Hepatorenal Syndrome: A Severe, but Treatable, Cause of Kidney Failure in Cirrhosis

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Hepatorenal syndrome (HRS) is a unique type of kidney failure that occurs in advanced cirrhosis. It is characterized by functional impairment of the kidneys due to vasoconstriction of the renal arteries in the setting of preserved tubular function and absence of significant histologic abnormalities. Renal vasoconstriction in HRS is due to severe vasodilation of the splanchnic arteries associated with portal hypertension, leading to a decrease in effective arterial blood volume and arterial pressure. HRS commonly develops after a trigger, usually a bacterial infection, that disrupts the arterial circulation, but it also may occur spontaneously. There are 2 forms of HRS: type 1 is characterized by an acute progressive decrease in kidney function and very short survival without treatment, whereas type 2 features stable less severe kidney failure and longer survival compared with type 1. A liver transplant is the preferred treatment for HRS. Pharmacologic treatment with vasoconstrictors to reverse splanchnic vasodilation, together with albumin, is effective in 40%-50% of patients with type 1 HRS and improves survival. The drug of choice is the vasopressin analogue terlipressin. Renal replacement therapy should not be used as first-line therapy.

INDEX WORDS: Cirrhosis; ascites; chronic liver diseases.

CASE PRESENTATION

A 45-year-old man with cirrhosis due to hepatitis C virus infection was admitted to the liver unit with weakness and increasing jaundice of recent onset. The patient had long-standing cirrhosis with previous episodes of ascites and hepatic encephalopathy and was listed for liver transplant 3 months before the admission. He was not receiving prophylaxis with quinolones for prevention of spontaneous bacterial peritonitis. The most recent laboratory test results showed serum creatinine level of 1 mg/dL (88 μmol/L), corresponding to estimated glomerular filtration rate (eGFR) of 98 mL/min/1.73 m² [1.63 mL/s/1.73 m²] using MDRD (Modification of Diet in Renal Disease) Study equation), serum bilirubin level of 4.8 mg/dL (82 μmol/mL), serum albumin level of 2.8 g/dL (28 g/L), and prothrombin time of 42%. There was no evidence of excessive urinary losses, marked loss of body weight, vomiting, diarrhea, or gastrointestinal bleeding. Daily medications included spironolactone, 100 mg, and furosemide, 40 mg. On physical examination, the patient showed marked jaundice, lethargy, flapping tremor, large ascites without abdominal tenderness, and pedal edema. Blood pressure was 100/60 mm Hg and heart rate was 90 beats/min. Laboratory data at admission showed decreased kidney and liver function, with serum creatinine level of 3 mg/dL (265 μmol/L; eGFR, 28 mL/min/1.73 m² [0.47 mL/s/1.73 m²]), serum sodium level of 127 mEq/L (127 mmol/L), serum bilirubin level of 18 mg/dL (308 mmol/L), serum albumin level of 2.7 g/dL (27 g/L), and prothrombin time of 45%. Urinalysis showed no signs of infection or intrinsic acute or chronic kidney diseases, with protein excretion of 100 mg per gram of creatinine, sodium excretion of 5 meq/L (5 mmol/L), urine osmolality of 450 mOsm/Kg, and absence of red blood cells or casts. Blood and urine culture results were negative. Paracentesis was diagnostic of spontaneous bacterial peritonitis, with 1,500 leukocytes/μL (90% polymorphonuclear cells) and yielded a culture positive for Escherichia coli. Diuretics were withheld and intravenous (IV) ceftriaxone (2 g followed by 1 g/24 h) therapy was started. Albumin was given at a dose of 1.5 g/kg the first day and 1 g/kg at day 3 of treatment. Blood tests taken 48 hours after diuretics were withheld showed plasma renin activity of 11.6 ng/mL/h (reference range, 1-1.2 ng/mL/h), plasma aldosterone concentration of 122 ng/dL (3.38 nmol/L; reference range, 25-40 ng/dL [0.69-1.11 nmol/L]), and plasma norepinephrine concentration of 652 pg/mL (3.85 nmol/L; reference range, 200-214 pg/mL [1.18-1.26 nmol/L], findings consistent with reduced effective arterial blood volume. Despite improvement of infection with antibiotics, there was a progressive decrease in kidney function, with serum creatinine level reaching 5 mg/dL (442 μmol/mL; eGFR, 15 mL/min/1.73 m² [0.25 mL/s/1.73 m²]) at the time of resolution of the infection. Arterial pressure did not decrease throughout the infection.

