Hepatorenal Syndrome: Pathophysiology and Management

Hani M. Wadei,*† Martin L. Mai,*† Nasimul Ahsan,*† and Thomas A. Gonwa*†

*Departments of *Transplantation and †Medicine, Division of Nephrology and Hypertension, Mayo Clinic College of Medicine, Jacksonville, Florida*

In the late 19th century, reports by Frerichs (1861) and Flint (1863) noted an association among advanced liver disease, ascites, and oliguric renal failure in the absence of significant renal histologic changes (1). Almost 100 yr later, in a seminal article by Hecker and Sherlock (2), the pathogenesis of hepatorenal syndrome (HRS) was unraveled. The authors demonstrated the lack of major renal histologic changes despite the severity of kidney failure, linked the deterioration in renal function to impairment of the systemic circulation, and concluded that the underlying mechanism of kidney failure is peripheral arterial vasodilation. On the basis of this hypothesis, their patients were treated with norepinephrine with dramatic but short-lived improvement in urine volume and without a significant change in serum creatinine or urea concentrations. The functional nature of HRS was confirmed further by the ability to transplant kidneys from patients with HRS and the normalization of renal function after liver transplantation (3,4). Subsequent studies by Epstein *et al.* (5) demonstrated without doubt that splanchnic and systemic vasodilation together with intense renal vasoconstriction is the pathophysiologic hallmark of HRS. However, despite improved understanding, the prognosis of HRS remained poor, and in the 1970s, the term "terminal functional renal failure" was synonymous with HRS (6). During the last 2 decades, knowledge of the pathogenesis and management of HRS has improved greatly. The present article provides an update on these recent developments.

Definition

HRS is a reversible functional renal impairment that occurs in patients with advanced liver cirrhosis or those with fulminant hepatic failure. It is characterized by marked reduction in GFR and renal plasma flow (RPF) in the absence of other cause of renal failure. The hallmark of HRS is intense renal vasoconstriction with predominant peripheral arterial vasodilation. Tubular function is preserved with the absence of proteinuria or histologic changes in the kidney. Two subtypes of HRS have been identified: Type 1 HRS is a rapidly progressive renal failure that is defined by doubling of initial serum creatinine to a level >2.5 mg/dl or by 50% reduction in creatinine clearance to a level <20 ml/min in <2 wk. Type 2 HRS is a moderate, steady renal failure with a serum creatinine of >1.5 mg/dl. In type 1 HRS, a precipitating factor frequently is identified, whereas type 2 HRS arises spontaneously and is the main underlying mechanism of refractory ascites.

Pathophysiology

HRS is the most advanced stage of the various pathophysiologic derangements that take place in patients with cirrhosis. The hallmark of HRS is intense renal vasoconstriction that starts at an early time point and progresses with worsening of the liver disease (7). The underlying mechanisms that are involved in HRS are incompletely understood but may include both increased vasoconstrictor and decreased vasodilator factors acting on the renal circulation. Type 2 HRS is gradually progressive and arises in association with the progression of cirrhosis, whereas type 1 is an acute deterioration in kidney function associated with severe renal vasoconstriction and failure of compensatory mechanisms that are responsible for maintenance of renal perfusion (8). Four interrelated pathways have been implicated in the pathophysiology of HRS. The possible impact of each one of these pathways on renal vasoconstriction and the development of HRS varies from one patient to the other. These pathways include:

1. Peripheral arterial vasodilation with hyperdynamic circulation and subsequent renal vasoconstriction;
2. Stimulation of the renal sympathetic nervous system (SNS);
3. Cardiac dysfunction contributing to the circulatory derangements and renal hypoperfusion;
4. Action of different cytokines and vasoactive mediators on the renal circulation and other vascular beds.

Peripheral Arterial Vasodilation

In the setting of liver dysfunction and portal hypertension, the effective circulating volume decreases secondary to (*1*) increase in splanchnic blood pooling as a result of increased resistance of blood flow through the cirrhotic liver and (*2*) vasodilation of the systemic and splanchnic circulation resulting from increased vasodilator production (discussed in the Cytokines and Vasoactive Mediators section). The low effective circulating volume unloads the high-pressure baroreceptors in the carotid body and aortic arch with subsequent compensatory activation of the SNS, the renin-angiotensin-aldosterone system (RAAS) and nonosmotic release of vasopressin. This results in a hyperdynamic circulation with increased cardiac output (CO), decreased systemic vascular resistance, hypotension, and

