrease in cardiac output and an accentuation of the arterial vasodilation. Patients who developed type-1 HRS showed significantly higher values of cytokines, plasma renin activity, and sympathetic nervous activity and lower cardiac output and glomerular filtration rate at infection diagnosis than patients not developing renal failure. These results confirm previous studies showing that in patients with SBP the severity of the inflammatory response and the degree of impairment of systemic hemodynamics and renal function prior to the infection are important predictors of type-1 HRS.[24]

The second study consisted of a longitudinal investigation of 66 nonazotemic cirrhotic patients with ascites.[43] Forty percent of patients developed HRS (type 1 or type 2). These patients were studied at inclusion and following the development of HRS. In the initial study, those patients who went on to develop HRS had significantly lower mean arterial pressure and cardiac output, and significantly higher plasma renin activity and norepinephrine concentration compared with those who did not develop HRS. Moreover, those who developed HRS had a further decrease in arterial pressure and cardiac output and an increase in renin and norepinephrine without changes in peripheral vascular resistance

Table 3 Chronological Changes of Vasoactive Systems and Cardiovascular Function from Nonazotemic Cirrhosis with Ascites (NA) to Type-2 HRS*

	NA-1	NA-2	At Diagnosis of Type-2 HRS
Mean arterial pressure (mm Hg)†	88 ± 9	86 ± 10	79 ± 7
Plasma renin activity (ng/mL.h)†	3 ± 2	7.5 ± 3.7	11.9 ± 4.8
Norepinephrine (pg/mL)†	221 ± 256	412 ± 155	628 ± 320
Systemic vascular resistance (dynes.second/cm^{-5})	962 ± 256	1058 ± 265	1014 ± 276
Cardiac output (L/min)†	7.2 ± 1.8	6.2 ± 1.4	5.8 ± 1.2
Heart rate (bpm)	87 ± 15	84 ± 12	80 ± 14
Hepatic blood flow (mL/min)†	1123 ± 328	1064 ± 223	824 ± 180
Hepatic venous pressure gradient (mm Hg)†	16.5 ± 3	19 ± 3	19.5 ± 2

*Data from Ruiz-del-Arbol L, Monescillo A, Arocena C, et al. Circulatory function and hepatorenal syndrome in cirrhosis. Hepatology 2005;42:439–447.
NA-1, baseline measurement in nonazotemic cirrhotic patients who did not develop hepatorenal syndrome during the follow-up; NA-2, baseline measurement in nonazotemic cirrhotic patients who developed type-2 hepatorenal syndrome during the follow-up. bpm, beats per minute.
†$p < 0.01$.

(Table 3). These findings strongly suggest that circulatory dysfunction in cirrhosis is due to both an increase in arterial vasodilation and a decrease in cardiac function (Fig. 3), and that HRS occurs in the setting of severe reduction in effective arterial blood volume secondary to an impairment in cardiovascular function. In this study, baseline increased plasma renin activity and reduced cardiac output were found to be the only independent predictors of HRS.

HRS IN CIRRHOSIS IS A COMPLEX SYNDROME THAT AFFECTS ORGANS OTHER THAN THE KIDNEY

Traditionally, patients with HRS were considered to have mainly two different problems, a terminal and irreversible liver failure due to advanced cirrhosis and a functional renal failure secondary to renal vasoconstriction. The link between the diseased liver and the failing kidney was a deterioration in systemic hemodynamics.

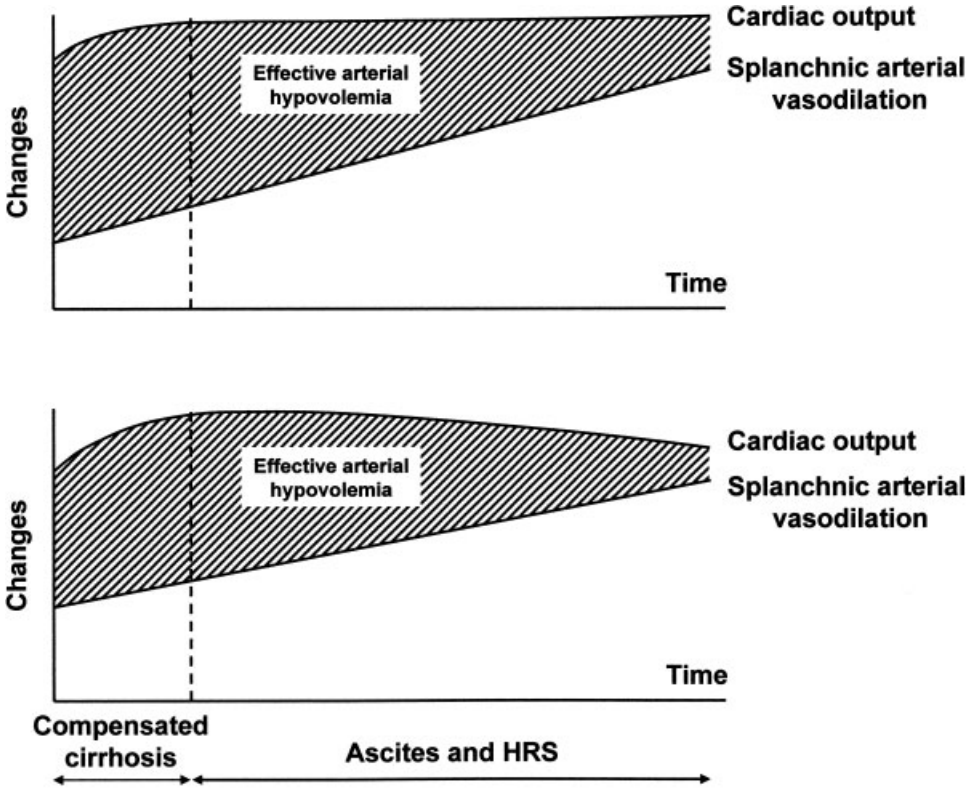

Figure 3 Peripheral vasodilation hypothesis (top graph) and modified peripheral vasodilation hypothesis (bottom graph). According to this latter hypothesis, impairment in arterial blood volume in cirrhosis could be the consequence of a progression of splanchnic arterial vasodilation and a decrease in cardiac output.

During the last decade, however, increasing evidence suggest that HRS is a much more complex syndrome affecting organs other than the liver and the kidney. Moreover, data have been presented suggesting that the impairment in circulatory function affects the intrahepatic circulation and that this may contribute to the severity of hepatic failure in HRS. Liver failure in HRS could, therefore, be partially reverted if circulatory dysfunction is improved.