A diagnosis was made of type 1 hepatorenal syndrome (HRS) triggered by spontaneous bacterial peritonitis. Treatment with terlipressin (1 mg/4 h IV) and albumin (1 g/kg the first day, followed by 40 g/d) was started. Treatment was not started earlier because of the lack of data for the efficacy and safety of terlipressin in patients with type 1 HRS and ongoing infections. The patient was not treated with renal replacement therapy (RRT) because there was no severe volume overload, hyperkalemia, or metabolic acidosis. Administering albumin and terlipressin was associated with marked improvement in kidney function, with a decrease in serum creatinine level, increase in arterial pressure (Fig 1), and marked decreases in plasma renin activity, aldosterone, and norepinephrine concentrations (3.8 ng/mL/h, 46 ng/dL [1.28 nmol/L], and 250 pg/mL [1.48 nmol/L], respectively, at the end of treatment compared with 11.6 ng/mL/h, 122 ng/dL [3.38 nmol/L], and 652 pg/mL [3.85 nmol/L] at baseline), indicating a remarkable improve-
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INTRODUCTION

Investigations performed in the late 1950s to early 1970s provided conclusive evidence indicating that HRS is a unique form of kidney failure that occurs in patients with cirrhosis and is due to marked vasoconstriction of the renal circulation. Since then, it has become evident that the kidney failure of HRS is of circulatory origin. An extremely dilated splanchnic arterial bed triggers a marked disturbance in the systemic circulation, ultimately leading to kidney failure due to vasoconstriction of the kidney arteries. Although once considered an irreversible and untreatable condition (except for liver transplant), studies performed within the past decade have shown that HRS may be reversible with pharmacologic treatment. This review provides an overview of the pathogenesis, clinical findings, differential diagnosis, and management of HRS, with particular emphasis on pharmacologic treatment.

DEFINITION AND INCIDENCE

The current definition of HRS proposed by the International Ascites Club states that “HRS is a potentially reversible syndrome that occurs in patients with cirrhosis, ascites and liver failure that is characterized by impaired kidney function, marked alterations in cardiovascular function, and over-activity of the sympathetic nervous system and renin-angiotensin system. Severe renal vasoconstriction leads to a decrease of GFR. HRS may appear spontaneously or can follow a precipitating event.” This definition was first proposed in 1999 and subsequently modified in 2007. In the former definition, the existence of an ongoing bacterial infection precluded the diagnosis of HRS, whereas in the most recent definition, HRS may be diagnosed in the presence of an infection, except if there is septic shock.5

The definition of acute kidney injury (AKI) proposed by the Acute Kidney Injury Network (AKIN) for kidney failure developing in the general population of hospitalized patients has been suggested to also apply to kidney failure that occurs in patients with cirrhosis.6 However, this classification has not been validated in patients with cirrhosis. Therefore, it seems reasonable to keep the term HRS for the unique form of kidney failure of functional origin, with preserved tubular function, that occurs in cirrhosis and wait until prospective studies evaluating the usefulness of the AKIN definition in cirrhosis are reported. In the future, the use of kidney biomarkers theoretically may help differentiate HRS from AKI. In this regard, 2 recent studies suggest that urine neutrophil gelatinase-associated lipocalin (NGAL) levels could be useful in the differential diagnosis between HRS and AKI in cirrhosis.8,9

There are very few studies of the incidence of HRS. Older studies indicated that the incidence of HRS in a general population of patients with cirrhosis and ascites was high, ~40% after 5 years of follow-up.10 Recent data indicate a much lower incidence of 11% at 5 years.11 However, the latter study included only...
patients experiencing an initial episode of ascites; these individuals have less advanced disease, which may be associated with a lower incidence of HRS relative to the wider population of patients with ascites.

