American Journal of Gastroenterology
© 2005 by Am. Coll. of Gastroenterology
Published by Blackwell Publishing

ISSN 0002-9270
doi: 10.1111/j.1572-0241.2005.40952.x

Hepatorenal Syndrome: A Dreaded Complication of End-Stage Liver Disease

Andrés Cárdenas, M.D., M.M.Sc.
Instructor in Medicine, Division of Gastroenterology and Hepatology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts

Hepatorenal syndrome is the dreaded complication of end-stage liver disease characterized by functional renal failure due to renal vasoconstriction in the absence of underlying kidney pathology. The pathogenesis of hepatorenal syndrome is the result of an extreme underfilling of the arterial circulation secondary to an arterial vasodilation located in the splanchnic circulation. This underfilling triggers a compensatory response with activation of vasoconstrictor systems leading to intense renal vasoconstriction. The diagnosis is based on established diagnostic criteria aimed at excluding nonfunctional causes of renal failure. The prognosis of patients with hepatorenal syndrome is extremely poor especially in those who have a rapidly progressive course. Liver transplantation is the best option in suitable candidates, but it is not always applicable due to the short survival expectancy and donor shortage. Pharmacological therapies based on the use of vasoconstrictor drugs (terlipressin, midodrine, octreotide, or noradrenline) are the most promising in the aim of successfully offering a bridge to liver transplantation. Other treatments such as transjugular intrahepatic portosystemic shunts and albumin dialysis are effective but experience is very limited. Although there is limited information on the prevention of hepatorenal syndrome, intravenous albumin infusion in patients with spontaneous bacterial peritonitis and with oral pentoxifylline in patients with acute alcoholic hepatitis seems to effectively prevent hepatorenal syndrome in these two settings.

(Am J Gastroenterol 2005;100:460–467)

INTRODUCTION

Renal failure commonly complicates the clinical course of patients with cirrhosis. Although there are several causes of renal failure in the setting of advanced liver disease such as volume depletion, shock (hemorrhagic or septic), exposure to nephrotoxic drugs, or intrinsic renal disease (*i.e.*, glomerulonephritis), renal failure in cirrhosis most commonly occurs in the absence of these factors. This type of renal dysfunction is known as hepatorenal syndrome (HRS), a unique form of functional renal failure that develops in patients with cirrhosis, liver failure, and portal hypertension. Although HRS occurs predominantly in advanced cirrhosis, it may also develop in other chronic liver diseases associated with severe liver failure and portal hypertension, such as alcoholic hepatitis or in acute liver failure (1–4).

HRS is common with a reported incidence of about 10% among hospitalized patients with cirrhosis and ascites (5). Nonetheless, the probability of developing HRS in patients with cirrhosis and ascites is nearly 20% at 1 yr and increases to 40% at 5 yr (5). Patients with ascites and marked sodium and water retention with dilutional hyponatremia as well as those with marked arterial hypotension have a high risk of developing HRS (5). Two types of HRS are observed in clinical practice (1). Type 1 HRS is an aggressive form with a very poor prognosis and type 2 HRS develops slowly over weeks; these patients usually have diuretic-resistant ascites and have a slightly better prognosis compared with those with type 1 HRS.

There are several mechanisms that play a contributory role in pathogenesis of HRS, including extrarenal and intrarenal factors, abnormalities in systemic hemodynamics, and the diseased liver causing portal hypertension and hepatic failure. This review will describe the pathogenesis, clinical features, diagnostic approach, and current treatment of HRS in cirrhosis.

PATHOPHYSIOLOGY

The pathophysiologic hallmark of HRS is severe vasoconstriction of the renal circulation (6, 7). The underlying mechanisms are complex and include interactions among changes in the systemic arterial circulation, increased portal pressure, activation of vasoconstrictor factors, and suppression of vasodilator factors acting on the renal circulation (Table 1). A common pathway for these derangements is the development of an intense splanchnic arterial vasodilation, mainly due to an increased production of local vasodilators substances (mainly nitric oxide), which triggers an important compensatory response by activating vasoconstrictor and antinatriuretic systems such as the renin-angiotensin-aldosterone system (RAAS), the sympathetic nervous system (SNS),

Table 1. Vasoactive Factors Involved in the Regulation of Renal Perfusion in Cirrhosis and the Pathogenesis of Hepatorenal Syndrome

Vasodilators
Prostacyclin
Prostaglandin E2
Nitric oxide
Atrial natriuretic peptide
Kallikrein-kinin system
Vasoconstrictors
Angiotensin II
Norepinephrine
Neuropeptide Y
Endothelin-1
Adenosine
Thromboxane A2
Cysteinyl leukotrienes
F2-isoprostanes

and arginine vasopressin (AVP) accounting for sodium and water retention as well as renal vasoconstriction (7–10) (Fig. 1).