Renal Failure

HRS develops at the last phase of cirrhosis, when patients already present severe circulatory dysfunction, arterial hypotension, marked activation of the renin-angiotensin aldosterone system, sympathetic nervous system, and antidiuretic hormone, renal sodium and water retention, ascites, and dilutional hyponatremia. The mechanism of the renal vasoconstriction that causes HRS is complex. Since renal perfusion in decompensated cirrhosis correlates inversely with the activity of the renin-angiotensin and sympathetic nervous systems,[36,38,44,45] HRS is thought to be related to the extreme stimulation of these systems. The urinary excretion of prostaglandin E2, 6-keto prostaglandin F1α (a prostacyclin metabolite), and kallikrein is decreased in patients with HRS, which is compatible with a reduced renal production of these vasodilatory substances.[46,47] Renal failure in HRS could, therefore, be the consequence of an imbalance between the activity of the systemic vasoconstrictor systems and the renal production of vasodilators. Additionally, once renal hypoperfusion develops, renal vasoconstriction could be amplified by the stimulation of other intrarenal vasoactive systems. For example, renal ischemia increases the generation of angiotensin-II by the juxtagomerular apparatus, the intrarenal production of adenosine (a renal vasoconstrictor which in addition potentiates the vascular effect of angiotensin-II), and the synthesis of endothelin. Other intrarenal vasoconstrictors that have been involved in HRS are leukotrienes and F2-isoprostanes.[48] Renal vasoconstriction in HRS is, therefore, related to the simultaneous effect of numerous vasoactive substances on the intrarenal circulation.

Vasoconstruction of Cutaneous, Muscular, and Cerebral Circulation in HRS

Brachial and femoral blood flows are markedly reduced in patients with HRS, indicating a vasoconstriction in the cutaneous and muscular arterial vascular beds.[36] The resistive index in the mean cerebral artery is also increased in these patients, indicating cerebral vasoconstriction[39] (Fig. 4). The degree of vasoconstriction in these vascular territories in decompensated cirrhosis (patients with ascites with and without HRS) correlates directly with the degree of renal vasoconstriction and with the plasma levels of renin. Impairment in circulatory function in cirrhosis is therefore associated with generalized nonsplanchnic arterial vasoconstriction.

The clinical consequences of the decreased muscular blood flow in advanced cirrhosis have not been explored. Patients with type-2 HRS and refractory ascites frequently present muscle cramps. Although the pathogenesis of this abnormality is unknown, muscle cramps disappear or improve following plasma volume expansion with albumin,[49] suggesting that they could be related to this reduction in muscular blood flow. Hepatic encephalopathy is common in patients with HRS. There are many possible mechanisms of this complication, including the precipitating event of HRS, which can also cause hepatic encephalopathy, and the deterioration of hepatic function observed in these patients. Cerebral vasoconstriction, however, could be an additional factor.

Cardiac Dysfunction

The normal response to arterial hypotension consists of a stimulation of the renin-angiotensin and sympathetic nervous systems. Angiotensin-II and the sympathetic nervous activity produce arterial vasoconstriction and increase the systemic vascular resistance. Moreover, these hormones also increase heart rate, ventricular contractility, and cardiac output. These two mechanisms increase arterial pressure to normal or near-normal levels. In patients with type-2 HRS, arterial vasodilation is followed by an appropriate response of the vasoactive neurohormonal systems. There is a marked increase in the plasma levels of renin and norepinephrine and vasoconstriction in the extrasplanchnic organs that maintains arterial pressure.[36,39] However, the cardiac response is clearly abnormal in these patients. Development of type-2 HRS is associated with a slight decrease in cardiac output. Moreover, despite the intense activation of the sympathetic nervous activity, no change in heart rate is observed (Table 3).[43] These data clearly indicate that there is an impairment in cardiac inotropic and chronotropic functions in patients with type-2 HRS. In patients with type-1 HRS, the deterioration of cardiac function is even more evident. Type-1 HRS occurs in the setting of a severe decrease in cardiac output, which may reach values below normal. The heart rate remains unchanged despite a dramatic activation of the renin-angiotensin and sympathetic nervous systems.[42]

The pathogenesis of the impaired cardiac response to arterial vasodilation in HRS is unknown. A specific cardiomiopathy characterized by attenuated systolic and diastolic responses to stress stimuli, electrophysiological repolarization changes, and enlargement and hypertophy of cardiac chambers is common in patients with advanced cirrhosis.[50] This cirrhotic cardiomiopathy has been thought to play a role in the

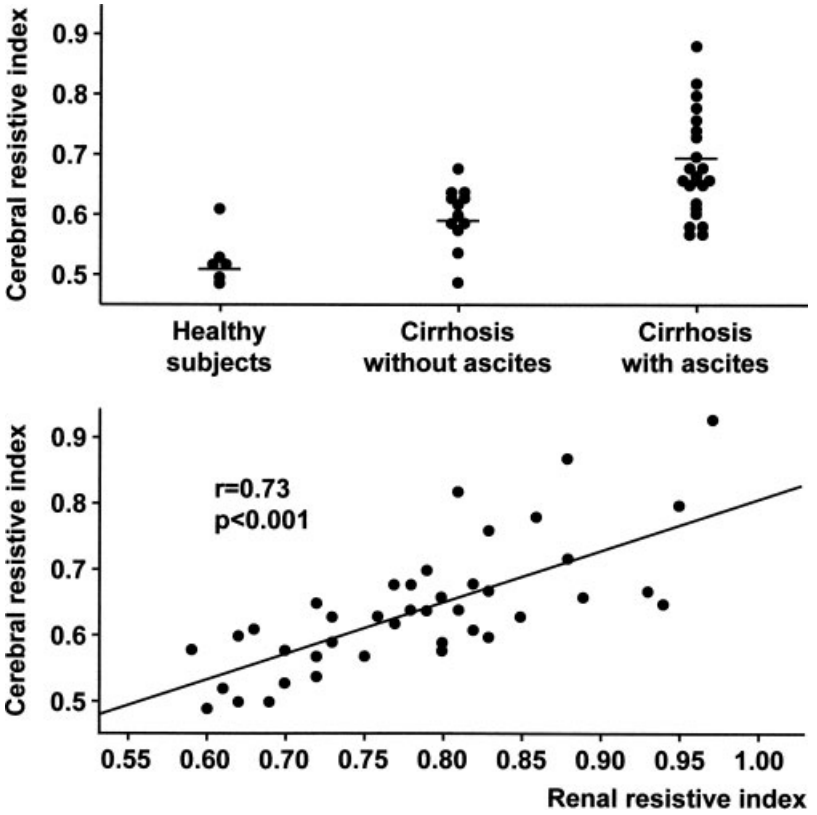

Figure 4 Resistive index in the middle cerebral artery in patients with compensated cirrhosis, patients with ascites, and healthy subjects (upper graph). Relationship between the renal resistive index and the resistive index in the middle cerebral artery in cirrhotic patients (lower graph). (Reproduced with permission from Guevara M, Bru C, Ginès P, et al. Increased cerebrovascular resistance in cirrhotic patients with ascites. Hepatology 1998;28:39–44.)

pathogenesis of heart failure seen after the insertion of a transjugular intrahepatic portosystemic shunt (TIPS),[51,52] major surgery, or liver transplantation,[53,54] and in HRS.[42,43] Other features, however, suggest that the impairment in the cardiac inotropic function in HRS is not organic but is mainly functional in nature and related to a decrease in venous return.[55] First, the reduced cardiac output in patients with HRS occurs in the setting of a decrease in cardiopulmonary pressures, which is compatible with a fall in cardiac preload. Second, circulatory dysfunction in HRS can be reverted by the intravenous (I.V.) administration of albumin associated with vasoconstrictors or after the insertion of a TIPS. Both treatments increase venous return and cardiac output. Finally, expansion of plasma volume with albumin is highly effective in the prevention of type-1 HRS in patients with SBP.[56] The impairment in chronotropic cardiac function is probably related to a down-regulation of β-adrenergic receptors secondary to the chronic stimulation of the sympathetic nervous system.