**PATHOPHYSIOLOGY**

The characterization of HRS as being a functional defect has been established by the absence of significant morphologic abnormalities in the kidney histology,12 normalization of or improvement in kidney function after liver transplant,13,14 and reversibility of the syndrome by pharmacologic treatment with vasoconstrictors and albumin.15 A substantial amount of evidence indicates that the main cause of decreased kidney function leading to HRS in cirrhosis is impairment in circulatory function.16-22 The defect in systemic arterial circulation involves reduced systemic vascular resistance caused by primary arterial vasodilation of the splanchnic circulation, which in turn is caused by portal hypertension.4,16,17,23-25 The vasodilation of the splanchnic arterial circulation likely is a result of greater production and activity of vasodilators, in particular, nitric oxide, endogenous cannabinoids, and carbon monoxide.4,17,23-25 Experimental and clinical studies of patients with cirrhosis suggest that bacterial translocation from the intestinal lumen to mesenteric lymph nodes may be an important factor and clinical studies of patients with cirrhosis suggest that bacterial translocation elicits an inflammatory response, with proinflammatory cytokines produced in greater amounts in the splanchnic area, leading to vasodilation of the splanchnic arterial vessels.28,29 Bacterial translocation’s key role in circulatory dysfunction in advanced cirrhosis26,27 is substantiated by the observation that administering the antibiotic norfloxacin, which selectively decontaminates the intestinal tract, improves circulatory function and reduces the likelihood of the development of HRS.30-32

The pathophysiology of HRS is summarized in Fig 2. In early stages of cirrhosis, when patients generally experience no symptoms, the increased resistance to blood flow within the liver is moderate and therefore portal hypertension is also moderate. Mechanisms leading to portal hypertension involve a passive increase in intrahepatic resistance due to fibrosis, dysfunction of liver endothelial cells, and increased portal blood flow due to vasodilation of splanchnic arteries (reviewed in25). In this context, there is a small decrease in systemic vascular resistance as a result of splanchnic arterial vasodilation. The effect of the decrease in systemic resistance in arterial pressure is balanced by increased cardiac output, so that arterial pressure and effective arterial blood volume are maintained at normal levels (Fig 1).16,17 In advanced stages of cirrhosis, the vasodilation of the splanchnic arteries increases due to progressive bacterial translocation and enhanced synthesis of vasodilator factors. Neoangiogenesis in mesenteric arteries and impaired response to vasoconstrictors also contribute to the reduced vascular resistance in the splanchnic circulation.33 The progressive decrease in arterial resistance in the splanchnic circulation is associated with an unremitting reduction in total systemic vascular resistance. This occurs primarily because the splanchnic circulation is a major part of the systemic arterial circulation, yet other mechanisms, such as the release of vasodilator factors from the splanchnic to the systemic circulation, also may contribute (reviewed in34). In advanced stages, systemic vascular resistance is so greatly reduced that additional increases in cardiac output cannot make up for it. As a result, there is underfilling of the arterial circulation due to the disparity between intravascular blood volume and the greatly enlarged intravascular arterial circulation, a condition known as effective arterial hypovolemia.16,17,21,35,36 Moreover, evidence indicates that there is a decrease in cardiac output, probably related to the so-called cirrhotic cardiomyopathy, that also contributes to arterial underfilling.18,19,37,38 Although relative adrenal insufficiency has been reported in cirrhosis, to date, no evidence has been presented to suggest that it may contribute to circulatory dysfunction in HRS.39 In the scenario of extreme underfilling of the arterial circulation, the body seeks to maintain arterial pressure by activating the vasoconstrictor systems, including the sympathetic nervous system, renin-angiotensin system, and, in late stages, nonosmotic hypersecretion of arginine vasopressin.17 Although these systems assist in preserving effective arterial blood volume and arterial pressure, they strongly influence kidney function, particularly retention of sodium and solute-free water. As a consequence, ascites and edema develop, as well as hypervolemic hyponatremia. If the vasoconstriction systems are activated to a high degree, renal vasoconstriction occurs, which leads to greatly decreased glomerular filtration and the development of HRS4,15-17 (Fig 2).