vasoconstriction of the renal vessels. With cirrhosis progression, further splanchnic vasodilation occurs, creating a vicious cycle that favors more systemic vasodilation and subsequent renal vasoconstriction (9). Although this hypothesis provides a rational and simple explanation to the hemodynamic changes that take place in cirrhosis and HRS, it has not been tested in human studies. However, the markedly reduced systemic vascular resistance despite elevated norepinephrine, renin, and aldosterone levels is well documented and is compatible with peripheral vasodilation (10,11). Studies by Fernandez-Seara and others (12,13) demonstrate that the degree of hepatic decompensation directly correlates with the degree of hyperdynamic circulation and inversely correlates with the arterial BP, with the most extreme hemodynamic changes noted in patients with HRS. Finally, the improvement in the hemodynamic and neurohormonal parameters and reversal of HRS with systemic vasoconstrictor administration (discussed below) provide additional support to the peripheral vasodilation role in renal hypoperfusion and vasoconstriction (14–19). It becomes sensible, then, to ask why renal vasoconstriction persists despite the presence of systemic vasodilation. Iwao et al. (13) demonstrated that with liver disease progression and before the development of HRS, femoral artery blood flow decreases, whereas mesenteric blood flow continues to rise. Importantly, Fernandez-Seara et al. (12) showed a correlation between the reduced femoral blood flow and the renal blood flow (RBF) in patients with decompensated cirrhosis, including patients with HRS. Similar correlation is also noted between the cerebral and the upper extremities blood flows and the RBF (20,21). In addition, studies in animal models and humans with cirrhosis consistently demonstrate that the splanchnic circulation is the main vascular bed responsible for the peripheral vasodilation, especially in advanced liver disease (12,22–24). These findings suggest that at an early stage, both the splanchnic and the peripheral circulations are vasodilated and contribute to the genesis of the hyperdynamic circulation. However, with cirrhosis progression, the splanchnic circulation becomes the primary vascular bed responsible for the maintenance of the hyperdynamic state, with subsequent stimulation of the compensatory vasoconstrictor mechanisms leading to vasoconstriction of extrasplanchnic vascular beds, including the kidney.

Stimulation of the Renal SNS

The sympathetic nervous tone is known to be increased in patients with cirrhosis (25,26). Kostreva et al. (27) observed that increasing intrahepatic pressure by vena cava ligation in anesthetized dogs results in rise in renal sympathomimetic activity. This reflex persists despite carotid sinus denervation, bilateral cervical vagotomy, and phrenectomy and abolishes only after sectioning of the anterior hepatic nerves. Further studies by Levy and Wexler (28) demonstrated delayed sodium retention and ascites formation in cirrhotic dogs after hepatic denervation. Similarly, Lang et al. (29) showed reduction in GFR and RPF after inducing hepatocyte swelling using an intramesenteric glutamine infusion. Severing the renal, hepatic, or spinal nerves abolishes this response. On the basis of these observations, a hepatorenal reflex that is activated by increase in he-

patic sinusoidal pressure or reduction in sinusoidal blood flow is suggested. A similar splenorenal reflex also is observed in animal models with portal hypertension (30). Support for this concept in humans comes from the studies by Jalan et al. (31), who demonstrated acute reduction in RBF in a patient with cirrhosis after acute transjugular intrahepatic shunt insertion (TIPS) occlusion. In another study, lumbar sympathectomy increased GFR in five patients with HRS and GFR <25 ml/min but not in three others with GFR >25 ml/min, suggesting that renal sympathetic nerve activity contributes to renal vasoconstriction in a selected group of patients with HRS (32). Hence, the current evidence is lacking a primary role for hepatorenal or splenorenal reflex in HRS in humans. However, the renal sympathetic system may play a contributory role in HRS in selected patients.