Intrahepatic Vasoconstriction

Angiotensin-II, noradrenaline, and vasopressin have powerful effects on the intrahepatic circulation. They produce arterial vasoconstriction and increase the intrahepatic resistance to the portal venous flow at different levels (small portal venules, sinusoids, and small hepatic venules). In patients with cirrhosis these effects are increased due to a reduced intrahepatic synthesis of nitric oxide.[57] It is, therefore, not surprising that the stimulation of the endogenous vasoactive systems in HRS could be associated with an aggravation of portal hypertension and a marked reduction in hepatic blood flow.[42,43] This has been shown recently by Ruiz-del-Arbol et al.[43] They studied hepatic hemodynamics in a large series of nonazotemic cirrhotics with tense ascites when they had normal serum creatinine concentration and after a follow-up of several months when patients developed type-1 or type-2 HRS. The hepatic venous pressure gradient was significantly higher in the follow-up study than in the baseline study in patients developing type-1 HRS. Type-1 HRS was also associated with a dramatic reduction in hepatic blood flow. In patients developing type-2 HRS, significant differences were only observed in the hepatic blood flow (Table 3). In a second investigation from the same group, hepatic hemodynamics were assessed in patients with SBP at infection diagnosis and following infection resolution.[42] There was only a 1-week interval between the studies.

Hepatic venous pressure gradient increased markedly in patients who developed type-1 HRS but not in patients with normal renal function. Changes in intrahepatic hemodynamics in the two studies correlated significantly with the increase in plasma renin activity. This finding suggests that circulatory dysfunction associated with hepatorenal syndrome adversely influences intrahepatic hemodynamics. Acute deterioration of hepatic function is a common event in patients with type-1 HRS. Variceal bleeding is also frequent in patients with severe bacterial infections and HRS. The intense reduction in hepatic blood flow and the increase in portal pressure associated with type-1 HRS could play a role in the development of these complications.

Relative Adrenal Insufficiency

Two recent studies indicate that relative adrenal dysfunction is a common problem in patients with cirrhosis and acute-on-chronic liver failure secondary to severe sepsis.[58,59] In the first study,[58] adrenal insufficiency was detected in 80% of patients with HRS but only in 34% with serum creatinine below 1.5 mg/dL. A close relationship, therefore, existed between adrenal insufficiency and HRS in patients with severe infection. Other features associated with adrenal insufficiency were severe liver failure, arterial hypotension and vasopressor dependency, and hospital mortality. Since normal adrenal function is essential for an adequate response of the arterial circulation to endogenous vasoconstrictors, adrenal insufficiency could be an important contributory mechanism of circulatory dysfunction associated with HRS in patients with severe bacterial infections. The second study[59] recently showed that treatment with hydrocortisone in cirrhotic patients with severe sepsis and adrenal insufficiency is associated with a rapid improvement in systemic hemodynamics, reduction of vasoconstrictor requirements, and higher hospital survival. The mechanisms of adrenal dysfunction in cirrhosis with severe sepsis have not been explored. Since adrenal dysfunction is particularly prevalent in patients with HRS, a reduction in adrenal blood flow secondary to regional vasoconstriction is a possible mechanism. Cytokines directly inhibit adrenal cortisol synthesis. The inflammatory response associated with bacterial infections is, therefore, another potential pathogenic mechanism.

TYPE-1 AND TYPE-2 HRS ARE NOT DIFFERENT EXPRESSIONS OF A COMMON SYNDROME BUT RATHER DIFFERENT ENTITIES

Clinical data suggest that type-1 and type-2 HRS are different syndromes and not different expressions of a common underlying disorder. Renal failure in type-1 HRS is severe and progressive whereas in type-2 it is moderate and steady. As expected, circulatory function is also stable in type-2 HRS, whereas a rapidly progressive impairment in circulatory function occurs in type-1 HRS. Type-1 HRS is frequently associated with a precipitant event, mainly SBP. In contrast, type-2 HRS develops spontaneously in most cases. Finally, the main clinical consequence of type-1 HRS is severe hepatorenal failure and death, whereas in type-2 HRS it is refractory ascites. Type-2 HRS probably represents the genuine functional renal failure of cirrhosis. It would be the extreme expression of the impairment in circulatory function that spontaneously develops up to the final stages of the disease (Figs. 2, 3). In contrast, type-1 HRS appears to share similarities with acute renal failure associated with other conditions such as septic shock or severe pancreatitis. In fact, as indicated previously, features of multiorgan failure including acute impairment in cardiovascular, renal, hepatic, and cerebral function and relative adrenal insufficiency are common in patients with type-1 HRS but rare in patients with type-2 HRS (Fig. 5).

TREATMENTS FOR TYPE-1 HRS

Liver Transplantation

Liver transplantation is the treatment of choice for any patient with advanced cirrhosis, including those with type-1 and type-2 HRS.[60–63] Immediately after transplantation, a further impairment in GFR may be observed and many patients require hemodialysis (35% of patients with HRS as compared with 5% of patients without HRS).[60] Because cyclosporine or tacrolimus may contribute to this impairment in renal function, it has been suggested to delay the administration of these drugs until a recovery of renal function is noted, usually 48 to 96 hours after transplantation. After this initial impairment in renal function, GFR starts to improve and reaches an average of 30 to 40 mL/min by 1 to 2 months postoperatively. This moderate renal failure persists during follow-up, is more marked than that observed in transplantation patients without HRS, and is probably due to a greater nephrotoxicity of cyclosporine or tacrolimus in patients with renal impairment prior to transplantation. The hemodynamic and neurohormonal abnormalities associated with HRS disappear within the first month after the operation and patients regain a normal ability to excrete sodium and free water.