Vasoactive mediators, which act on intrarenal circulation, also may contribute to HRS. Increased synthesis of a number of vasoactive factors in the intrarenal circulation, such as thromboxane A2, cysteinyl leukotrienes, F2-isoprostanes, and endothelin 1, has been described, yet their contributions to the pathogenesis of HRS are still undefined.16 It is unlikely that endothelin 1 has a role because treatment with the endothelin antagonist tezosentan does not lead to improvement in kidney function in patients with type 2 HRS.40 Contrary to classic belief, vascular beds other than those in renal circulation also are vasoconstricted in HRS; for example, in the extremities and cerebral
In HRS, cardiopulmonary pressures remain within normal limits and there is no evidence of circulatory overload despite the intense sodium and fluid retention. The likely explanation for this behavior is that the fluid retained within the kidneys exists from the intravascular compartment, particularly in the splanchnic venous circulation, thus forming ascites because of the high hydrostatic pressure and increased filtration coefficient in the splanchnic capillaries. In addition, fluid exits from the capillaries of the legs to form edema.

**CLINICAL TYPES OF HRS**

HRS may occur in 2 different clinical patterns, according to the severity and rate of progression of kidney failure (Box 1). The main clinical features of type 1 HRS are those of acute kidney failure with a rapid increase in serum creatinine level. If untreated, serum creatinine levels usually increase rapidly to >5 mg/dL (>440 μmol/L). In approximately two-thirds of cases, there is hypervolemic hyponatremia on account of disruptions to solute-free water excretion. Serum potassium levels usually are around the upper normal limit or slightly higher. Potassium-sparing diuretics obviously are absolutely contraindicated because they may induce severe hyperkalemia.

**Box 1. Clinical Types of HRS**

- **Type 1**: Rapidly progressive decrease in kidney function, defined as a 100% increase in serum creatinine to a final value >2.5 mg/dL (>221 μmol/L) in <2 weeks. The clinical presentation is usually that of acute kidney failure. Average median survival is only 2 weeks if not treated.
- **Type 2**: Stable or slowly progressive decrease in kidney function that does not meet the criteria of type 1. The clinical picture is that of ascites refractory to diuretic therapy. Average median survival is ~6 months.

Abbreviation: HRS, hepatorenal syndrome.
Source: Salemo et al.

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**Figure 2.** Pathogenesis of circulatory abnormalities in (left) compensated cirrhosis and (right) hepatorenal syndrome. Reproduced from Ginès & Schrier with permission of the Massachusetts Medical Society.
Given that HRS constitutes functional kidney failure, the urine features are similar to those of prerenal azotemia, including low urine sodium and fractional excretion of sodium and high urine osmolality and urine to plasma osmolality ratio.4 Ascites and edema are constantly present. Urine volume usually is not extremely reduced and some patients may have normal urine volumes.47 A transition from HRS to acute tubular necrosis (ATN) in patients with progressive kidney failure not responding to treatment has been suggested, but no studies have been reported to date evaluating this possibility.

In addition to severe kidney failure, patients with type 1 HRS have signs of severe circulatory dysfunction, evidenced by arterial hypotension (mean arterial pressure usually is ~70 mm Hg) and very low systemic vascular resistance. This arterial hypotension occurs despite marked activation of the vasoconstrictor systems and severe vasoconstriction in extrarenal vascular beds.4,41-43 In some patients, the differential diagnosis between type 1 HRS and severe sepsis is difficult and represents a clinical challenge. As discussed later, all patients with cirrhosis presenting with acute kidney failure should be checked for signs of infection. Cardiac output may be low in patients with type 1 HRS, either in absolute values or relative to the decrease in total systemic vascular resistance.18-20,38 Despite this possible decrease in cardiac output, patients with type 1 HRS do not show signs of circulatory overload.18,44,48