Cardiac Dysfunction

Increased heart rate and CO are characteristic features of the hyperdynamic state of advanced liver disease. Under these conditions, it is hard to conceive that myocardial performance is impaired in patients with cirrhosis. This concept was challenged by studies that demonstrated decreased cardiac function in cirrhotic animals (33,34). In humans, Bernardi et al. (35) evaluated cardiac function in 22 nonalcoholic patients with cirrhosis and demonstrated impaired myocardial contractility both at rest and on exercise that correlated with the degree of cirrhosis. Similarly, diastolic dysfunction is documented in patients with cirrhosis, the degree of which parallels the degree of liver dysfunction (36,37). Importantly, these cardiac changes reverse 9 to 12 mo after liver transplantation, suggesting that the diseased liver rather than the cause of liver disease (e.g., alcohol) is responsible for the cardiac dysfunction (36). Cardiac dysfunction also may explain the elevated plasma natriuretic peptide level that has been observed in some but not all patients with cirrhosis, despite reduced central venous pressure (38). In one study of 52 decompensated patients with cirrhosis, natriuretic peptide level correlated with the Child-Pugh score and the ventricular wall thickness (39). The mechanism of impaired cardiac function is complex and may include (1) neurohumoral hyperactivity leading to myocardium growth and fibrosis with disturbed relaxation; (2) diminished myocardial β adrenergic receptor signal transduction; and (3) an inhibitory effect of circulating cytokines, including TNF-α and nitric oxide (NO), on ventricular function (37,40,41). In alcoholic patients, a variable degree of alcoholic cardiomyopathy also can be a contributing factor. The role of cardiac dysfunction in HRS was recently studied by Ruiz-del-Arbol et al. (42), who demonstrated reduction in CO at time of diagnosis of spontaneous bacterial peritonitis (SBP) without a change in systemic vascular resistance in patients who had cirrhosis and subsequently developed HRS. CO further decreased after resolution of infection in the HRS group but not in those without renal failure (42). The same group studied the systemic and hepatic hemodynamics of 66 patients with cirrhosis and tense ascites and normal serum creatinine at baseline with repeat measurement in 27 patients who subsequently developed HRS. At baseline, arterial BP and CO was significantly lower whereas

RAAS and SNS activity were significantly higher in the group that developed HRS with further reduction in CO at the onset of renal dysfunction (43). The findings of these two studies suggest that a decrease in CO identifies a group of patients who are at risk for HRS and implicate decreased CO or its cause in HRS occurrence. Although these results contradict a previous report that showed poor correlation between decreased CO and reduction in RBF, RBF is known to overlap between patients who have cirrhosis with and without HRS (44,45). It certainly is possible, then, that some patients with cirrhosis despite their high CO have a relatively depressed cardiac response to stress (*e.g.*, infections) that contributes to the systemic hypotension and renal hypoperfusion. In the absence of increased metabolic demand, this cardiac dysfunction remains clinically silent masked by the afterload reduction that is observed in cirrhosis. Clinical experience suggests that cardiac reserve may be diminished and acute heart failure may manifest in otherwise stable patients after TIPS or liver transplantation (46,47). Cardiac dysfunction, along with its contribution to HRS, clearly needs further studies to determine whether it is involved directly in the pathogenesis of HRS or merely serves as a marker of an alternative factor that is involved in HRS development.

Cytokines and Vasoactive Mediators

Because RBF overlaps between patients who have cirrhosis with and without HRS, other factors that are involved in the regulation of intrarenal hemodynamics and GFR are operative in HRS (45,48,49). These factors include vasoactive agents that affect both the systemic and the renal circulation. Studied vasoactive agents include NO, TNF-α, endothelin, endotoxin, glucagon, and intrarenal vasodilating prostaglandins. Of the systemic agents, NO has gained wide attention. NO production is increased in cirrhosis as a result of upregulation of endothelial NO synthase (eNOS) activity from increased shear stress in the splanchnic and systemic circulation as well as endotoxin-mediated eNOS activation (50,51). Increased inducible NOS activity has also been demonstrated (52). In animal models, NO is responsible for the reduced pressor effect of endogenous vasoconstrictors in the splanchnic circulation (53). Moreover, inhibition of NO synthesis corrects circulatory abnormalities and reverses neurohormonal changes in cirrhotic rats (54). In humans, inhibition of NOS activity in 10 patients with cirrhosis and ascites decreased forearm blood flow and increased vascular resistance (55). Similarly, acute NOS inhibition increases systemic vascular resistance in patients with decompensated cirrhosis and decreases plasma renin activity and urinary prostaglandin E2 excretion (56). Patients with cirrhosis and ascites have higher NO plasma concentrations than normal individuals or those with compensated cirrhosis, and high serum NO level correlates with high plasma RAAS activity and antidiuretic hormone levels as well as low urinary sodium excretion (57,58). The concentration of NO is higher in portal venous plasma than in peripheral venous plasma, suggesting increased splanchnic production of NO (59). Although there is enthusiasm for a role for NO in peripheral vasodilation, there still is a controversy about whether NO is the primary factor in the genesis and maintenance of the hyperdynamic circulation (60).

In addition, the vasodilating effect of NO is expected to antagonize renal vasoconstriction; however, in HRS, renal vasoconstriction progresses despite elevated NO levels. The explanation of this is not clear, but Lluch *et al.* (61) suggested that the increase in the plasma level of asymmetric dimethylarginine, a natural eNOS inhibitor, in terminal liver failure may antagonize the elevated NO level and hence promote renal vasoconstriction in HRS.