In addition, regulation of renal circulation in cirrhosis plays an important role as it depends on the interaction between vasoconstrictor and vasodilator factors acting on the renal vasculature (Table 1). In the early stages of cirrhosis renal blood flow may be kept within normal limits due to the effect of local vasodilators that antagonize the renal vascular effect of the systemic vasoconstrictors. When there is stimulation of the endogenous vasoconstrictors, there is also activation of renal vasodilators (prostaglandins, nitric oxide, and natriuretic peptides) in order to maintain renal perfusion and glomerular filtration rate (GFR) (11). Although the renal production of prostaglandins and circulating levels of natriuretic peptides are increased in patients with cirrhosis and ascites without HRS, with disease progression circulating vasoconstrictors overcome the effect of renal vasodilators, leading to severe renal vasoconstriction and reduction in GFR (12). In some cases a precipitating cause of circulatory dysfunction such as spontaneous bacterial peritonitis (SBP) leads to worsening of renal vasoconstriction (13). Once vasoconstriction develops, intrarenal mechanisms perpetuate HRS due to the development of intrarenal vicious cycles in which hypoperfusion leads to an imbalance in intrarenal vasoactive systems that in turn cause more vasoconstriction.

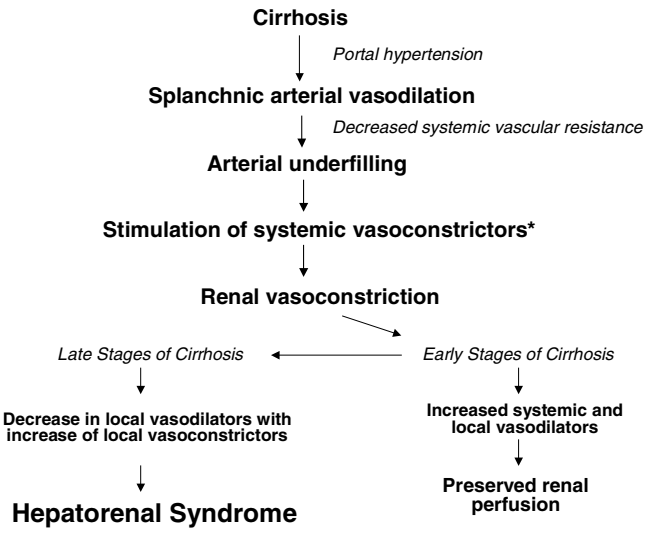

Figure 1. Pathogenesis of hepatorenal syndrome as proposed by the peripheral arterial vasodilation theory. *Renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system (SNS), endothelin, and arginine vasopressin.

The theory that better explains the relationship among changes in the renal circulation, activation of vasoconstrictor mechanisms, and presence of marked disturbances in systemic hemodynamics is the arterial vasodilation theory (7) (Fig. 1). This theory suggests that renal hypoperfusion and vasoconstriction represent an extreme expression of arterial underfilling secondary to a marked vasodilation of the splanchnic vascular bed. Arterial underfilling clinically manifested by arterial hypotension leads to a baroreceptor-mediated activation of RAAS and SNS with vasoconstriction not only in the renal circulation but also in other vascular beds. However, the splanchnic area would escape the effect of vasoconstrictors due to an enhanced local production of vasodilator factors. In the early stages of cirrhosis, renal perfusion initially would be maintained within normal limits despite activation of RAAS and SNS due to increased levels of renal vasodilators. However, with progression of disease, renal perfusion cannot be maintained because of extreme arterial underfilling causing maximal activation of vasoconstrictor systems and decreased activity of renal vasodilators. At this critical point HRS ensues.

CLINICAL AND LABORATORY FINDINGS

There are no specific clinical findings in HRS. The majority of patients have features of advanced liver disease with hyperbilirubinemia, elevated prothrombin time, thrombocytopenia, hepatic encephalopathy, hypoalbuminemia, and a large amount ascites. In addition, patients display low arterial blood pressure and reduced systemic vascular resistance as well as tachycardia and increased cardiac output. In addition, a substantial number of patients may have cirrhotic cardiomyopathy, a condition characterized by systolic and diastolic dysfunction of the left ventricle, which is clinically silent but that may contribute to profound hemodynamic changes occurring in HRS, particularly when precipitated by SBP (14, 15). Renal failure in HRS is often associated with severe oliguria (urine volume < 500 ml/24 h), intense urinary sodium retention (urine sodium < 10 meq/L), and spontaneous dilutional hyponatremia (serum sodium < 130 meq/L).

As described above there are two types of HRS (1) (Table 2). Type 1 HRS is characterized by a rapid and progressive impairment of renal function as defined by a doubling of the initial serum creatinine to a level higher than 2.5 mg/dl in <2 wk. Serum creatinine levels in HRS are usually lower than

Table 2. Clinical types of Hepatorenal Syndrome

Type 1.	Rapid and progressive impairment of renal function as defined by a doubling of the initial serum creatinine to a level higher than 2.5 mg/dl or a 50% reduction of the initial 24-h creatinine clearance to a level lower than 20 ml/min in <2 wk.
Type 2.	Impairment in renal function (serum creatinine > 1.5 mg/dl) that does not meet the criteria of type 1.

values observed in patients with acute renal failure without liver disease due to a reduced muscle mass and low endogenous production of creatinine in cirrhosis (16). Nonetheless, there are no other reliable noninvasive methods of determining renal function in cirrhosis and therefore the diagnosis of HRS is still based on the level of serum creatinine. In contrast to type 1 HRS, type 2 HRS is characterized by a more subtle course with serum creatinine levels around 1.5–2.0 mg/dl (1). The main clinical consequence of type 2 HRS is diuretic-resistant ascites. As expected, survival is longer in this group of patients than in those with type 1 HRS, but is shorter than that of patients with ascites without renal failure.

