

New Treatments of Hepatorenal Syndrome

Vicente Arroyo, M.D.,¹ Carlos Terra, M.D.,¹ and Pere Ginès, M.D.¹

ABSTRACT

Hepatorenal syndrome (HRS) is a common complication of advanced cirrhosis, characterized by renal failure and major abnormalities in the systemic circulatory function. Renal failure is caused by intense vasoconstriction of the renal circulation. The syndrome is probably the final consequence of an extreme underfilling of the arterial circulation, secondary to vasodilatation in the splanchnic vascular bed and a decrease in cardiac output due to central hypovolemia. The diagnosis of HRS is based on the exclusion of other causes of renal failure. The survival of patients with HRS is very short, particularly when there is rapidly progressive renal failure (type-1 HRS). Liver transplantation is the best therapeutic option but its applicability is low. During the past few years effective treatment for HRS, such as vasoconstrictor drugs (vasopressin analogues, α -adrenergic agonists) associated with intravenous albumin infusion and transjugular intrahepatic portosystemic shunts (TIPS), have been introduced. They improve circulatory function, normalize serum creatinine, and may improve survival. Sequential treatment with vasoconstrictors plus albumin and TIPS is an attractive therapeutic possibility. Plasma volume expansion with albumin at infection diagnosis in patients with spontaneous bacterial peritonitis and the administration of pentoxiphiline in patients with severe alcoholic hepatitis significantly reduce the development of type-1 HRS.

KEYWORDS: Renal failure, cirrhosis, portal hypertension, circulatory dysfunction

Hepatorenal syndrome (HRS) is a common complication in patients with advanced cirrhosis. It is characterized by renal vasoconstriction and very low renal perfusion and glomerular filtration rate (GRF)^{1,2} in the absence of significant histological renal lesions sufficient to justify the impairment in renal function. HRS is the extreme expression of the circulatory dysfunction of cirrhosis, and patients present arterial hypotension and intense stimulation of the renin-angiotensin and sympathetic nervous system and antidiuretic hormone. Circulatory dysfunction in cirrhosis has been classically considered to be the consequence of an arterial vasodilation in the splanchnic circulation. However, more recent data suggest that a reduction in cardiac function may also play a significant role. The annual incidence of HRS in patients with cirrhosis and ascites

has been estimated as 8%.³ HRS is the complication of cirrhosis associated with the worst prognosis, and, for many years, it has been considered a terminal event of the disease. However, as a consequence of the introduction of effective treatments of HRS, survival has improved, and a significant number of patients may now benefit from liver transplantation.

DIAGNOSIS AND CLINICAL TYPES OF HEPATORENAL SYNDROME

Diagnosis

There is consensus that the diagnosis of HRS is established when serum creatinine has risen above 1.5 mg/dL

¹Liver Unit, Institut of Digestive and Metabolic Diseases, Hospital Clinic, University of Barcelona, Spain.

Address for correspondence and reprint requests: Vicente Arroyo, M.D., c/ Villarroel 170, Liver Unit, Institut of Digestive and Metabolic Diseases, Hospital Clinic, University of Barcelona, Barcelona 08036, Spain.

Immunosuppression, Organ Allocation, and Other Issues in Liver Transplantation; Guest Editor, Marion Peters, M.D.

Semin Liver Dis 2006;26:254–264. Copyright © 2006 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA. Tel: +1(212) 584-4662.

DOI 10.1055/s-2006-947293. ISSN 0272-8087.

Table 1 International Ascites Club's Diagnostic Criteria for Hepatorenal Syndrome

Major criteria

- Chronic or acute liver disease with advanced hepatic failure and portal hypertension
- Low glomerular filtration rate, as indicated by serum creatinine > 1.5 mg/dL or 24-hour 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/dL 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

Reprinted with permission from Arroyo et al.⁴

or creatinine clearance has decreased to less than 40 mL/min⁴ (Table 1). For many years the diagnosis was based on traditional parameters used to diagnose functional renal failure (oliguria, low urine sodium concentration, urine-to-plasma osmolality ratio greater than unity, normal fresh urine sediment, and no proteinuria). However, acute tubular necrosis in patients with cirrhosis and ascites is usually characterized by oliguria, low urine sodium concentration, and urine osmolality greater than plasma osmolality.⁵ In contrast, a relatively high urinary sodium concentration has been observed in some patients with HRS.⁶

Because of this lack of specific tests, the diagnosis of HRS should be based on the exclusion of other disorders that can cause renal failure in cirrhosis.⁴ Acute renal failure of prerenal origin related 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. The presence of shock before the onset of renal failure points toward a diagnosis of acute tubular necrosis. Cirrhotic patients with infections may develop transient renal failure, which resolves after resolution of the infection. Therefore, HRS in cirrhotic patients with bacterial infections should be diagnosed in patients without septic shock and only if renal failure persists following infection resolution. Cir-

rotic patients are predisposed to develop renal failure in the setting of treatments with aminoglycosides,⁷ nonsteroidal anti-inflammatory drugs,⁸ and vasodilators (renin-angiotensin system inhibitors, prazosin, nitrates).⁹ 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 related to intrinsic renal diseases, particularly glomerulonephritis. These cases can be recognized by the presence of proteinuria, hematuria, or both.