Patients with HRS who undergo transplantation have more complications, spend more days in the intensive care unit, and have a higher in-hospital mortality rate than transplantation patients without HRS. The long-term survival of patients with HRS who undergo liver transplantation, however, is good, with a 3-year probability of survival of 60%. This survival rate is only

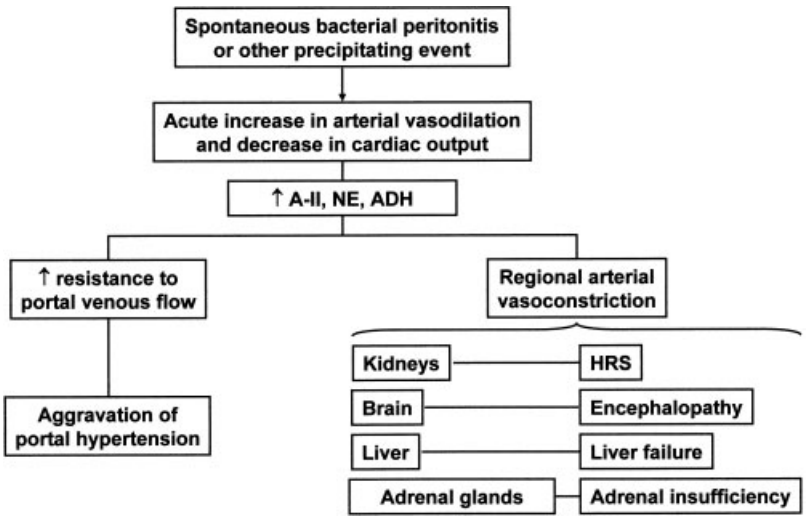

Figure 5 HRS as a part of a multiorgan failure. A-II, angiotensin-II; NE, norepinephrine; ADH, antidiuretic hormone; HRS, hepatorenal syndrome.

slightly lower than that of patients without HRS (which ranges between 70% and 80%).[61]

The main problem of liver transplantation in type-1 HRS is its applicability. Due to their extremely short survival, most patients die before transplantation. The introduction of the model for end-stage liver disease score, which includes serum creatinine, bilirubin, and the international normalized ratio, for listing has partially solved the problem since patients with HRS are generally allocated the first places of the waiting list. Treatment of HRS with vasoconstrictors and albumin (see below) increases survival in a significant proportion of patients (and, therefore, the number of patients reaching liver transplantation), decreases early morbidity and mortality after transplantation, and prolongs long-term survival.

Vasoconstrictors and Albumin

The I.V. administration of vasoconstrictor agents (vasopressin, ornipressin, terlipressin, noradrenaline) or the combination of oral midodrine (an α-agonistic agent) and I.V. or subcutaneous octreotide during 1 to 3 weeks is an effective treatment of type-1 HRS. Twelve pilot studies including 176 patients with HRS (141 with type-1 HRS) have so far been published on this topic.[64–75] In most patients, I.V. albumin was also given. The overall rate of positive response was 63.6% (112 patients). In nine of these studies (including 150 patients) a positive response was considered when there was reversal of HRS as defined by a decrease of serum creatinine below 1.5 mg/dL. This feature was observed in 96 patients (64%). A second important observation was that type-1 HRS does not recur after discontinuation of the treatment in most patients. Six studies including 74 patients have reported data on this feature. Fifty-two patients responded to therapy and HRS recurred in only 12. These findings contrast sharply with those of seven studies in patients with type-1 HRS not receiving specific treatment or treated with plasma volume expansion alone or associated with vasodilators (dopamine) or octreotride or with peritoneovenous shunting.[23,24,56,66,73,76,77] Reversal of HRS was observed in only 4 out of the 137 patients (2.9%) included in these studies. Survival data were recorded in 13 studies (8 using vasoconstrictors and 5 using other treatments). Forty (41.6%) and 29 (30%) of the 96 patients with type-1 HRS treated with vasoconstrictors were alive 1 and 3 months after treatment, respectively. The corresponding figures in 65 patients receiving other treatments were 2 (3%) and 0 (0%), respectively. Thirty-four patients treated with vasoconstrictors reached liver transplantation.

A retrospective survey in 99 patients with type-1 HRS admitted to 22 hospitals in France and treated with terlipressin (all cases) and albumin (70% of cases) showed a rate of improvement in renal function of 58%.[78] The probability of survival was 40% at 1 month and 22% at 3 months. Improvement of survival was related to reversal of HRS. Thirteen patients received a liver transplant. This study, which reflects what occurs in regular clinical practice, confirms the results previously described in several pilot studies including short series of patients.

Two randomized controlled studies finished recently comparing albumin versus albumin plus terlipressin in patients with type-1 HRS (Sanyal et al and Guevara et al, unpublished results), and they confirm the results obtained in the pilot studies. Reversal of HRS was significantly more frequent in patients treated with terlipressin and albumin. On the other hand, survival of patients responding to treatment was significantly longer than that of patients not responding to treatment or treated with albumin alone.

These studies clearly indicate that vasoconstrictors associated with I.V. albumin should be recommended

for the management of patients with type-1 HRS since they normalize serum creatinine in a high proportion of patients and may improve survival. Terlipressin has been the most widely used vasoconstrictor agent in type-1 HRS. It is very effective and is associated with a low incidence of side effects. The efficacy of the association of oral midodrine and I.V. or subcutaneous octreotide is probably due exclusively to the vasoconstrictor effect of midodrine. Noradrenaline has also been shown to be effective and safe and there is a randomized controlled trial in a small number of patients with type-1 and type-2 HRS (mainly type-2) indicating that it is as effective as terlipressin.[75] However, whereas there is much experience with terlipressin, noradrenaline and midodrine have been used only in few studies. Based on these considerations, terlipressin should be the drug of choice for the treatment of type-1 HRS. Reversal of type-1 HRS in two pilot studies in which terlipressin was given alone (7 out of 28 patients, 25%)[69,71] was lower than that observed in the studies in which vasoconstrictors were associated with I.V. albumin, suggesting that albumin is an important component in the pharmacological treatment of type-1 HRS. Two recent studies[16,79] suggest that the beneficial effect of albumin on circulatory and renal function in patients with type-1 HRS is related not only to the expansion of the plasma volume but also to a direct vasoconstrictor effect on the peripheral arterial circulation.

Terlipressin dosage should be progressive, starting with 0.5 to 1 mg/4 to 6 h. If serum creatinine does not decrease by more than 30% in 3 days, the dose should be doubled. The maximal dose of terlipressin has not been defined, although there was consensus that patients not responding to 12 mg/day will not respond to higher doses. Albumin should be given starting with a priming dose of 1 g/kg of body weight followed by 20 to 40 g/day. It is advisable to monitor central venous pressure. In patients responding to therapy, treatment should be continued until normalization of serum creatinine (< 1.5 mg/dL).