In some patients, type 1 HRS develops spontaneously without any identifiable precipitating factor, whereas in others it can occur in close association with systemic bacterial infections, in particular SBP, acute alcoholic hepatitis, and large volume paracentesis without albumin expansion. SBP precipitates type 1 HRS in approximately 20% of cases despite appropriate treatment and resolution of the infection (13). Similarly, large-volume paracentesis (>5 L) without albumin expansion may precipitate type 1 HRS in up to 15% of cases (17). This complication is one of the reasons intravenous albumin is routinely administered after large volume paracentesis in cirrhotics with ascites. Renal failure occurs in approximately 10% of cirrhotic patients with gastrointestinal bleeding (18). The development of renal failure occurs almost mainly in patients who develop hypovolemic shock, and in most cases is associated with ischemic hepatitis, which suggests that renal failure in patients with gastrointestinal bleeding is probably related to the development of acute tubular necrosis and not HRS (18).

There are several predictive factors associated with a greater risk of developing HRS in cirrhotic patients with ascites (5). For the most part these are related to circulatory and renal function. The most easily recognized are severe urinary sodium retention, spontaneous dilutional hyponatremia, and low mean arterial blood pressure (<80 mmHg). Interestingly, neither the degree of liver failure, as assessed by classic parameters of liver function (serum bilirubin, albumin, and prothrombin time) or the Child–Pugh classification, correlate with the risk of developing HRS.

PROGNOSIS

HRS carries the worst prognosis of all the complications of cirrhosis. Without treatment, the median survival time of patients with type 1 HRS is <2 wk and practically all patients die within 8–10 wk after the onset of renal failure (Fig. 2) (5, 19). On the other hand, patients with type 2 HRS have a longer median survival time of approximately 6 months (Fig. 2) (5, 19).

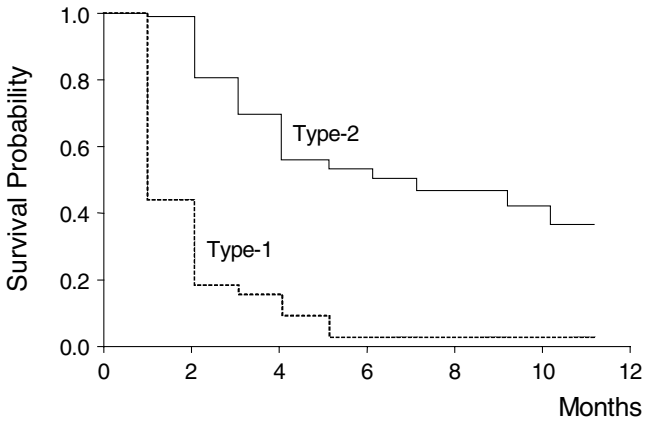

Figure 2. Survival of patients with cirrhosis and type 1 and 2 hepatorenal syndrome. (From Gines *et al*. Hepatorenal syndrome. Lancet 2003;362:1819–27, with permission).

DIAGNOSIS

The diagnosis of HRS is one of exclusion that depends mainly on the level of serum creatinine. Unfortunately, serum creatinine does not provide an exact estimation of GFR in cirrhosis since its level is lower than expected due to a low endogenous production of creatinine related to the reduced muscle mass and the diseased liver that frequently occurs in advanced cirrhosis (16). Creatinine clearance is slightly better but still overestimates GFR by 50% and in addition, is difficult to perform because it depends on the adequate collection of urine volume over 24 h, which in many cases is inadequate, especially in oliguric patients (16, 20). Since the use of inulin clearance for estimation of GFR is expensive and cumbersome, the serum creatinine concentration is currently used to estimate GFR in cirrhosis (1, 19). In fact the diagnosis of HRS is only made when serum creatinine is >1.5 mg/dl (1).

Due to the lack of specific diagnostic tests to distinguish between HRS and other causes of renal failure that may occur in cirrhosis, the diagnosis of HRS is based on several criteria described in Table 3 (1). Low GFR is defined as serum creatinine >1.5 mg/dl without diuretic therapy for at least 5 days. Other criteria include the absence of clinical conditions that predispose to the development of acute renal failure (*i.e.*, volume depletion, shock, bacterial infections, or nephrotoxic drugs), no improvement of renal function following diuretic withdrawal and plasma expansion, no proteinuria, and a normal renal ultrasound. Most cases of HRS have urine sodium below 10 mEq/L and urine osmolality above plasma osmolality because of a preserved tubular function. Nevertheless, a minority of patients may have higher urine

Table 3. Diagnostic Criteria of Hepatorenal Syndrome

Major criteria*
1. Low glomerular filtration rate, as indicated by serum creatinine >1.5 mg/dl.
2. Exclusion of shock, ongoing bacterial infection, volume depletion, and use of nephrotoxic drugs.
3. No improvement in renal function despite stopping diuretics and volume repletion with 1.5 L of saline.
4. No proteinuria or ultrasonographic evidence of obstructive uropathy or parenchymal renal disease.