Clinical Types

There are two types of HRS.⁴ Type 1 HRS is characterized by 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, gastrointestinal hemorrhage, major surgical procedure, or acute hepatitis superimposed on cirrhosis. Besides renal failure, patients with type 1 HRS after spontaneous bacterial peritonitis (SBP) show signs and symptoms of severe liver insufficiency (jaundice, coagulopathy, and hepatic encephalopathy) and circulatory dysfunction (arterial hypotension, very high plasma levels of renin and norepinephrine) that worsen with the impairment in renal function.^{10,11} 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.³

Type 2 HRS is characterized by a moderate and steady decrease in renal function. Patients with type 2 HRS show signs of liver failure and arterial hypotension but to a lesser degree than patients with type 1 HRS. The dominant feature is refractory ascites. Patients with type 2 HRS are predisposed to develop type 1 HRS following infections or other precipitating events.¹⁰⁻¹² Median survival of patients with type 2 HRS (6 months) is worse than that of patients with nonazotemic cirrhosis with ascites¹³ (Fig. 1).

FACTORS ASSOCIATED WITH HEPATORENAL SYNDROME**Peripheral Arterial Vasodilation**

Portal hypertension in cirrhosis is associated with arterial vasodilation in the splanchnic circulation related to the local release of vasodilatory substances (nitric oxide, calcitonin gene-related peptide, substance P, carbon monoxide, and endogenous cannabinoids).¹⁴⁻¹⁹ Early in the course of the disease, this decrease in systemic vascular resistance is compensated by a hyperdynamic circulation (increased heart rate and cardiac output).²⁰⁻²²

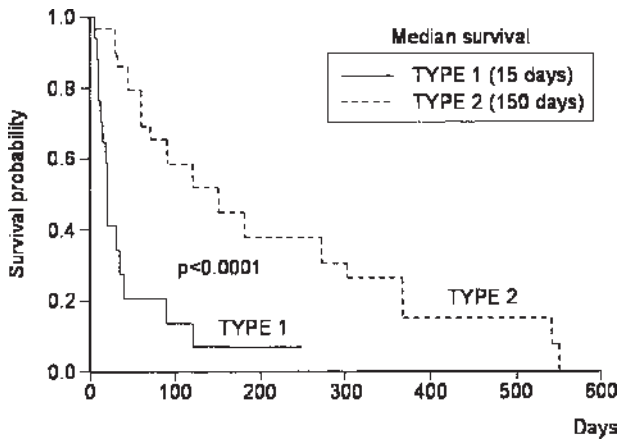


Figure 1 Survival of patients with cirrhosis after the diagnosis of type 1 or type 2 HRS. (Reprinted from Ginès P, Guevara M, Arroyo V, Rodes J. Hepatorenal syndrome. *Lancet* 2003;362:1819–1827, with permission from Elsevier.)

However, as the disease progresses and arterial vasodilation increases, this is insufficient to correct the effective arterial hypovolemia.²³ Arterial hypotension develops, leading to stimulation of the renin-angiotensin and sympathetic nervous systems, sodium and water retention, and ascites formation. The stimulation of antidiuretic hormone occurs later in the course of the disease. Patients then develop 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. As the splanchnic arterial circulation is resistant to the effect of these endogenous vasoconstrictors because of the local release of vasodilators,^{24,25} the maintenance of arterial pressure is due to the vasoconstrictor effect of angiotensin II, noradrenaline, and vasopressin in extra-splanchnic vascular territories such as the kidneys, muscle, skin, and brain.^{26–29} HRS develops at the latest phase of the disease when there is 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 consequent marked decrease in renal perfusion and GFR.

Reduction in Cardiac Output

Most hemodynamic studies in cirrhosis have been performed in nonazotemic patients with and without ascites, but their findings have been extended to the entire population with decompensated cirrhosis. On the basis of these data, it has been assumed that HRS is the extreme expression of the arterial vasodilation present in these patients. However, in the few studies assessing cardiovascular function in patients with HRS or refrac-

tory ascites, cardiac output was found to be significantly reduced compared with that in patients without HRS.^{30,31} 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 feature.^{32,33}

In the first study,³² systemic and hepatic hemodynamics were measured in 23 patients with SBP at infection diagnosis and following 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 not detected because of the vascular effect of angiotensin II and noradrenaline. 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 who did not develop renal failure. 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.