Transjugular Intrahepatic Portosystemic Shunt

Three pilot studies have evaluated TIPS in type-1 HRS.[74,80,81] In the first study,[80] 14 patients with type-1 HRS (12 with alcoholic cirrhosis, 9 with active alcoholism) and 17 with refractory ascites (some of them with type-2 HRS) not suitable for liver transplantation were treated with TIPS. Patients with bilirubin > 15 mg/dL, Child-Pugh score > 12 points, or hepatic encephalopathy were excluded. Eleven out of the 31 patients developed de novo hepatic encephalopathy or deterioration of previous hepatic encephalopathy. The 3-, 6-, and 12-month survival rates in patients with type-1 HRS were 64%, 50%, and 20%, respectively. The second study[81] was performed in 7 patients (4 alcoholics) with type-1 HRS and a Child-Pugh score < 12 points. Marked decrease in serum creatinine was observed in 6 patients and reversal of HRS in 4. Five patients developed episodes of hepatic encephalopathy after TIPS but they responded satisfactorily to medical treatment. Five patients were alive after 1 month of TIPS but only 2 after 3 months. The third study[74] was performed in 14 patients (13 with alcoholic cirrhosis) with type-1 HRS treated initially with vasoconstrictors (midodrine and octreotide) plus albumin. Reversal of HRS was obtained in 10 patients. TIPS devices were subsequently inserted in 5 of these 10 patients who had bilirubin < 5 mg/dL, international normalized ratio < 2, and Child-Pugh score < 12 points. Normalization of GFR was obtained in all cases and patients were alive between 6 to 30 months after TIPS. TIPS, therefore, is effective in normalizing serum creatinine in a significant proportion of patients with cirrhosis and severe azotemia and is an alternative treatment to vasoconstrictors in type-1 HRS.

Extracorporeal Albumin Dialysis

Three pilot studies including 29 patients (26 with type-1 HRS and 21 with alcoholic cirrhosis and/or severe acute alcoholic hepatitis) aimed at assessing molecular adsorbents recirculating system (MARS) in patients with type-1 HRS have been reported.[82–84] Since MARS incorporates a standard dialysis machine or a continuous veno-venous hemofiltration monitor and GFR was not measured, it is not possible to know the effect of this treatment on renal function. The decrease in serum creatinine observed in most patients could be related to the dialysis process. However, clear beneficial effects on systemic hemodynamics and on hepatic encephalopathy were observed. The survival rate 1 and 3 months after treatment was 41% (12 patients) and 34% (10 patients), respectively. A recent randomized controlled trial in a large series of cirrhotic patients with hepatic encephalopathy,[85] many of them with HRS, has demonstrated a clear beneficial effect of MARS on the rate and time of recovery of encephalopathy. Since the end point of this trial was encephalopathy, no conclusion can be obtained in relation to survival.

TREATMENTS FOR TYPE-2 HRS

In patients with type-2 HRS, most of whom may reach a liver transplant, the main clinical problem is refractory ascites. Therefore, treatment of type-2 HRS should consider not only survival but also the control of ascites.

Transjugular Intrahepatic Portosystemic Shunt

Five trials comparing TIPS versus paracentesis in patients with refractory and/or recidivant ascites have so far been published.[52,86–89] In total, 172 patients were

treated by TIPS. Unfortunately, very few of these patients had HRS. Patients with serum creatinine >3 mg/dL were excluded from three studies. Only two studies gave the number of patients with HRS included (6 out of 53). Finally, mean serum creatinine was below 1.5 mg/dL in the groups treated by TIPS in these five studies. Therefore, data from these five trials are not valid for the assessment of TIPS in the management of patients with type-2 HRS.

There are only two pilot studies specifically assessing TIPS in type-2 HRS.[80,90] In one study,[90] a significant reduction of serum creatinine (from 2.1 ± 0.3 to 1.4 ± 0.3 mg/dL 1 month after TIPS) was observed in eight out of nine patients. This was associated with a significant improvement in the control of ascites. Four of these patients died, two within the first month and two 12 and 14 months after the procedure. The remaining five patients had longer survival. No data were given on the type and rate of complications associated with TIPS. A second study included 14 patients with type-1 HRS and 17 with type-2 HRS treated by TIPS.[80] Mean baseline serum creatinine concentration in patients with type-2 HRS was only 1.44 ± 0.3 mg/dL, but mean creatinine clearance was 28 ± 14 mL/min. A significant improvement in serum creatinine and creatinine clearance was observed in the whole group of 31 patients as was as an improvement in the control of ascites in 24 cases. Six patients developed TIPS dysfunction and 11 developed hepatic encephalopathy during follow-up. The 1-year probability of survival in the 17 patients with type-2 HRS treated by TIPS was 70%. TIPS is therefore effective in reversing type-2 HRS, although more data on complication rate and survival are needed before advocating a widespread use of this procedure. The introduction of covered stents should be a stimulus to re-evaluate the role of TIPS in the management of refractory ascites and type-2 HRS.

Vasoconstrictors and Albumin

Three pilot studies provided data on the effect of terlipressin plus albumin in 39 patients with type-2 HRS.[67,71,90] Reversal of HRS was obtained in most cases (21 cases, 80%). In one of these studies[90] the course of renal function after stopping treatment was assessed in 11 patients and HRS recurred in all cases. There were no data on survival. This high prevalence of HRS recurrence has been confirmed recently in a second study by Alessandria et al.[75] In a randomized comparative study of terlipressin versus noradrenaline in 22 patients with type-1 and type-2 HRS, reversal of HRS was obtained in 17 patients. HRS recurrence was observed in 8 patients, 5 with type-2 HRS. The current state of knowledge on vasoconstrictor therapy in type-2 HRS is therefore very poor. It appears to be not as effective as in type-1 HRS due to the high rate of HRS recurrence.

PREVENTION OF HRS

Three randomized controlled studies in large series of patients have shown that HRS can be prevented in specific clinical settings. In the first study,[56] the administration of albumin (1.5 g/kg I.V. at infection diagnosis and 1 g/kg I.V. 48 hours later) to patients with cirrhosis and SBP markedly reduced the incidence of circulatory dysfunction and type 1 HRS (10% incidence of type-1 HRS in patients receiving albumin versus 33% in the control group). Hospital mortality rate (10% versus 29%) and the 3-month mortality rate (22% versus 41%) were lower in patients receiving albumin.