Minor criteria
1. Urine volume lower than 500 ml/day.
2. Urine sodium lower than 10 mEq/L.
3. Urine osmolality > plasma osmolality.
4. Urine red blood cells <50 per high-power field.
5. Serum sodium concentration lower than 130 mEq/L.

*Only major criteria are necessary for the diagnosis of hepatorenal syndrome.

sodium and low urine osmolality, similar to values found in acute tubular necrosis (1, 21). Conversely, some cirrhotic patients with acute tubular necrosis may have low urine sodium and high urine osmolality. For these reasons, urinary indices are not considered major criteria for the diagnosis of HRS (1, 19).

Other causes of renal failure in cirrhosis such as prerenal failure secondary to volume depletion, acute tubular necrosis, drug-induced nephrotoxicity, renal failure due to radiocontrast agents, and glomerulonephritis in patients with hepatitis B or C should be excluded before the diagnosis of HRS is made. Causes that may predispose to prerenal failure such as volume depletion due to vomiting or diarrhea, or renal fluid losses due to excessive diuretic therapy are common in cirrhotic patients and should be sought after. In prerenal failure due to volume depletion, renal function improves after the intravenous administration of fluids (*i.e.*, 1,500 cc of isotonic saline), whereas no improvement occurs in patients with HRS. Shock before the development of renal failure in a cirrhotic patient precludes the diagnosis of HRS, and usually indicates acute tubular necrosis. In regard to bacterial infections, the diagnosis of HRS should only be made if renal failure persists after complete resolution of the infection. Proteinuria (>500 mg/day) and/or ultrasonographic abnormalities in the kidneys indicate organic renal disease or obstructive uropathy.

MANAGEMENT

General Measures

Type 1 HRS develops in the setting of advanced liver disease in most cases but in some others it occurs in the setting of acute liver failure. In either case patients are very sick and unstable and require hospitalization, preferably in an intensive care unit. Continuous monitoring of vital signs, fluid intake, daily weights, blood chemistries, and urinary output should be performed. Central line access with central venous pressure measurement is helpful in assessing volume status, particularly when intravenous fluid challenge of a plasma expander is administered to rule out renal failure due to intravascular volume depletion. Although useful, this measure is not necessary in all cases. Adequate measures to ensure proper nutrition including a low salt diet are extremely important as these patients are frequently malnourished. In patients with dilutional hyponatremia fluid restriction of 1 L/day is recommended (22). Since the majority of patients have ascites, diagnostic paracentesis must be performed to rule out SBP. Diuretics must be stopped as they can cause worsening renal failure and severe hyperkalemia (in the case of spironolactone). In patients with tense ascites, a therapeutic tap of 5 L associated with albumin infusion (6–8 g/L tapped) may aid in providing comfort. However, it is not known if this amount (5 L) or a larger amount of ascites can be safely tapped in type 1 HRS without causing further deterioration of renal function. The most important aspect of management is to assess the patient for candidacy of liver transplantation. However in order to better prepare patients for liver transplantation renal function must be reversed if possible in order to obtain a better outcome after transplantation. Available therapies for type 1 HRS include the use of splanchnic vasoconstrictors and transjugular portosystemic shunts (TIPS) (Fig. 3).

Patients with type 2 HRS are less sick and for the most part have refractory ascites that can be managed on outpatient basis with large volume paracentesis and albumin expansion (2). Suitable candidates need to be evaluated for liver transplantation. Limited data suggest that these patients also respond well to vasoconstrictors and TIPS (23, 24).

Vasoconstrictor Therapy

A variety of phamacologic interventions have been used to treat HRS. The use of renal vasodilators such as dopamine and prostaglandin analogues was abandoned due to side effects and lack of adequate data confirming their benefit

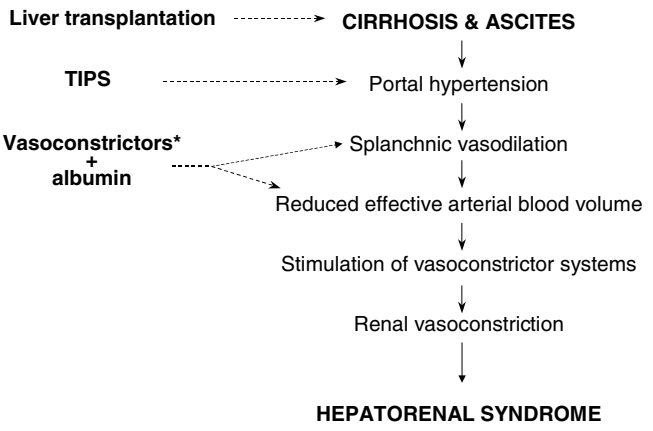

Figure 3. Proposed therapies for Hepatorenal Syndrome in relation to the pathophysiological events leading to its development. TIPS: transjugular intrahepatic portosystemic shunt. Vasoconstrictors*: terlipressin, midodrine, octreotide, and noradrenaline.