The second study³³ was a longitudinal study of 66 nonazotemic cirrhotic patients with cirrhosis and tense ascites. Forty percent of patients developed HRS. These patients were studied at inclusion and following the development of HRS. In the initial study, the patients who went on to develop HRS had significantly lower mean arterial pressure and cardiac output and than compared with those who did not develop HRS. Moreover, those who developed HRS had a further decrease in arterial pressure and cardiac output and increase in renin and norepinephrine without changes in peripheral vascular resistance (Table 2). These findings are in agreement with the previous study and support the concept that HRS occurs in the setting of worsening of arterial vasodilation and decrease in cardiac output. In this study, basal increased plasma renin activity and reduced cardiac output were found to be the only independent predictors of survival.

Regional Hemodynamics and Multiorgan Failure Associated with HRS

For many years, patients with HRS were considered to have two major problems. The first was a terminal and irreversible liver failure related to an advanced cirrhosis. The second was a functional renal failure secondary to a systemic circulatory dysfunction. During the past

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

	NA-1	NA-2	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.h)*	221 ± 256	412 ± 155	628 ± 320
Systemic vascular resistance (dyn.s/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

NA-1, baseline measurement in nonazotemic cirrhotic patients who did not develop hepatorenal syndrome during follow-up; NA-2, baseline measurement in nonazotemic cirrhotic patients who developed type 2 hepatorenal syndrome during follow-up; type 2 HRS, measurement obtained in NA-2 patients after development of type 2 hepatorenal syndrome.

* $p < 0.01$.

Reprinted with permission from Ruiz-del-Arbol et al.³³

decade, however, increasing evidence suggests that HRS is an extremely complex syndrome affecting organs other than the liver and the kidney. Moreover, data have been presented indicating that circulatory dysfunction associated with HRS affects not only the intrarenal circulation but also the intrahepatic circulation and that this may contribute to the severity of hepatic failure in HRS. Liver failure in HRS could, therefore, be potentially reversible if circulatory dysfunction is improved.

RENAL DYSFUNCTION

The mechanism of the renal vasoconstriction that causes HRS is complex. Because renal perfusion in decompensated cirrhosis correlates inversely with the activity of the renin-angiotensin and sympathetic nervous systems,^{27,28,34-37} HRS is thought to be related to extreme stimulation of these systems. The urinary excretion of prostaglandin E₂, 6-keto-prostaglandin F_{1α} (a prostacyclin metabolite), and kallikrein is decreased in patients with HRS, which is compatible with reduced renal production of these vasodilatory substances.^{38,39} 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. Finally, renal hypoperfusion in HRS could also be amplified by the stimulation of intrarenal vasoconstrictors. For example, renal ischemia increases the generation of angiotensin II by the juxtaglomerular apparatus; the production of adenosine, which, in addition of being a renal vasoconstrictor, potentiates the vascular effect of angiotensin II; and the synthesis of endothelin. Other intrarenal vasoconstrictors that have been implicated in HRS are leukotrienes and F₂-isoprostanines.⁴⁰ Renal vasoconstriction in HRS is, therefore, the consequence of the simultaneous effect of numerous vasoactive mechanisms on the intrarenal circulation. Sodium retention in patients with type 2 HRS is due to decreased filtered sodium and increased sodium reabsorption in the proximal tubule. The amount of sodium reaching the loop of Henle and distal nephron, the sites of action of furosemide and spironolactone,

respectively, is very low. The delivery of furosemide and spironolactone to the renal tubules is also reduced because of the renal hypoperfusion. It is, therefore, not surprising that patients with type 2 HRS respond poorly to diuretics.⁴¹

THE CUTANEOUS, MUSCULAR, AND CEREBRAL BLOOD FLOWS 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.²⁸ The resistive index in the mean cerebral artery is also increased in these patients, indicating cerebral vasoconstriction.²⁹ 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.

Hepatic encephalopathy is common in patients with type 1 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 seen in these patients. Cerebral vasoconstriction, however, could be an additional factor.

CARDIAC DYSFUNCTION

The physiological response consists of a homeostatic activation of the renin-angiotensin and sympathetic nervous systems. Angiotensin II and the sympathetic nervous activity produce arterial vasoconstriction and increase the systemic vascular resistance. On the other hand, they 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 increase in the plasma levels of renin and norepinephrine. The activation of these systems produces vasoconstriction in the extrasplanchnic

organs and maintains arterial pressure.^{28,29} However, the cardiac response is abnormal. 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.³³ These data, therefore, indicate a significant 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. The heart rate remains unchanged despite a dramatic activation of the renin-angiotensin and sympathetic nervous systems.³³ Not surprisingly, the syndrome is associated with an intense reduction of arterial pressure and marked vasoconstriction in the extrasplanchnic organs.