The second study was performed in cirrhotic patients at a high risk of developing SBP and type-1 HRS.[91] Primary prophylaxis of SBP using long-term oral norfloxacin was given to 35 patients with low protein ascites (<15 g/L) and advanced liver failure (Child-Pugh score ≥ 9 points with serum bilirubin ≥ 3 mg/dL) or impaired renal function (serum creatinine level ≥ 1.2 mg/dL; blood urea nitrogen level ≥ 25 mg/dL, or serum sodium level ≤ 130 mEq/L). Thirty-three patients received placebo. Norfloxacin administration was associated with a significant decrease in 1-year probability of development of SBP (7% versus 61%) and type-1 HRS (28% versus 41%) and with a significant increase in the 3-month and 1-year probability of survival (94% versus 62% and 60% versus 48%, respectively). In this study, patients developing SBP received I.V. albumin (1.5 g/kg I.V. at infection diagnosis and 1 g/kg I.V. 48 hours later) and only 1 patient developed HRS associated with SBP. Type-1 HRS, however, was the principal cause of death in this study. Therefore, oral norfloxacin prevented type-1 HRS in these patients by a mechanism different from the prevention of SBP. Several studies have shown that in patients with cirrhosis in addition to bacterial translocation there is translocation of products of bacterial origin (endotoxin, bacterial DNA) that induce a systemic inflammatory reaction, activation of nitric oxide, and impairment in circulatory function.[92–94] The administration of oral norfloxacin in these patients prevents this translocation of bacterial products and improves circulatory function with a significant increase in arterial pressure and systemic vascular resistance and suppression of plasma renin activity and plasma norepinephrine concentration.[92,94] An improvement in circulatory function, which makes patients less susceptible to type-1 HRS, is, therefore, the most likely mechanism of the beneficial effect of oral norfloxacin found in this study.

In the third study,[95] the administration of the tumor necrosis factor inhibitor pentoxyfilline (400 mg three times a day) to patients with severe acute alcoholic hepatitis reduced the occurrence of HRS (8% in the pentoxyfilline group versus 35% in the placebo group) and the hospital mortality (24% versus 46%, respectively). Because bacterial infections and acute alcoholic

hepatitis are important precipitating factors of type 1 HRS, these prophylactic measures may decrease the incidence of this complication.

ABBREVIATIONS

GRF	glomerular filtration rate
HRS	hepatorenal syndrome
MARS	molecular adsorbents recirculating system
SBP	spontaneous bacterial peritonitis
TIPS	transjugular intrahepatic portosystemic shunt

REFERENCES

1. Ginès P, Rodés J. Clinical disorders of renal function in cirrhosis with ascites. In: Arroyo V, Ginès P, Rodés J, Schrier RW, eds. Ascites and Renal Dysfunction in Liver Disease: Pathogenesis, Diagnosis, and Treatment. Malden: Blackwell Science; 1999:36–62
2. Hecker R, Sherlock S. Electrolyte and circulatory changes in terminal liver failure. Lancet 1956;271:1121–1125
3. Ginès A, Escorsell A, Ginès P, et al. Incidence, predictive factors, and prognosis of the hepatorenal syndrome in cirrhosis with ascites. Gastroenterology 1993;105:229–236
4. Koppel MH, Coburn JW, Mims MM, et al. Transplantation of cadaveric kidneys from patients with hepatorenal syndrome: evidence for functional nature of renal failure in advanced liver disease. N Engl J Med 1969;280:1367–1373
5. Iwatsuki S, Popovtzer MM, Corman JL, et al. Recovery from hepatorenal syndrome after orthotopic liver transplantation. N Engl J Med 1973;289:1155–1159
6. Ginès P, Guevara M, Arroyo V, Rodés J. Hepatorenal syndrome. Lancet 2003;362:1819–1827
7. Arroyo V, Terra C, Ginès P. Advances in the pathogenesis and treatment of type-1 and type-2 hepatorenal syndrome. J Hepatol 2007;46:935–946
8. Arroyo V, Terra C, Ginès P. New treatments of hepatorenal syndrome. Semin Liver Dis 2006;26:254–264
9. Arroyo V, Ginès P, Gerbes A, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. Hepatology 1996;23:164–176
10. Salerno F, Gerbes A, Ginès P, Wong F, Arroyo V. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. Gut 2007;56:1310–1318
11. Papadakis MA, Arieff AI. Unpredictability of clinical evaluation of renal function in cirrhosis: prospective study. Am J Med 1987;82:945–952
12. Caregaro L, Menon F, Angeli P, et al. Limitations of serum creatinine level and creatinine clearance as filtration markers in cirrhosis. Arch Intern Med 1994;154:201–205
13. Sherman DS, Fish DN, Teitelbaum I. Assessing renal function in cirrhotic patients: problems and pitfalls. Am J Kidney Dis 2003;41:269–278
14. Cabrera J, Arroyo V, Ballesta AM, et al. Aminoglycoside nephrotoxicity in cirrhosis: value of urinary beta-2-microglobulin to discriminate functional renal failure from acute tubular damage. Gastroenterology 1982;82:97–105
15. Dudley FJ, Kanel GC, Wood LJ, Reynolds TB. Hepatorenal syndrome without avid sodium retention. Hepatology 1986; 6:248–251
16. Fernandez J, Monteagudo J, Bargallo X, et al. A randomized unblinded pilot study comparing albumin versus hydroxyethyl starch in spontaneous bacterial peritonitis. Hepatology 2005;42:627–634
17. Terra C, Guevara M, Torre A, et al. Renal failure in patients with cirrhosis and sepsis unrelated to spontaneous bacterial peritonitis: value of MELD score. Gastroenterology 2005; 129:1944–1953
18. Fasolato S, Angeli P, Dallagnese L, et al. Renal failure and bacterial infections in patients with cirrhosis: epidemiology and clinical features. Hepatology 2007;45:223–229
19. Hampel H, Bynum GD, Zamora E, El Serag HB. Risk factors for the development of renal dysfunction in hospitalized patients with cirrhosis. Am J Gastroenterol 2001;96:2206–2210
20. Brater DC, Anderson SA, Browncartwright D, Toto RD. Effects of nonsteroidal antiinflammatory drugs on renal function in patients with renal insufficiency and in cirrhotics. Am J Kidney Dis 1986;8:351–355
21. Westphal JF, Brogard JM. Drug administration in chronic liver disease. Drug Saf 1997;17:47–73
22. Toledo C, Salmeron JM, Rimola A, et al. Spontaneous bacterial peritonitis in cirrhosis: predictive factors of infection resolution and survival in patients treated with cefotaxime. Hepatology 1993;17:251–257
23. Follo A, Llovet JM, Navasa M, et al. Renal impairment after spontaneous bacterial peritonitis in cirrhosis: incidence, clinical course, predictive factors and prognosis. Hepatology 1994;20:1495–1501
24. Navasa M, Follo A, Filella X, et al. Tumor necrosis factor and interleukin-6 in spontaneous bacterial peritonitis in cirrhosis: relationship with the development of renal impairment and mortality. Hepatology 1998;27:1227–1232
25. Rodés J, Arroyo V, Bosch J. Clinical types and drug-therapy of renal impairment in cirrhosis. Postgrad Med J 1975;51: 492–497
26. Goyal RK, Hirano I. Mechanisms of disease: the enteric nervous system. N Engl J Med 1996;334:1106–1115
27. Gupta S, Morgan TR, Gordan GS. Calcitonin gene-related peptide in hepatorenal syndrome: a possible mediator of peripheral vasodilation. J Clin Gastroenterol 1992;14:122–126
28. Bendtsen F, Schifter S, Henriksen JH. Increased circulating calcitonin gene-related peptide (CGRP) in cirrhosis. J Hepatol 1991;12:118–123
29. Martin PY, Ginès P, Schrier RW. Nitric oxide as a mediator of hemodynamic abnormalitites and sodium and water retention in cirrhosis. N Engl J Med 1998;339:533–541
30. Schrier RW, Arroyo V, Bernardi M, et al. Peripheral arterial vasodilation hypothesis: a proposal for the initiation of renal sodium and water-retention in cirrhosis. Hepatology 1988; 8:1151–1157
31. Benoit JN, Granger DN. Splanchnic hemodynamics in chronic portal hypertension. Semin Liver Dis 1986;6:287–298
32. Vorobioff J, Bredfeldt JE, Groszmann RJ. Increased blood flow through the portal system in cirrhotic rats. Gastroenterology 1984;87:1120–1126
33. Vorobioff J, Bredfeldt JE, Groszmann RJ. Hyperdynamic circulation in portal-hypertensive rat model: a primary factor for maintenance of chronic portal-hypertension. Am J Physiol 1983;244:G52–G57
34. Lee FY, Albillos A, Colombato LA, Groszmann RJ. The role of nitric-oxide in the vascular hyporesponsiveness to