(25). Other drugs such as endothelin blockers (BQ123) and N-acetylcysteine are promising, but larger uncontrolled as well as controlled studies, are needed to confirm their role in the therapy of HRS (26, 27). Systemic vasoconstrictors with plasma expansion are probably the best therapy now that several uncontrolled studies have confirmed a beneficial role in HRS (28–39). Vasoconstrictors with plasma expansion are used because the initial event in the pathogenesis of HRS is arterial splanchnic vasodilation causing a decrease in effective arterial blood volume with activation of endogenous vasoconstrictors systems; this approach suppresses these systems and reverses renal vasoconstriction with improvement of renal function.

Vasoconstrictors used for HRS include vasopressin analogues (ornipressin and terlipressin), somatostatin analogues (octreotide), and alpha-adrenergic agonists (midodrine and noradrenaline). In most studies vasoconstrictors were given in combination with albumin, which improves the efficacy of treatment. Vasopressin analogues have a marked vasoconstrictor effect in the splanchnic circulation and have been used for several years in the management of acute variceal bleeding in cirrhotic patients. Ornipressin, although effective in HRS, caused significant ischemic side effects and was abandoned (28). The most studied vasopressin analogue in HRS is terlipressin. The administration of terlipressin and albumin is associated with a significant improvement of GFR and reduction of serum creatinine below 1.5 mg/dl in approximately 60–75% of patients with type 1 HRS (23, 30–36). Although one of the initial concerns about using terlipressin was the development of ischemia (heart and/or extremities), this has not been the case. There is a low incidence of ischemic side effects (approximately $<5\%$) as demonstrated by several studies that pool over 150 patients (30–36). Patients with Child–Pugh scores >13 and those who do not receive albumin expansion do not respond well to this treatment (31, 32). Reversal of HRS occurs over several days but despite improvement in GFR and serum creatinine to normal or near-normal levels, GFR remains below normal values in most patients who respond (30, 32). Recurrence after stopping treatment in responders is uncommon (15% of patients) and a repeat course of terlipressin with albumin is usually effective (30, 32). A drawback of terlipressin is that it is not available in many countries including the United States and therefore alpha-adrenergic agonists are a reasonable alternative given that they are widely available. Administration of midodrine in association with octreotide, an inhibitor of the release of glucagon and other vasodilator peptides, and albumin also improves renal function in cirrhotic patients with HRS although information about this therapeutic approach is limited (37, 38). In one recent study of 14 patients with type 1 HRS treated with midodrine, octreotide, and albumin, 10 had a good response (serum creatinine remained stable at <1.5 mg/dl for 3 days) and were subsequently treated with TIPS if not contraindicated by INR >2.0, serum bilirubin >5 mg/dl, and a Child–Pugh score >12. Five patients underwent TIPS with excellent outcome and one of them received living donor liver transplantation. Interestingly, renal function continued to improve and completely normalized in these 5 patients. Of the 5 who responded to vasoconstrictors and albumin but did not get TIPS, 2 underwent successful liver transplantation, but 3 died as a consequence of liver failure, sepsis, and arrhythmia. There was improved survival in all responders, but the real impact of TIPS in improving survival is difficult to assess given the low number of patients treated. The findings of this study indicate that reversal of HRS achieved by the pharmacological is further enhanced by TIPS placement in appropriate candidates leading to complete normalization of renal function (38). Finally, the administration of noradreline in association with intravenous albumin resulted in a significant improvement of renal function in a small group of 12 cirrhotic patients with type 1 HRS (39).

One of the primary goals of phamacological therapy is that of successfully reversing renal failure so that suitable liver transplant candidates can undergo transplantation with less morbidity and have similar survival to patients without HRS. A recent study revealed that patients treated successfully with vasopressin analogues and albumin before liver transplantation had a similar posttransplantation outcome and survival similar to patients transplanted without HRS (40). This study supports the concept that HRS should be treated aggressively before liver transplantation because improvements in renal function are associated with better outcomes. Nontransplant candidates also benefit from such therapy by reducing morbidity and mortality. In three studies, patients who responded to the therapy of HRS (decrease of creatinine to <1.5 mg/dl) with terlipressin and albumin and octreotide, midodrine, and albumin had an increased survival compared to those who did not respond to this therapy (31, 32, 38). The recommended doses and duration of vasoconstrictor therapy are summarized in Table 4.