The pathogenesis of the impaired cardiac response to arterial vasodilation in HRS is unknown. A specific cardiomyopathy characterized by attenuated systolic and diastolic contractile responses to stress stimuli, electrophysiological repolarization changes, and enlargement and hypertrophy of cardiac chambers is common in patients with advanced cirrhosis.⁴² However, several features suggest that the decreased cardiac output in HRS is more related to a functional than to an organic cardiomyopathy. First, the reduced cardiac output in patients with type 1 HRS occurs in the setting of a decreased in cardiopulmonary pressures, which is compatible with a low cardiac preload. Second, circulatory dysfunction in HRS can be reverted by the intravenous (IV) administration of albumin associated with vasoconstrictors or after the insertion of a transjugular intrahepatic portacaval shunt (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.⁴³

CHANGES IN THE INTRAHEPATIC CIRCULATION ASSOCIATED WITH HRS

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. In patients with cirrhosis, the vasoconstrictor effect of these substances in the hepatic circulation is increased because of reduced synthesis of nitric oxide.⁴⁴ It is, therefore, not surprising that the stimulation of the endogenous vasoactive systems in HRS is associated with worsening of portal hypertension and a marked reduction in hepatic blood flow.^{32,33}

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.

ADRENAL DYSFUNCTION

Adrenal dysfunction is a common problem in patients with acute liver failure and in patients with cirrhosis and acute or chronic liver failure secondary to severe sepsis.^{45,46} In patients with cirrhosis, adrenal insufficiency was detected in 80% of patients with HRS but in only 34% with serum creatinine below 1.5 mg/dL. A close relationship, therefore, exists between adrenal insufficiency and HRS in patients with severe infection. Other features associated with adrenal insufficiency were severe liver failure, arterial hypotension, and vasopressor dependence. Because normal adrenal function is essential for an adequate response of the arterial circulation to endogenous vasoconstrictors, adrenal insufficiency could be an important mechanism of circulatory dysfunction associated with HRS in patients with severe bacterial infections.

PATHOGENESIS OF TYPE 1 AND TYPE 2 HEPATORENAL SYNDROME

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 develops spontaneously up to the last phases of the disease (Fig. 2). In contrast, type 1 HRS appears to be more like the 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, with relative adrenal insufficiency, are common in patients with type 1 HRS but rare in patients with type 2 HRS (Fig. 3).

TREATMENT OF TYPE 1 HEPATORENAL SYNDROME AND STRATEGIES FOR FUTURE STUDIES

Most data currently available on the treatment of HRS derive from retrospective studies or prospective

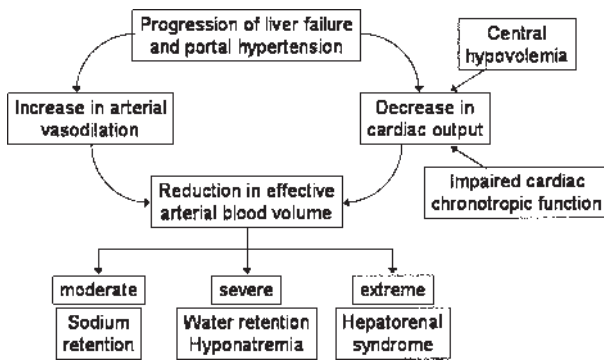


Figure 2 Mechanism of renal dysfunction in type 2 HRS.

comparative pilot investigations including very few patients. Therefore, at present the efficacy of treatment of HRS is based on weak data.

Liver Transplantation

Liver transplantation is the treatment of choice of HRS.^{47–51} Immediately after transplantation, a further impairment in GFR may be observed and many patients require hemodialysis (35% of patients with HRS compared with 5% of patients without HRS).⁴⁷ 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 the 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 in-

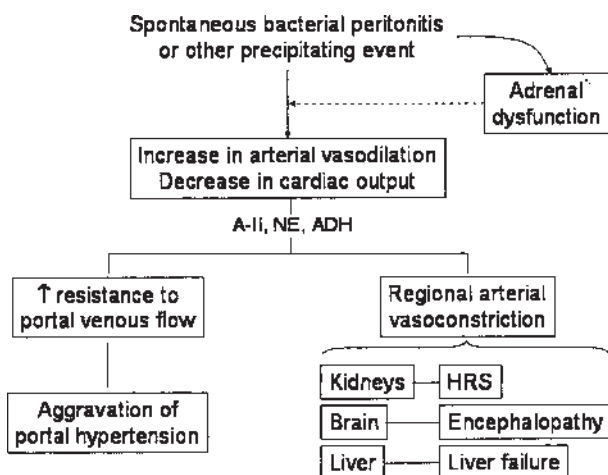


Figure 3 Type 1 HRS as a part of multiorgan failure. A-II, angiotensin II; NE, norepinephrine; ADH, antidiuretic hormone.

tensive 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 slightly reduced compared with that of transplantation in patients without HRS (which ranges between 70 and 80%).⁴⁹

The main problem of liver transplantation in type 1 HRS is its applicability. Because of their extremely short survival, most patients die before transplantation. The introduction of the model for end-stage liver disease (MELD) score, which includes serum creatinine, bilirubin, and the international normalized ratio, for listing has partially solved the problem because patients with HRS are allocated higher places on the waiting list.