In the kidney, the renal vasoconstriction is counterbalanced by increased intrarenal production of vasodilating prostaglandins and kallikreins. Urinary excretion of vasodilating prostaglandins is higher in patients with cirrhosis and ascites compared with normal individuals with subsequent decline in urinary prostaglandin excretion in those with HRS (62,63). Similarly, the administration of cyclooxygenase inhibitors to patients with cirrhosis and ascites precipitates a syndrome that is indistinguishable from HRS, indicating a role for vasodilating prostaglandins in maintaining GFR (64). In addition, immunohistochemical studies demonstrate reduced cyclooxygenase staining in renal medullary tissue of patients with HRS, whereas the enzyme is detected in kidneys of patients with other causes of acute renal failure (ARF) (65). Factors that are associated with reduced prostaglandin production in HRS are unknown, but intense renal vasoconstriction may contribute to reduced prostaglandin synthesis (66). Conversely, intrarenal or systemic prostaglandin infusion in patients with HRS failed to improve renal function, suggesting that decreased prostaglandin production is not the sole player in HRS (67,68). Figure 1 illustrates the proposed pathophysiologic mechanisms that are involved in HRS.
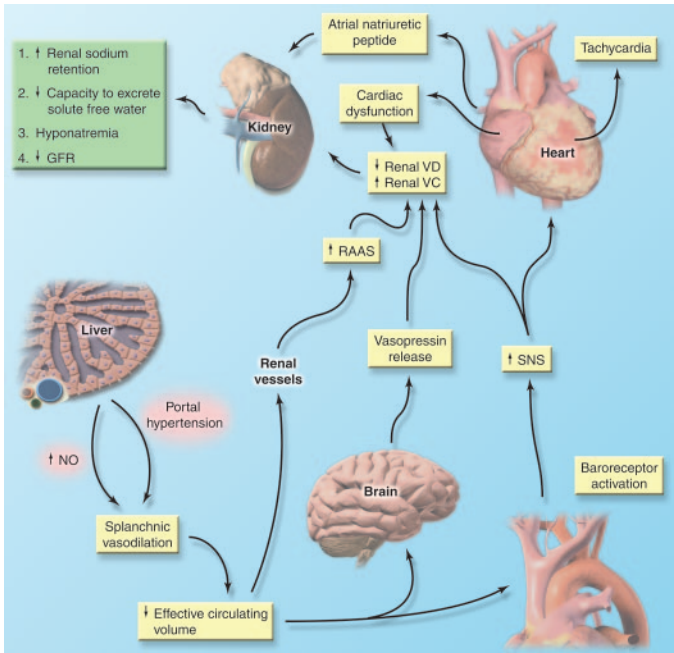

Figure 1. Pathophysiologic mechanisms of hepatorenal syndrome (HRS). Renal VD, renal vasodilators; Renal VC, renal vasoconstrictors; SNS, sympathetic nervous system.

Precipitating Factors

In type 1 HRS, a precipitating event is identified in 70 to 100% of patients with HRS, and more than one event can occur in a single patient (14,69–71). Identifiable precipitating factors include bacterial infections, large-volume paracentesis without albumin infusion, gastrointestinal bleeding, and acute alcoholic hepatitis. Of the bacterial infections, a clear chronological and pathogenetic relationship is established for SBP: 20 to 30% of patients with SBP develop HRS despite appropriate treatment and resolution of infection (72,73). Similarly, large-volume paracentesis without albumin expansion precipitates type 1 HRS in 15% of cases, and 25% of patients who present with acute alcoholic hepatitis eventually develop HRS (74,75). Although ARF after gastrointestinal hemorrhage occurs more frequently in patients with cirrhosis compared with those without liver disease with similar amount of bleeding (8 *versus* 1%; $P < 0.05$), ARF develops almost exclusively in patients with hypovolemic shock, making acute tubular necrosis (ATN) a more plausible diagnosis (76). Intravascular volume depletion by overzealous diuretic use has been considered a triggering factor for HRS; however, evidence to support this is lacking (77).