Transjugular Intrahepatic Portosystemic Shunt (TIPS)

TIPS is a nonsurgical method of portal decompression used as an alternative therapy for cirrhotic patients bleeding from esophageal or gastric varices who are refractory to endoscopic and medical treatment. TIPS reduces portal pressure and returns some of the volume of blood pooled in the splanchnic circulation to the systemic circulation. This event suppresses RAAS and SNS activity and ameliorates their vasoconstrictor effect on the renal circulation (38, 41). Small uncontrolled studies indicate that TIPS may improve renal function and GFR as well as reduce the activity of RAAS and SNS in cirrhotics with type 1 HRS (24, 38, 42). Improvement in renal function after TIPS placement alone is generally slow with success in approximately 60% of patients (24, 42). However, the effects on renal function and the clinical course of patients after TIPS insertion are variable as some have a delayed response and others actually do worse. One problem with the studies assessing TIPS for type 1 HRS is that patients included were highly selected and those with advanced Child–Pugh score >12 were excluded due to the risk of worsening liver failure and/or hepatic encephalopathy.

Table 4. Recommendations for Using Vasoconstrictors in Type 1 Hepatorenal Syndrome

1.	Goal of treatment: Reduction of serum creatinine below 1.5 mg/dl.
2.	Recommended drugs and doses:
A.	*Terlipressin* 0.5 mg intravenously every 4 h; can increase dose in a stepwise fashion (*i.e.*, every 2–3 days) to 1 mg/4 h and then up to 2 mg/4 h in cases showing no decrease in creatinine (30–36).
B.	*Midodrine* 2.5–7.5 mg orally three times daily with an increase to 12.5 mg three times daily if needed and octreotide 100 ug subcutaneously three times daily with an increase to 200 ug three times daily if needed (37, 38).
C.	*Noradrelaline* 0.5–3 mg/h continuous intravenous infusion (39).
3.	Concomitant intravenous albumin infusion (1 g/kg on the first day, followed by 20–50 g/day)* should be considered in all patients.
4.	Avoid in patients with cardiac diseases, peripheral vascular disease, and/or cerebrovascular disease, due to the potential risk of ischemic events.
5.	Duration of therapy: between 1 and 2 wk

*This dose of albumin has been arbitrarily proposed. It is not known whether smaller doses of albumin or use of other plasma expanders are beneficial in HRS.

Unfortunately, it is these groups of patients that commonly develop type 1 HRS.

In patients with type 2 HRS, TIPS improves renal function and reduces ascites (24, 43–46). However, experience from a large series of cirrhotic patients undergoing TIPS for refractory ascites indicate that those with hepatic encephalopathy, liver failure, and severe coagulopathy are prone to more complications (43, 46). Although uncontrolled studies suggest that TIPS alone improves prognosis in patients with type 1 and 2 HRS (24), the impact of this therapy on patient survival remains to be assessed.

Dialysis

Small uncontrolled studies using hemodialysis and peritoneal dialysis suggest that both are ineffective mainly due to a high incidence of severe side effects, including arterial hypotension, coagulopathy, gastrointestinal bleeding, and increased mortality. In some centers, hemodialysis is routinely used to treat patients with HRS awaiting for liver transplantation, still the effectiveness of dialysis in this setting has not been appropriately studied. Continuous arterio-venous or veno-venous hemofiltration have also been used but their efficacy remains to be determined. Although hemodialysis is not routinely recommended in HRS; it may be a reasonable option in suitable liver transplant candidates as a bridge to transplantation when there is no response to vasoconstrictors or TIPS or patients develop severe volume overload, metabolic acidosis, or refractory hyperkalemia.

Recently, the beneficial effect of an extracorporeal albumin dialysis system (MARS) was reported in 13 patients with Child C cirrhosis and type 1 HRS (47). This system is a dialysis method that enables the selective removal of albumin-bound substances that accumulate in liver failure by the use an albumin-containing dialysate. In this study 5 patients were treated with hemodialysis and standard medical therapy (low-dose dopamine and albumin) and 8 patients were treated with the same plus MARS. The authors reported a significant decrease in bilirubin and creatinine, an improvement in serum sodium, urine volume, mean arterial blood pressure, and decreased mortality in the MARS group. The procedure was well tolerated in all patients. Unfortunately, no parameters evaluating other systemic hemodynamics such as cardiac output or peripheral vascular resistance were done. In addition, there were no measurements of renal function like renal blood flow and GFR. A shortcoming of this study is that improvement in serum values of bilirubin, creatinine, and sodium could represent the effect of the dialysis and not a significant change in hepatic and renal function. Although promising, these results require further evaluation in order to consider dialysis as a therapy, or more importantly as a bridge to liver transplantation in patients with HRS.

Liver Transplantation

Liver transplantation is the best treatment for suitable candidates with HRS, as it offers a cure to both the diseased liver and the circulatory and renal dysfunction. Unfortunately, transplantation for type 1 HRS is limited by the fact that a significant proportion of patients die before the operation because they have a short survival and a prolonged waiting time in most centers. Priority for liver transplantation in the United States is based on the Model for End-stage Liver Disease (MELD) score, which includes three variables; bilirubin, serum creatinine, and international normalized ratio (INR) (48). Patients with HRS usually have high MELD scores, but are only given priority based on the total score. For example, a patient with HRS and a serum creatinine of 3.0 mg/dl may have a near normal bilirubin and INR and although very sick he will not have a high enough score that would move him up the list. Other countries have different allocation systems that give higher priority to patients with type 1 HRS. Regardless of the system used for organ allocation, patients with type 1 HRS need to be appropriately treated before transplantation. As mentioned previously, patients with HRS treated with vasopressin analogues and albumin before transplantation have a good outcome similar to that of non-HRS patients (40).