Other Effective Treatments

VASOCONSTRICTORS AND ALBUMIN

The IV administration of vasoconstrictor agents (vasopressin, ornipressin, terlipressin, noradrenaline) or the combination of oral midodrine (an α -agonistic agent) and IV or subcutaneous octreotide during 1 to 3 weeks is an effective treatment for type 1 HRS. Eleven pilot studies including 154 patients with HRS (132 with type 1 HRS) have been published on this topic.^{52–62} In most patients IV albumin was also given. The overall positive response rate was 61.6% (95 patients). In eight of these studies (including 128 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 79 patients (61.7%). A second important observation was that type 1 HRS does not recur in most patients after discontinuation of the treatment. Five studies including 65 patients have reported data on this feature. Forty-four patients responded to therapy and HRS recurred in only nine. These findings contrast sharply with those of seven studies involving patients with type 1 HRS not receiving specific treatment or treated with plasma volume expansion alone or associated with vasodilators (dopamine) or octreotide or with peritoneovenous shunting.^{11,12,43,54,61,63,64} Reversal of HRS was observed in only 4 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. The corresponding figures for 65 patients receiving other treatments were 2 (3%) and 0 (0%), respectively. Nineteen patients treated with vasoconstrictors reached liver transplantation.

A survey of 99 patients with type 1 HRS admitted to 22 hospitals in France and treated with terlipressin (all

Table 3 Treatment of Hepatorenal Syndrome (HRS) with Vasoconstrictors and Albumin (Group 1) and Standard Medical Therapy (Group 2): Review of 18 Studies

	Group 1 (n = 154)	Group 2 (n = 137)	MCFS* (n = 99)
Reversal of HRS [†]	61.7%	2.9%	58%
HRS recurrence	20%	—	—
Survival 1 month	41.6%	3%	40%
Survival 3 months	30%	0%	22%
Liver transplantation	12.3%	—	13%

*Multicenter French Study using terlipressin plus albumin.

[†]Decrease of serum creatinine to less than 1.5 mg/dL.

cases) and albumin (70% of cases) showed improvement in renal function in 58%.⁶⁵ 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 obtained in the pilot studies previously described (Table 3).

These studies clearly indicate that vasoconstrictors associated with IV albumin should be recommended for the management of patients with type 1 HRS because they normalize serum creatinine in a high proportion of patients and may improve survival.

Ornipressin was the first vasoconstrictor used. It is very effective but is associated with high rate of ischemic side effects. Terlipressin has been the most widely used vasoconstrictor agent in type 1 HRS. It is also very effective with few side effects. The efficacy of the association of oral midodrine and IV or subcutaneous octreotide is probably due exclusively to the vasoconstrictor effect of midodrine.⁶⁴ Noradrenaline has also been shown to be effective and safe. However, whereas there is a large experience with terlipressin, noradrenaline and midodrine have been used in only a 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 of 28 patients, 25%)^{57,59} was lower than that in the studies in which vasoconstrictors were associated with IV albumin, suggesting that the albumin is an important component in the pharmacological treatment of type 1 HRS. Two recent studies^{66,67} 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 should, therefore, be given together with albumin in the initial studies.

Terlipressin dosage should be progressive, starting with 0.5 mg every 4 hours. 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 a 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 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).

Potentially Effective Treatments

TRANSJUGULAR INTRAHEPATIC PORTACAVAL SHUNT

Three pilot studies have evaluated TIPS in type 1 HRS.^{62,68,69} In the first study,⁶⁸ 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. Patients with bilirubin greater than 15 mg/dL, Child-Pugh score above 12, or hepatic encephalopathy were excluded. Eleven 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 study⁶⁹ was performed in seven patients (4 alcoholics) with type 1 HRS and a Child-Pugh score less than 12. A marked decrease in serum creatinine was observed in six patients and reversal of HRS in four. Five patients developed episodes of hepatic encephalopathy after TIPS but responded satisfactorily to medical treatment. Five patients were alive after 1 month of TIPS but only two after 3 months. The third study⁶² 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 achieved in 10 patients. TIPS was subsequently inserted in 5 of these 10 patients who had bilirubin less than 5 mg/dL, international normalized ratio less than 2, and Child-Pugh score less than 12. Normalization of GFR was obtained in all cases, and they were alive between 6 to 30 months after TIPS.

The extremely poor prognosis of patients with type 1 HRS raises questions about the use of many

potentially effective treatments, including TIPS. Up to now, very few patients have been treated by TIPS and most of them had alcoholic cirrhosis. More studies are, therefore, needed. At present, TIPS could be used as a treatment of type 1 HRS only in the setting of prospective studies or randomized controlled trials. Covered stents should be preferred because they are associated with lower rate of shunt dysfunction.