Finally, in addition to kidney and circulatory failure, the great majority of patients with type 1 HRS have features of advanced liver disease, with jaundice, coagulopathy, low albumin levels, hepatic encephalopathy, poor nutritional status, and large ascites and edema. A significant proportion of patients with type 1 HRS have acute-on-chronic liver failure.39

In sharp contrast to the progressive kidney failure of type 1 HRS, some patients have moderately severe kidney failure of functional origin that remains stable for variable periods. This condition is known as type 2 HRS, and patients usually have serum creatinine levels of ~2.0 mg/dL (~176.8 μmol/L). Patients with type 2 HRS generally have less severe clinical concerns than those with type 1 HRS and their main clinical problem is ascites, which usually is resistant to diuretic therapy because of the combined influence of profound sodium retention, reduced GFR, and markedly increased levels of aldosterone and norepinephrine.4,5,46 During follow-up, some patients with type 2 HRS develop type 1 HRS,30 which may arise spontaneously or as a result of some complication, usually a bacterial infection. Patients with type 2 HRS have much longer survival expectancy than their counterparts with type 1 HRS (Fig 3).46 It currently is unknown whether type 1 and type 2 HRS represent 2 different entities or a single entity with the same underlying pathophysiology, but different intensity.

**PRECIPITATING FACTORS**

HRS develops without a discernable trigger in some patients, whereas in others, it occurs directly after effective arterial blood volume is decreased by another condition.51-55 Bacterial infections and, in particular, spontaneous bacterial peritonitis, are leading triggers of HRS.4,5,51-54 Approximately one-third of patients with spontaneous bacterial peritonitis develop HRS at the time of infection or immediately thereafter, in the absence of septic shock.5,52 Of these patients, about one-third experience reversal of HRS when the infection is resolved.55-58 However, in the remainder, the condition is not reversible and they develop either stable (type 2) or progressive HRS (type 1).55,56,59 Patients who develop type 1 HRS as a result of spontaneous bacterial peritonitis have a dismal outcome, with almost 100% hospital mortality if not treated appropriately (discussed later).53,55 Infections other than spontaneous bacterial peritonitis also may cause HRS, but its frequency and severity usually is lower than that of patients with spontaneous bacterial peritonitis.56,57,60

Other conditions that may act as precipitating factors of HRS are gastrointestinal bleeding and large-volume paracentesis (>5 L) in the absence of albumin administration. Even so, the development of kidney failure after gastrointestinal bleeding is not very common in patients who have cirrhosis (~10%) and it is almost fully confined to patients with hypovolemic shock. In most instances, it is associated with ischemic hepatitis, which implies that the kidney failure most likely is related to ATN and not HRS.47,61 Large-volume paracentesis without albumin may trigger HRS in 15% or more of cases.62 This risk is one of the main rationales for administering IV albumin when large-volume paracenteses are performed.63 Diuretic

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**Figure 3.** Survival of patients with cirrhosis according to type of hepatorenal syndrome (HRS). Reproduced from Alessandria et al46 with permission of John Wiley & Sons.
treatment also has been suggested as a potential trigger of HRS, but there are no clear supportive data for this.

Several factors have been suggested to be linked to an increased risk of HRS, including severe sodium retention, hypervolemic hyponatremia, low mean arterial blood pressure (<80 mm Hg), and low cardiac output. Of note, there is no demonstrated correlation with either the extent of liver failure, gauged by typical assessments of liver function (serum bilirubin, albumin, and prothrombin time) or Child-Pugh classification.10,18,19,64