Because cyclosporine and FK506 treatment may contribute to renal impairment postoperatively, other drugs such as azathioprine, steroids, IL-2 receptor antagonists, or antilymphocyte agents should preferably be used until diuresis and improvement of renal function is observed, usually in 2–4 days after transplantation. The 3 yr probability of survival of transplanted patients with HRS treated with terlipressin and albumin is excellent (100%) and slightly better than that of cirrhotic patients without HRS (40) (83%) (Fig. 4).

Prevention

HRS can be prevented in two clinical settings. First, in patients with SBP the administration of albumin (1.5 g/kg at

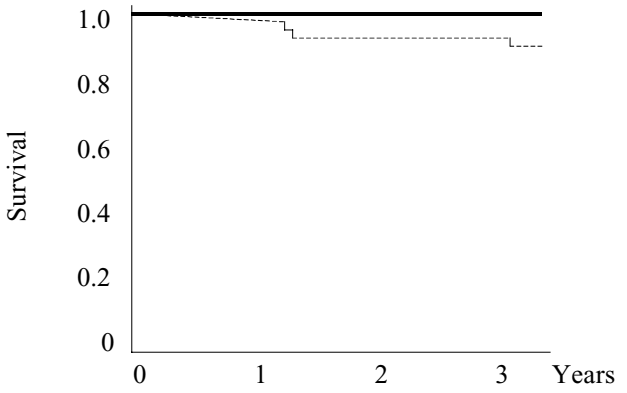

Figure 4. Three-year probability of survival after transplantation of patients with hepatorenal syndrome treated with vasopressin analogues before transplantation (continuous line) and patients without renal failure (discontinuous line). (From Restuccia T *et al*. Effects of treatment of hepatorenal syndrome before transplantation on posttransplantation outcome. A case-control study. J Hepatol 2004;40:140–6, with permission).

diagnosis of infection and 1 g/kg 48 h later) prevents the circulatory dysfunction and subsequent development of HRS (49). Since it appears that SBP may trigger HRS by decreasing effective arterial blood volume, the rationale for albumin administration is to prevent arterial underfilling and subsequent activation of vasoconstrictor systems during the infection (49). The dose of albumin was arbitrarily chosen and it is not known whether smaller doses or other types of plasma expanders are beneficial in preventing renal failure in the setting of SBP. The incidence of HRS in patients with SBP receiving albumin together with antibiotic therapy is 10%, compared with an incidence of 33% in patients not receiving albumin (49). Most importantly, hospital mortality was lower in patients receiving albumin (10%) *versus* those not receiving plasma expansion (29%) (49). Second, in patients with acute alcoholic hepatitis the administration of pentoxifylline, an inhibitor of tumor necrosis factor, (400 mg t.i.d. orally for 28 days) reduces the incidence of HRS and mortality (8% and 24%, respectively) with respect to a control group (35% and 46%, respectively) (3). Although there are no follow-up studies confirming these results, these two approaches are widely used in the clinical setting due to the wide accessibility of albumin and pentoxifylline in most centers.

ACKNOWLEDGMENT

The author would like to thank Dr. Pere Gines and Dr. Michael Curry for reviewing the manuscript.

Reprint requests and correspondence: Andres Cardenas, M.D., M.M.Sc., Division of Gastroenterology and Hepatology, Beth Israel Deaconess Medical Center, Harvard Medical School, 110 Francis Street Ste 8E, Boston, MA 02215.