MOLECULAR ADSORBENT RECIRCULATING SYSTEM

(MARS)

Three pilot studies including 29 patients (26 with type 1 HRS and 21 with alcoholic cirrhosis or severe acute alcoholic hepatitis or both) aimed at assessing the molecular adsorbent recirculating system (MARS) in patients with type 1 HRS have been reported.⁷⁰⁻⁷² Because MARS incorporates a standard dialysis machine or a continuous venovenous hemofiltration monitor and GFR was not measured, it is not possible to know the effect of this treatment in 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 randomized controlled trial in a large series of cirrhotic patients with hepatic encephalopathy,⁷³ many of them with HRS, demonstrated a clear beneficial effect of MARS on the rate and time of recovery of encephalopathy. Because the endpoint of this trial was encephalopathy, no conclusion could be reached in relation to survival.

As indicated previously, the extremely poor prognosis associated with type 1 HRS does not justify the use of therapies with unproven beneficial effects. The use of MARS in patients with type 1 HRS, therefore, cannot be recommended outside prospective pathophysiological or therapeutic studies.

TREATMENT OF TYPE 2 HRS

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

Effective Treatments

TIPS

There are only two pilot studies specifically assessing TIPS in type 2 HRS.^{68,74} In one study⁷⁴ a significant improvement of serum creatinine (from 2.1 ± 0.3 to 1.4 ± 0.3 1 month after TIPS) was observed in eight 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.⁶⁸ 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 well as an improvement in the control of ascites in 24 cases. Six patients 1-year probability of survival in the 17 patients with type 2 HRS treated by TIPS was 70%. More studies are clearly needed before advising the use of TIPS in patients with type 2 HRS.

Potentially Effective Treatments

VASOCONSTRICTORS AND ALBUMIN

Three pilot studies provided data on the effect of terlipressin plus albumin in 26 patients with type 2 HRS.^{55,59,74} Reversal of HRS was obtained in most cases (21 cases, 80%). In one of these studies⁷⁴ of 11 patients, the course of renal function after stopping treatment was assessed, and HRS recurred in all cases. There were no data on survival.

The current state of knowledge on vasoconstrictor therapy in type 2 HRS is therefore very poor.

PREVENTION OF HEPATORENAL SYNDROME

Two randomized controlled studies in large series of patients have shown that HRS can be prevented in specific clinical settings. In the first study,⁴³ the administration of albumin (1.5 g/kg IV at infection diagnosis and 1 g/kg IV 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). The hospital mortality rate (10% versus 29%) and the 3-month mortality rate (22% versus 41%) were lower in patients receiving albumin. In a second study,⁷⁵ administration of the tumor necrosis factor inhibitor pentoxifylline (400 mg three times a day) to patients with severe acute alcoholic hepatitis reduced the occurrence of HRS (8% in the pentoxifylline 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.

SUMMARY

HRS is a common complication of advanced cirrhosis, characterized by renal failure and major abnormalities in the systemic circulatory function. Renal failure is caused by intense vasoconstriction of the renal circulation. The syndrome is probably the final consequence of an extreme underfilling of the arterial circulation secondary to vasodilatation in the splanchnic vascular bed and a decrease in cardiac output related to central hypovolemia. The diagnosis of HRS is based on the exclusion of other causes of renal failure. The survival of patients with HRS is very short, particularly when there is rapidly progressive renal failure (type 1 HRS). Liver transplantation is the best therapeutic option but its applicability is low. During the past few years, effective treatments for HRS, such as vasoconstrictor drugs (vasopressin analogues, α -adrenergic agonists) associated with IV albumin infusion and TIPS, have been introduced. They improve circulatory function, normalize serum creatinine, and may improve survival. Sequential treatment with vasoconstrictors plus albumin and TIPS is an attractive therapeutic possibility. Plasma volume expansion with albumin at infection diagnosis in patients with SBP and the administration of pentoxifylline in patients with severe alcoholic hepatitis significantly reduce the development of type 1 HRS

ACKNOWLEDGMENTS

This study was supported in part by grants from Instituto de Salud Carlos III (C03/2). Dr. Carlos Terra was supported by a fellowship grant from Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES).

ABBREVIATIONS

GFR	glomerular filtration rate
HRS	hepatorenal syndrome
MARS	molecular adsorbent recirculating system
SBP	spontaneous bacterial peritonitis
TIPS	transjugular intrahepatic portacaval shunt