methoxamine in portal hypertensive rats. Hepatology 1992; 16:1043–1048
35. Sieber CC, Lopez-Talavera JC, Groszmann RJ. Role of nitric oxide in the in vitro splanchnic vascular hyporeactivity in ascitic cirrhotic rats. Gastroenterology 1993;104:1750–1754
36. Maroto A, Ginès P, Arroyo V, et al. Brachial and femoral artery blood-flow in cirrhosis: relationship to kidney dysfunction. Hepatology 1993;17:788–793
37. Maroto A, Ginès A, Salo J, et al. Diagnosis of functional kidney failure of cirrhosis with doppler sonography: prognostic value of resistive index. Hepatology 1994;20:839–844
38. Fernandez-Seara J, Prieto J, Quiroga J, et al. Systemic and regional hemodynamics in patients with liver cirrhosis and ascites with and without functional renal failure. Gastroenterology 1989;97:1304–1312
39. Guevara M, Bru C, Ginès P, et al. Increased cerebrovascular resistance in cirrhotic patients with ascites. Hepatology 1998;28:39–44
40. Tristani FE, Cohn JN. Systemic and renal hemodynamics in oliguric hepatic failure: effect of volume expansion. J Clin Invest 1967;46:1894–1906
41. Lebrec D, Kotelanski B, Cohn JN. Splanchnic hemodynamic factors in cirrhosis with refractory ascites. J Lab Clin Med 1979;93:301–309
42. Ruiz-del-Arbol L, Urman J, Fernandez J, et al. Systemic, renal, and hepatic hemodynamic derangement in cirrhotic patients with spontaneous bacterial peritonitis. Hepatology 2003;38:1210–1218
43. Ruiz-del-Arbol L, Monescillo A, Arocena C, et al. Circulatory function and hepatorenal syndrome in cirrhosis. Hepatology 2005;42:439–447
44. Schroeder ET, Eich RH, Smulyan H, Gould AB, Gabuzda GJ. Plasma renin level in hepatic cirrhosis: relation to functional renal failure. Am J Med 1970;49:186–191
45. Henriksen JH, Ring-Larsen H. Hepatorenal disorders: role of the sympathetic nervous system. Semin Liver Dis 1994;14:35–43
46. Arroyo V, Planas R, Gaya J, et al. Sympathetic nervous activity, renin-angiotensin system and renal excretion of prostaglandin-e2 in cirrhosis: relationship to functional renal failure and sodium and water excretion. Eur J Clin Invest 1983;13:271–278
47. Rimola A, Ginès P, Arroyo V, et al. Urinary excretion of 6-keto-prostaglandin F1 alpha, thromboxane B2 and prostaglandin E2 in cirrhosis with ascites: relationship to functional renal failure (hepatorenal syndrome). J Hepatol 1986;3:111–117
48. Moore KP. Arachidonic acid metabolites and the kidney in cirrhosis. In: Arroyo V, Ginès P, Rodés J, Schrier RW, eds. Ascites and Renal Dysfunction in Liver Disease: Pathogenesis, Diagnosis, and Treatment. Malden: Blackwell Science; 1999:249–272
49. Angeli P, Albino G, Carraro P, et al. Cirrhosis and muscle cramps: evidence of a causal relationship. Hepatology 1996;23: 264–273
50. Ma Z, Lee SS. Cirrhotic cardiomyopathy: getting to the heart of the matter. Hepatology 1996;24:451–459
51. Braverman AC, Steiner MA, Picus D, White H. High-output congestive heart failure following transjugular intrahepatic portal-systemic shunting. Chest 1995;107:1467–1469
52. Ginès P, Uriz J, Calahorra B, et al. Transjugular intrahepatic portosystemic shunting versus paracentesis plus albumin for refractory ascites in cirrhosis. Gastroenterology 2002;123: 1839–1847
53. Myers RP, Lee SS. Cirrhotic cardiomyopathy and liver transplantation. Liver Transpl 2000;6:S44–S52
54. Therapondos G, Flapan AD, Plevris JN, Hayes PC. Cardiac morbidity and mortality related to orthotopic liver transplantation. Liver Transpl 2004;10:1441–1453
55. Lee SS. Cardiac dysfunction in spontaneous bacterial peritonitis: a manifestation of cirrhotic cardiomyopathy? Hepatology 2003;38:1089–1091
56. Sort P, Navasa M, Arroyo V, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. N Engl J Med 1999;341:403–409
57. Wiest R, Groszmann RJ. Nitric oxide and portal hypertension: its role in the regulation of intrahepatic and splanchnic vascular resistance. Semin Liver Dis 1999;19: 411–426
58. Tsai MH, Peng YS, Chen YC, et al. Adrenal insufficiency in patients with cirrhosis, severe sepsis and septic shock. Hepatology 2006;43:673–681
59. Fernandez J, Escorsell A, Zabalza M, et al. Adrenal insufficiency in patients with cirrhosis and septic shock: effect of treatment with hydrocortisone on survival. Hepatology 2006;44:1288–1295
60. Gonwa TA, Morris CA, Goldstein RM, Husberg BS, Klintmalm GB. Long-term survival and renal function following liver transplantation in patients with and without hepatorenal syndrome: experience in 300 patients. Transplantation 1991;51:428–430
61. Gonwa TA, Klintmalm GB, Levy M, et al. Impact of pretransplant renal function on survival after liver transplantation. Transplantation 1995;59:361–365
62. Seu P, Wilkinson AH, Shaked A, Busuttil RW. The hepatorenal syndrome in liver transplant recipients. Am Surg 1991;57:806–809
63. Rimola A, Gavaler JS, Schade RR, el-Lankany S, Starzl TE, Van Thiel DH. Effects of renal impairment on liver transplantation. Gastroenterology 1987;93:148–156
64. Guevara M, Ginès P, Fernandez-Esparrach G, et al. Reversibility of hepatorenal syndrome by prolonged administration of ornipressin and plasma volume expansion. Hepatology 1998;27:35–41
65. Gulberg V, Bilzer M, Gerbes AL. Long-term therapy and retreatment of hepatorenal syndrome type 1 with ornipressin and dopamine. Hepatology 1999;30:870–875
66. Angeli P, Volpin R, Gerunda G, et al. Reversal of type 1 hepatorenal syndrome with the administration of midodrine and octreotide. Hepatology 1999;29:1690–1697
67. Uriz J, Ginès P, Cardenas A, et al. Terlipressin plus albumin infusion: an effective and safe therapy of hepatorenal syndrome. J Hepatol 2000;33:43–48
68. Mulkay JP, Louis H, Donckier V, et al. Long-term terlipressin administration improves renal function in cirrhotic patients with type 1 hepatorenal syndrome: a pilot study. Acta Gastroenterol Belg 2001;64:15–19
69. Colle I, Durand F, Pessione F, et al. Clinical course, predictive factors and prognosis in patients with cirrhosis and type 1 hepatorenal syndrome treated with terlipressin: a retrospective analysis. J Gastroenterol Hepatol 2002;17:882–888
70. Halimi C, Bonnard P, Bernard B, et al. Effect of terlipressin (Glypressin (R)) on hepatorenal syndrome in cirrhotic