**MANAGEMENT OF HRS**

**General Measures**

The general management of patients with cirrhosis and HRS depends on the severity of kidney failure and associated complications. Patients with type 1 HRS who are waiting for a liver transplant are managed appropriately in an intensive care setting. Considering the high mortality rate of type 1 HRS, decisions about the management of patients who are not candidates for transplant or who have important comorbid conditions should be made on an individual basis. A central venous catheter is important to keep track of central venous pressure in patients who will be treated with vasoconstrictors and albumin.73 Use of a bladder catheter may be associated with urinary tract infection and is not necessary except when marked oliguria is present. There should be vigilant monitoring of the possibility of associated complications, in particular bacterial infections and gastrointestinal bleeding, and any that arise should be treated as quickly as possible. IV fluids should be administered carefully because of severe kidney failure together with sodium and solute-free water retention due to cirrhosis. Excessive administration of fluids may result not only in an increase in ascites and edema, but also in substantial increases in central venous pressure and pulmonary edema.

Patients with type 2 HRS without associated complications are managed as outpatients. Spironolactone and other potassium-sparing diuretics generally should be avoided because of the risk of hyperkalemia, whereas loop diuretics, such as furosemide, usually
Vasopressors
- Terlipressin: 1 mg/4-6 h intravenously; the dose is increased up to a maximum of 2 mg/4-6 h after 3 days if there is no response to therapy, defined by a decrease in serum creatinine >25% of pretreatment values. Response to therapy is indicated by a marked decrease in the high serum creatinine levels, at least <1.5 mg/dL (<133 μmol/L). Treatment is usually given from 5-15 days
- Midodrine: 7.5 mg orally 3×/d, increased to 12.5 mg 3×/d if needed
- Octreotide: 100 μg subcutaneously 3×/d, increased to 200 μg 3×/d if needed
- Norepinephrine: 0.5-3 mg/h as continuous intravenous infusion aimed at increasing mean arterial pressure by 10 mm Hg. Treatment is maintained until serum creatinine decreases <1.5 mg/dL (<133 μmol/L)

Albumin administration
Concomitant administration of albumin together with vasoconstrictor drugs (1 g/kg body weight at day 1 followed by 20-40 g/d)

Abbreviation: HRS, hepatorenal syndrome.

Box 3. Pharmacologic Treatment of HRS

Management of Type 1 HRS

Administration of vasopressor drugs currently is considered the best therapy for managing type 1 HRS.15,63 This approach is intended to cause vasoconstriction of the greatly dilated splanchnic arterial bed, thus improving circulatory function. This in turn alleviates arterial underfilling, lessens the activation of the endogenous vasoconstrictor systems, and increases kidney perfusion and GFR. Treatment with vasodilator drugs is ineffective. Albumin infusion alone improves cardiac function, but is not associated with an improvement in kidney function.73 The available vasopressors are vasopressin analogues, such as terlipressin, which acts on V1 vasopressin receptors in vascular smooth muscle cells, and α-adrenergic agonists, such as noradrenaline or midodrine, which act on α1-adrenergic receptors in vascular smooth muscle cells. In most published reports, vasopressor drugs (frequently terlipressin) are given with IV albumin to further alleviate the arterial underfilling.75-82

Results from randomized controlled studies and systematic reviews show that treatment with the combination of terlipressin and albumin is associated with reversal of HRS in 40%-50% of patients, making this approach the preferred initial therapy (Box 3).69 Response to treatment with terlipressin and albumin is associated with a progressive decrease in serum creatinine concentration, increased urine output, and improvement in hyponatremia.80,81 Factors that predict a response to treatment are an increase in arterial pressure during treatment and low baseline creatinine level.63-86 α-Adrenergic agonists, such as noradrenaline or midodrine, are a reasonable alternative to terlipressin due to their low cost and broad availability; however, data for their use are limited.48,87-89 A systematic review of randomized controlled studies has shown that vasoconstrictor therapy of HRS improves survival.82 Responders to terlipressin and albumin in terms of improvement in kidney function after therapy have increased survival compared with nonresponders. After withdrawal of therapy, HRS recurs in <15% of patients, and in these cases, a second treatment with terlipressin usually is effective. The incidence of side effects (usually ischemic) that mandate discontinuation of treatment is ~12%. Attention should be paid to early detection of ischemic side effects.