REFERENCES

- 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, MA: Blackwell Science; 1999:36–62
- Hecker R, Sherlock S. Electrolyte and circulatory changes in terminal liver failure. *Lancet* 1956;271:1121–1125
- 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
- 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
- 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
- Dudley FJ, Kanel GC, Wood LJ, Reynolds TB. Hepatorenal syndrome without avid sodium retention. *Hepatology* 1986; 6:248–251
- 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
- Brater DC, Anderson SA, Brown-Cartwright 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
- Westphal JF, Brogard JM. Drug administration in chronic liver disease. *Drug Saf* 1997;17:47–73
- Toledo C, Salmerón 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
- Follo A, Llovet JM, Navasa M, et al. Renal impairment following spontaneous bacterial peritonitis in cirrhosis: incidence, clinical course, predictive factors and prognosis. *Hepatology* 1994;20:1495–1501
- 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
- Rodés J, Arroyo V, Bosch J. Clinical types and drug therapy of renal impairment in cirrhosis. *Postgrad Med J* 1975;51:492–497
- Goyal RK, Irano I. The enteric nervous system. *N Engl J Med* 1996;334:1106–1115
- Gupta S, Morgan TR, Gordan GS. Calcitonin-gene related peptide in hepatorenal syndrome. *J Clin Gastroenterol* 1992; 14:122–126
- Bendtsen F, Schifter S, Henriksen JH. Increased circulation calcitonin-gene related peptide (CGRP) in cirrhosis. *J Hepatol* 1991;12:118–123
- McNicol PL, Liu G, Shulkes A, Hardy KJ, Jones RM. Vasoactive intestinal peptide and calcitonin-gene related peptide and hemodynamics during human liver transplantation. *Transplant Proc* 1993;25:1830–1831
- Moller S, Bendtsen F, Schifter S, Henriksen JH. Relation of calcitonin gene-related peptide to systemic vasodilation and central hypovolaemia in cirrhosis. *Scand J Gastroenterol* 1996;31:928–933
- Hori N, Okanoue T, Sawa Y, Kashima K. Role of calcitonin gene-related peptide in the vascular system on the development of the hyperdynamic circulation in conscious cirrhotic rats. *J Hepatol* 1997;26:1111–1119
- Benoit JN, Granger DN. Splanchnic hemodynamics in chronic portal hypertension. *Semin Liver Dis* 1986;6:287–298
- Vorobioff J, Bredfeldt JE, Groszmann RJ. Increased blood flow through the portal system in cirrhotic rats. *Gastroenterology* 1984;87:1120–1126
- 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
23. Schrier RW, Arroyo V, Bernardi M, Epstein M, Henriksen JH, Rodes J. Peripheral arterial vasodilation hypothesis: a proposal for the initiation of renal sodium and water retention in cirrhosis. *Hepatology* 1988;8:1151-1157
 24. 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
 25. Sieber C, López-Talavera JC, Groszmann RJ. Role of nitric oxide in the in vitro splanchnic vascular hyporeactivity in ascitic cirrhotic rats. *Gastroenterology* 1993;104:1750-1754
 26. Maroto A, Gines A, Salo J, et al. Diagnosis of functional renal failure of cirrhosis by Doppler sonography: prognostic value of resistive index. *Hepatology* 1994;20:839-844
 27. Fernández-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
 28. Maroto A, Gines P, Arroyo V, et al. Brachial and femoral artery blood flow in cirrhosis: relationship to kidney dysfunction. *Hepatology* 1993;17:788-793
 29. Guevara M, Bru C, Ginés P, et al. Increased cerebral vascular resistance in cirrhotic patients with ascites. *Hepatology* 1998;28:39-44
 30. Tristani FE, Cohn JH. Systemic and renal hemodynamics in oliguric hepatic failure: effect of volume expansion. *J Clin Invest* 1967;46:1894-1906
 31. Lebrec D, Kotelansku B, Cohn JH. Splanchnic hemodynamic factors in cirrhosis with refractory ascites. *J Lab Clin Med* 1979;93:301-309
 32. 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
 33. Ruiz-del-Arbol L, Monescillo A, Arocena C, et al. Circulatory function and hepatorenal syndrome in cirrhosis. *Hepatology* 2005;42:439-447
 34. Schroeder ET, Eich RH, Smulyan H, Gould AB, Gabuzda GJ. Plasma renin levels in hepatic cirrhosis: relationship to functional renal failure. *Am J Med* 1970;49:186-191
 35. DiBona GF. Renal nerve activity in hepatorenal syndrome. *Kidney Int* 1984;25:841-853
 36. Henriksen JH, Ring-Larsen H. Hepatorenal disorders: role of the sympathetic nervous system. *Semin Liver Dis* 1994;14:35-43
 37. Dudley FJ, Esler MD. The sympathetic nervous system in cirrhosis. In: Arroyo V, eds. *Ascites and Renal Dysfunction in Liver Disease*. Malden, MA: Blackwell Science; 1999:198-219
 38. 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
 39. Rimola A, Gines 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
 40. Moore KP. Arachidonic acid metabolites and the kidney in cirrhosis. In: Arroyo V, ed. *Ascites and Renal Dysfunction in Liver Disease*. Malden, MA: Blackwell Science; 1999:249-272
 41. Arroyo V. Diuretic-resistant ascites in cirrhosis: mechanism and treatment. *Acta Gastroenterol Belg* 1990;53:249-255
 42. Ma Z, Lee SS. Cirrhotic cardiomyopathy: getting to the heart of the matter. *Hepatology* 1996;24:451-459
 43. 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
 44. Iwakiri Y, Groszmann RJ. The hyperdynamic circulation of chronic liver diseases: from the patient to the molecule. *Hepatology* 2006;43(suppl 1):S121-S131
 45. Harry R, Auzinger G, Wendon J. The clinical importance of adrenal insufficiency in acute hepatic dysfunction. *Hepatology* 2002;36:395-402
 46. Tsai MH, Peng YS, Chen YC, et al. Adrenal insufficiency in patients with cirrhosis, severe sepsis and septic shock. *Hepatology* 2006;43:673-681
 47. 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
 48. Lerut J, Goffette P, Laterre PF, Donataccio M, Reynaert MS, Otte JB. Sequential treatment of hepatorenal syndrome and posthepatic cirrhosis by intrahepatic portosystemic shunt (TIPS) and liver transplantation. *Hepatogastroenterology* 1995;42:985-987
 49. Gonwa TA, Klintmalm GB, Jennings LS, Goldstein RM, Husberg B. Impact of pretransplant renal function on survival after liver transplantation. *Transplantation* 1995;59:361-365
 50. Seu P, Wilkinson AH, Shaked A, Busuttill RW. The hepatorenal syndrome in liver transplant recipients. *Am Surg* 1991;57:806-809
 51. 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
 52. Guevara M, Ginès P, Fernández-Esparrach G, et al. Reversibility of hepatorenal syndrome by prolonged administration of ornipressin and plasma volume expansion. *Hepatology* 1998;27:35-41
 53. 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
 54. Angeli P, Volpin R, Gerunda G, et al. Reversal of type 1 HRS with the administration of midodrine and octreotide. *Hepatology* 1999;29:1690-1697
 55. Uriz J, Ginés P, Cardenas A, et al. Terlipressin plus albumin infusion: an effective and safe therapy of hepatorenal syndrome. *J Hepatol* 2000;33:43-48
 56. Mulkay JP, Louis H, Donckter 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
 57. 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
 58. Halimi C, Bonnard P, Bernard B, et al. Effect of terlipressin (Glypressin) on hepatorenal syndrome in cirrhotic patients: results of a multicentre pilot study. *Eur J Gastroenterol Hepatol* 2002;14:153-158