Received June 11, 2004; accepted June 28, 2004

REFERENCES

1. Arroyo V, Ginès P, Gerbes A, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. Hepatology 1996;23:164–76.
2. Ginès P, Cárdenas A, Arroyo V, et al. Management of cirrhosis and ascites. N Engl J Med 2004;350:1646–54.
3. 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;119:1637–48.
4. Moore K. Renal failure in acute liver failure. Eur J Gastroenterol Hepatol 1999;11:967–75.
5. Ginès A, Escorsell A, Ginès P, et al. Incidence, predictive factors, and prognosis of hepatorenal syndrome in cirrhosis. Gastroenterology 1993;105:229–36.
6. Epstein M, Berk DP, Hollenberg NK, et al. Renal failure in the patient with cirrhosis. The role of active vasoconstriction. Am J Med 1970;49:175–85.
7. 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;8:1151–7.
8. Martin PY, Ginès P, Schrier RW. Role of nitric oxide as mediator of hemodynamic abnormalities and sodium and water retention in cirrhosis. N Engl J Med 1998;339:533–41.
9. Dudley FJ, Esler MD. The sympathetic nervous system in cirrhosis. In: Arroyo V, Ginès P, Rodés J, Schrier RW, eds. Ascites and renal dysfunction in Liver disease. Malden (MA): Blackwell Science, 1999:198–219.
10. Arroyo V, Clària J, Saló J, et al. Antidiuretic hormone and the pathogenesis of water retention in cirrhosis with ascites. Semin Liver Dis 1994;14:44–58.
11. Moore K. 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. Malden (MA): Blackwell Science, 1999:249–72.
12. Cárdenas A, Uriz J, Ginés P, et al. Hepatorenal syndrome. Liver Transplantation 2000;4(Suppl 1):S63–S71.
13. 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;20:1495–501.
14. 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;38:1210–8.
15. Lee SS. Cardiac dysfunction in spontaneous bacterial peritonitis: A manifestation of cirrhotic cardiomyopathy? Hepatology 2003;38:1089–91.
16. 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;154:201–5.
17. Planas R, Ginès P, Arroyo V, et al. Dextran-70 versus albumin as plasma expanders in cirrhotic patients with tense ascites treated with total paracentesis. Results of a randomized study. Gastroenterology 1990;99:1736–44.
18. Cárdenas A, Ginès P, Uriz J, et al. Renal failure after upper gastrointestinal bleeding in cirrhosis. Incidence, clinical course, predictive factors and short-term prognosis. Hepatology 2001;34:671–6.
19. Ginès P, Guevara M, Arroyo V, et al. Hepatorenal syndrome. Lancet 2003;362:1819–27.
20. Roy L, Legault L, Pomier-Layrargues G. Glomerular filtration rate measurement in cirrhotic patients with renal failure. Clin Nephrol 1998;50:342–6.

21. Dudley FJ, Kanel GC, Wood JL, et al. Hepatorenal syndrome without sodium retention. Hepatology 1986;6:248–59.
22. Cárdenas A, Ginès P. Pathogenesis and treatment of dilutional hyponatremia in cirrhosis. In: Arroyo V, Forns X, Garcia-Pagan JC, Rodes J, eds. Progress in the treatment of liver diseases. Barcelona: Ars Medica, 2003:31–42.
23. 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;14:1363–8.
24. 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;47:288–95.
25. Arroyo V, Bataller R, Guevara M. Treatment of hepatorenal syndrome in cirrhosis. 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, 1999:492–510.
26. Soper CP, Latif AB, Bending MR. Amelioration of hepatorenal syndrome with selective endothelin-A antagonist. Lancet 1996;347:1842–3.
27. Holt S, Goodier D, Marley R, et al. Improvement in renal function in hepatorenal syndrome with N-acetylcysteine. Lancet 1999;353:294–5.
28. Guevara M, Gines P, Fernandez-Esparrach G, et al. Reversibility of hepatorenal syndrome by prolonged administration of ornipressin and plasma volume expansion. Hepatology 1998;27:35–41.
29. Gulberg V, Bilzer M, Gerbes AL. Long-term therapy and retreatment of hepatorenal syndrome type 1 with ornipressin and dopamine. Hepatology 1999;30:870–5.
30. Uriz J, Gines P, Cárdenas A, et al. Terlipressin plus albumin infusion: An effective and safe therapy of hepatorenal syndrome. J Hepatol 2000;33:43–8.
31. Moreau R, Durand F, Poynard T, et al. Terlipressin in patients with cirrhosis and type 1 hepatorenal syndrome: A retrospective multicenter study. Gastroenterology 2002;122:923–30.
32. Ortega R, Ginès 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;36:941–8.
33. 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;64:15–9.
34. 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;14:153–8.
35. 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;17:882–8.
36. 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;18:152–6.
37. Angeli P, Volpin R, Gerunda G, et al. Reversal of type 1 hepatorenal syndrome with the administration of midodrine and octreotide. Hepatology 1999;29:1690–97.
38. 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.
39. 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;36:374–80.
40. Restuccia T, Ortega R, Guevara M, et al. Effects of treatment of hepatorenal syndrome before transplantation on post-transplantation outcome. A case-control study. J Hepatol 2004;40:140–6.
41. Boyer TD. Transjugular intrahepatic portosystemic shunt: Current status. Gastroenterology 2003;124:1700–10.
42. Guevara M, Gines P, Bandi JC, et al. Transjugular intrahepatic portosystemic shunt in hepatorenal syndrome: Effects on renal function and vasoactive systems. Hepatology 1998;28:416–22.
43. Ginès P, Uriz J, Calahorra B, et al. Transjugular intrahepatic portosystemic shunting versus paracentesis plus albumin for refractory ascites in cirrhosis. Gastroenterology 2002;123:1839–47.
44. Ochs A, Rössle M, Haag K, et al. The transjugular intrahepatic portosystemic stent shunt procedure for refractory ascites. N Engl J Med 1995;332:1192–7.
45. 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;342:1701–7.
46. Sanyal AJ, Genning C, Reddy RK, et al. Nastra Group. The North American Study of Treatment for Refractory Ascites (NASTRA). Gastroenterology 2003;124:634–41.
47. Mitzer 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;6:277–86.
48. Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. Hepatology 2001;33:464–70.
49. 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;5:403–9.