RRT has been used in patients with type 1 HRS, particularly in candidates for liver transplant.80 Disappointingly, RRT has not been evaluated side by side with other forms of therapy in randomized comparative studies. RRT is not considered the first-line treatment for patients with type 1 HRS because it does not correct the underlying pathogenesis. Nevertheless, either continuous or intermittent RRT is an option for patients with type 1 HRS for whom vasoconstrictors are ineffective and who present signs of uremia, volume overload, severe metabolic acidosis, or hyperkalemia. The best modality of RRT is still an unresolved issue. In recent years, alternative methods to conventional RRT have been evaluated in type 1 HRS. These include molecular readsorbent recirculating systems (an alternative to dialysis that clears albumin-bound substances, including vasodilators) and fractionated plasma separation and adsorption (the Prometheus system), but more evidence is needed if these procedures are to be accepted as having therapeutic value for HRS.91-93 A recent small study evaluating a molecular readsorbent recirculating system as rescue therapy in patients with type 1 HRS not responding to treatment with vasoconstrictors showed no improvement in GFR and renal blood flow.94

An implantable stent inserted through a transjugular approach that reduces portal pressure by establishing communication between the portal vein and a hepatic vein (known as TIPS [transjugular intrahepatic portosystemic shunt]) has been proposed as an alternative treatment for type 1 HRS, but information is very limited.95,96 As a result, the current role of this device in the management of this condition is unknown. A recent study including a very small number of patients showed that vasoconstrictor therapy followed by stent placement was effective in patients with type 1 HRS.87 This approach using a sequential therapy merits evaluation in larger studies.
Liver transplant is the first choice of treatment for patients with cirrhosis and type 1 HRS. Because kidney failure is reversible after liver transplant, patients should not be treated with combined liver-kidney transplant. Combined liver-kidney transplant is appropriate only for patients who have been on RRT for more than 6-8 weeks who have a low likelihood of recovery of kidney function. A substantial problem in liver transplant for patients with type 1 HRS is the high mortality rate for patients on the waiting list owing to the short life expectancy and long waiting times at many transplant centers. This may be dealt with by assigning these patients a high priority for transplant. The question arises as whether to treat patients with type 1 HRS with vasoconstrictors before transplant with the aim of performing transplant on patients with normal or near-normal kidney function. Excellent survival has been reported with the 2 approaches, “transplant-without treating HRS” or “treat HRS before transplant.” However, information is scarce and studies either did not assess complications after transplant or included a small number of patients. Therefore, use of pharmacologic treatment of type 1 HRS before transplant remains an open question, although transplant of patients without kidney failure theoretically seems better than transplant of patients with acute severe kidney failure. A proposed algorithm of management of type 1 HRS based on the current knowledge is shown in Fig 4.

Management of Type 2 HRS

There are very few data regarding the use of vasoconstrictors in combination with albumin for patients who have type 2 HRS. Uncontrolled trials support the efficacy of vasoconstrictors in improving kidney function, but recurrence after treatment withdrawal is very frequent (P. Ginès, unpublished observations). More studies are required to more fully understand the role that vasoconstrictors plus albumin may have in treating type 2 HRS. TIPS may improve kidney function and reduce the risk of progression to type 1 HRS, but randomized studies are lacking. RRT is not indicated in the management of patients with type 2 HRS because of the lack of a severe decrease in kidney function. A proposed algorithm of management of type 2 HRS based on current knowledge is shown in Fig 5.

PREVENTION OF HRS

As discussed, the chance of HRS is considerable in patients with cirrhosis and spontaneous bacterial peritonitis, and a study published in 1999 showed that IV administration of albumin (1.5 g/kg body weight at diagnosis and 1 g/kg 48 hours later) can greatly reduce this risk. In that study, it was observed that patients with normal serum creatinine levels and normal or slightly increased serum bilirubin levels at the time of diagnosis of spontaneous bacterial peritonitis had very low risk of developing HRS even if albumin was not given. This has led to the suggestion that patients of this type should not be given albumin treatment. Nevertheless, because this was not a pre-defined subanalysis of the study, it seems reasonable to suggest that albumin should be administered to all patients with spontaneous bacterial peritonitis until this observation is confirmed in further prospective studies, as proposed in the guidelines of the European Association for the Study of the Liver (EASL).