patients: results of a multicentre pilot study. Eur J Gastroenterol Hepatol 2002;14:153–158
71. Ortega R, Ginès P, Uriz J, et al. Terlipressin therapy with and without albumin for patients with hepatorenal syndrome: results of a prospective, nonrandomized study. Hepatology 2002;36:941–948
72. Duvoux C, Zanditenas D, Hezode C, et al. Effects of noradrenalin and albumin in patients with type I hepatorenal syndrome: a pilot study. Hepatology 2002;36:374–380
73. Solanki P, Chawla A, Garg R, et al. Beneficial effects of terlipressin in hepatorenal syndrome: a prospective, randomized placebo-controlled clinical trial. J Gastroenterol Hepatol 2003;18:152–156
74. Wong F, Pantea L, Sniderman K. Midodrine, octreotide, albumin, and TIPS in selected patients with cirrhosis and type 1 hepatorenal syndrome. Hepatology 2004;40:55–64
75. Alessandria C, Ottobrelli A, Debernardi-Venon W, et al. Noradrenalin vs terlipressin in patients with hepatorenal syndrome: a prospective, randomized, unblinded, pilot study. J Hepatol 2007;47:499–505
76. Linas SL, Schaefer JW, Moore EE, Good JT, Giansiracusa R. Peritoneovenous shunt in the management of the hepatorenal syndrome. Kidney Int 1986;30:736–740
77. Pomier-Layrargues G, Paquin SC, Hassoun Z, Lafortune M, Tran A. Octreotide in hepatorenal syndrome: a randomized, double-blind, placebo-controlled, crossover study. Hepatology 2003;38:238–243
78. Moreau R, Durand F, Poynard T, et al. Terlipressin in patients with cirrhosis and type-1 hepatorenal syndrome: a retrospective multicenter study. Gastroenterology 2002;122:923–930
79. Fernandez J, Navasa M, Garcia-Pagan JC, et al. Effect of intravenous albumin on systemic and hepatic hemodynamics and vasoactive neurohormonal systems in patients with cirrhosis and spontaneous bacterial peritonitis. J Hepatol 2004;41:384–390
80. Brensing KA, Textor J, Perz J, et al. Long-term outcome after transjugular intrahepatic portosystemic stent-shunt in non-transplant cirrhotics with hepatorenal syndrome: a phase II study. Gut 2000;47:288–295
81. Guevara M, Ginès P, Bandi JC, et al. Transjugular intrahepatic portosystemic shunt in hepatorenal syndrome: effects on renal function and vasoactive systems. Hepatology 1998;28:416–422
82. Mitzner SR, Stange J, Klammt S, et al. Improvement of hepatorenal syndrome with extracorporeal albumin dialysis MARS: results of a prospective, randomized, controlled clinical trial. Liver Transpl 2000;6:277–286
83. Catalina MV, Barrio J, Anaya F, et al. Hepatic and systemic haemodynamic changes after MARS in patients with acute on chronic liver failure. Liver Int 2003;23:39–43
84. Jalan R, Sen S, Steiner C, et al. Extracorporeal liver support with molecular adsorbents recirculating system in patients with severe acute alcoholic hepatitis. J Hepatol 2003;38:24–31
85. Stange I, Hassanein TI, Mehta R, et al. Short-term survival of patients with severe intractable hepatic encephalopathy: the role of albumin dialysis. Hepatology 2005;42:286A
86. Lebrec D, Giuily N, Hadengue A, et al. Transjugular intrahepatic portosystemic shunts—comparison with paracentesis in patients with cirrhosis and refractory ascites: a randomized trial. J Hepatol 1996;25:135–144
87. Rossle M, Ochs A, Gulberg V, et al. A comparison of paracentesis and transjugular intrahepatic portosystemic shunting in patients with ascites. N Engl J Med 2000;342:1701–1707
88. Sanyal AJ, Genning C, Reddy KR, et al. The North American Study for the Treatment of Refractory Ascites. Gastroenterology 2003;124:634–641
89. Salerno F, Merli M, Riggio O, et al. Randomized controlled study of TIPS versus paracentesis plus albumin in cirrhosis with severe ascites. Hepatology 2004;40:629–635
90. Alessandria C, Venon WD, Marzano A, et al. Renal failure in cirrhotic patients: role of terlipressin in clinical approach to hepatorenal syndrome type 2. Eur J Gastroenterol Hepatol 2002;14:1363–1368
91. Fernandez J, Navasa M, Planas R, et al. Primary prophylaxis of spontaneous bacterial peritonitis delays hepatorenal syndrome and improves survival in cirrhosis. Gastroenterology 2007;133:818–824
92. Albillos A, de la Hera A, Gonzalez M, et al. Increased lipopolysaccharide binding protein in cirrhotic patients with marked immune and hemodynamic derangement. Hepatology 2003;37:208–217
93. Frances R, Benlloch S, Zapater P, et al. A sequential study of serum bacterial DNA in patients with advanced cirrhosis and ascites. Hepatology 2004;39:484–491
94. Rasaratnam B, Kaye D, Jennings G, Dudley F, Chin-Dusting J. The effect of selective intestinal decontamination on the hyperdynamic circulatory state in cirrhosis: a randomized trial. Ann Intern Med 2003;139:186–193
95. Akriviadis E, Botla R, Briggs W, et al. Pentoxifylline improves short-term survival in severe acute alcoholic hepatitis: a double-blind, placebo-controlled trial. Gastroenterology 2000;119:1637–1648