59. Ortega R, Ginés P, Uriz J, et al. Terlipressin therapy with and without albumin for patients with hepatorenal syndrome: results of a prospective, non-randomized study. *Hepatology* 2002;36:941–948
60. Duvoux C, Zanditenas D, Hezode C, et al. Effects of noradrenaline and albumin in patients with type 1 hepatorenal syndrome: a pilot study. *Hepatology* 2002;36:374–380
61. Solanki P, Chawla A, Garg R, Gupta R, Jain M, Sarin SK. Beneficial effects of terlipressin in hepatorenal syndrome: a prospective, randomized placebo-controlled clinical trial. *J Gastroenterol Hepatol* 2003;18:152–156
62. 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
63. Linas SL, Schaefer JW, Moore EE, Good JT Jr, Giansiracusa R. Peritoneovenous shunt in the management of the hepatorenal syndrome. *Kidney Int* 1986;30:736–740
64. 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
65. Moreau R, Durand F, Poynard T, et al. Terlipressin in patients with cirrhosis and type y HRS: a retrospective multicenter study. *Gastroenterology* 2002;122:923–930
66. 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
67. 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
68. Brensing KA, Textra J, Perz J, et al. Long-term outcome after transjugular intrahepatic portosystemic stent-shunt in non-transplant patients with hepatorenal syndrome: a phase II study. *Gut* 2000;47:288–295
69. Guevara M, Ginés P, Bandi JC, et al. Transjugular intrahepatic portosystemic shunt in hepatorenal syndrome: effects on renal function and vasoactive systems. *Hepatology* 1998;28:416–422
70. 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
71. 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(suppl 3):39–43
72. Jalan R, Sen S, Steiner C, Kapoor D, Alisa A, Williams R. Extracorporeal liver support with molecular adsorbents recirculating system in patients with severe acute alcoholic hepatitis. *J Hepatol* 2003;38:24–31
73. Stange J, Hassanein T, Lynch P, et al. Short-term survival of patients with severe intractable hepatic encephalopathy: the role of albumin dialysis. *Hepatology* 2005;42(suppl 1):286A
74. Alessandria C, Venon WD, Marzano A, Barletti C, Fadda M, Rizzetto M. Renal failure in cirrhotic patients: role of terlipressin in clinical approach to hepatorenal syndrome type 2. *Eur J Gastroenterol Hepatol* 2002;14:1363–1368
75. Akriviadis E, Botla R, Briggs W, Han S, Reynolds T, Shakil O. Pentoxifylline improves short-term survival in severe acute alcoholic hepatitis: a double-blind, placebo-controlled trial. *Gastroenterology* 2000;119:1637–1648