Long-term oral administration of norfloxacin (400
mg/d) in patients with ascitic fluid protein <15 g/L and associated decreased liver and/or kidney function (bilirubin >3 mg/dL [>51.3 μmol/L], Child-Pugh score >10, serum sodium <130 mEq/L [<130 mmol/L], and/or serum creatinine >1.2 mg/dL [>106.1 μmol/L]) reduces the risk of HRS and improves survival.25 These effects probably are related to prevention of bacterial translocation, suppression of proinflammatory cytokines, and improvement in circulatory function.26,27,30,31 In patients with acute alcoholic hepatitis, pentoxifylline was shown to decrease the incidence of HRS in one study104; however, these results were not confirmed in a study recently published in abstract form.105 Although hyponatremia in patients with ascites is a risk factor for HRS,10 there are no studies assessing whether vaptans, drugs that improve serum sodium levels by antagonizing selectively the V2 receptors in the kidney,106 may help prevent HRS.

**MANAGEMENT OF HRS ACCORDING TO GUIDELINES OF INTERNATIONAL SOCIETIES**

The most recent guidelines, published in 2010 by the European Association for the Study of the Liver (EASL), recommend terlipressin (1 mg/4-6 h as IV bolus) together with albumin as first-line treatment for patients with type 1 HRS.63 The aim of treatment is to decrease serum creatinine levels to <1.5 mg/dL (<133 μmol/L). Modifications of the dose are guided by changes in serum creatinine concentration; if serum creatinine level decreases by at least 25% after 3 days of treatment, the dose is maintained, and if not, the dose is increased to 2 mg/4-6 h. If there is recurrence at any time after treatment discontinuation, patients should be re-treated with terlipressin and albumin. Alternatives to terlipressin are noradrenaline and midodrine plus octreotide, both in combination with albumin, yet information about efficacy is very limited. Patients treated with vasoconstrictors should be followed up carefully throughout treatment for early detection of side effects, particularly cardiovascular events and pulmonary edema. Main contraindications to vasoconstrictor drugs are severe cardiovascular diseases. The use of TIPS is not recommended and RRT should be used only in patients not responding to vasoconstrictors who fulfill criteria for kidney support. As far as patients who are candidates for transplant is concerned, EASL guidelines recommend treatment of HRS with vasoconstrictors before liver transplant. Moreover, liver transplant alone is appropriate, with combined liver-kidney transplant reserved for only patients who have been on RRT for more than 6-8 weeks. Although the guidelines state that vasoconstrictor therapy is effective for the treatment of type 2 HRS, no specific recommendation is made to treat these patients due to limited data.

The AASLD (American Association for the Study of the Liver) guidelines published in 2009 recommend that patients with type 1 HRS be treated with midodrine and octreotide together with albumin.107 It should be noted that terlipressin is not available in the United States. These guidelines also emphasize that patients who are candidates for liver transplant should be referred immediately to transplant centers because of their low survival expectancy.

**ACKNOWLEDGEMENTS**

Support: Dr. Fagundes was recipient of a grant from the Instituto Reina Sofía de Investigación Nefrológica (IRSN). Some of the studies reported in this review were performed with the support of grants from the Fondo de Investigación Sanitaria (FIS PI080126 and EC/90077) and Ciber de Enfermedades Hepáticas y Digestivas (CIBEREHD). CIBEREHD is funded by the Instituto de Salud Carlos III, Ministerio de Sanidad, España.
Financial Disclosure: Dr Ginès has been an advisor for Otsuka Pharmaceuticals, Orphan Therapeutics, Ikaria, and Ferring Int. Dr Fagundes declares that she has no relevant financial interests.

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