How can a precipitating factor lead to HRS? Navasa *et al.* (66) suggested that renal failure in SBP is due to cytokine-induced aggravation of the circulatory dysfunction with further stimulation of the RAAS and SNS and worsening renal vasoconstriction. Exacerbation of renal hypoperfusion and aggravation of renal ischemia creates an intrarenal vicious cycle that favors more renal vasoconstrictor release and impairs renal vasodilator synthesis (78,79). This vicious cycle eventually will progress to HRS even if the underlying precipitating event has been corrected. Another possible explanation is that the deterioration in renal function is secondary to deterioration in cardiac function as a result of either the development of septic cardiomyopathy or worsening of a latent cirrhotic cardiomyopathy. Figure 2 outlines the role of precipitating factors in inducing HRS. In type 2 HRS and in some patients with type 1 HRS, no precipitating factor can be identified. The mechanism of renal failure in these cases is unclear, but it seems to be related to worsening liver disease with subsequent failure of compensatory mechanisms that aim to maintain adequate renal perfusion.

Incidence and Predicting Factors

Gines *et al.* (74) estimated the 1-yr probability of HRS in patients with cirrhosis at 18% and the 5-yr probability at 39%. Although this study was published before standardization of the diagnostic criteria for HRS by the International Ascites Club (IAC), more recent studies confirm that HRS still constitutes a significant risk for renal failure in patients with cirrhosis. A multicenter, retrospective study of 423 patients with cirrhosis and ARF demonstrated that the most common cause of ARF is either ATN (35%) or prerenal failure (32%). Types 1 and 2 HRS are the cause of ARF in 20 and 6.6% of cases, respectively (19). Similarly, in the study by Wong *et al.* (80), ATN and HRS were the most common causes of ARF in 102 patients who had
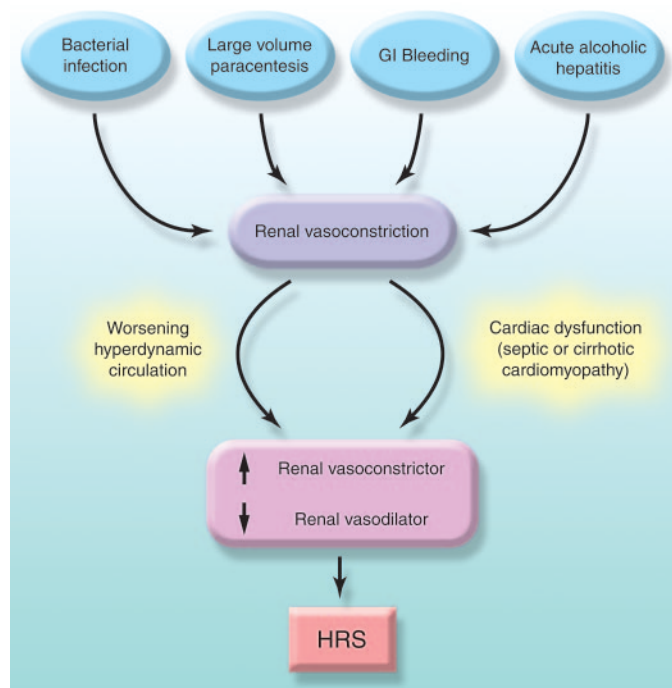

Figure 2. Role of a precipitating factor in HRS.

cirrhosis, were on renal replacement therapy (RRT), and were waiting for liver transplantation; 48% of those had HRS.

Early detection of renal vasoconstriction by Doppler ultrasound predicts future development of HRS in patients with cirrhosis. In a prospective study done by Platt *et al.* (7), patients with cirrhosis and elevated renal resistive indices and normal renal function have a 55% probability for developing subsequent kidney dysfunction compared with 6% with normal indices. HRS develops in 26% of patients with elevated resistive indices compared with 1% of those with normal indices ($P < 0.001$) (7). Factors that are reflective of severe hemodynamic derangements and marked neurohormonal activation also predict HRS. The most easily identified are dilutional hyponatremia, low urinary sodium, reduced plasma osmolality, and low arterial BP. On multivariate analysis, three independent predictors of HRS occurrence were identified: Hyponatremia, high plasma renin activity, and absence of hepatomegaly (74).

Diagnosis

The diagnosis of HRS is one of exclusion and should be made on the basis of the criteria outlined by the IAC (81) (summarized in Table 1). Only the major criteria are necessary to make the diagnosis, with an aim first to document a reduced GFR (<40 ml/min) and second to exclude other causes of renal failure. Renal function needs to be reassessed after diuretic withdrawal and after volume replacement. Every attempt must be made to exclude concurrent bacterial infection. It is important to mention that patients with cirrhosis and ARF mistakenly might be labeled as having HRS. Watt *et al.* (69) showed that only 59% of ARF that was diagnosed as HRS fulfilled the IAC criteria for the diagnosis.

Table 1. Diagnostic criteria of HRS[a]

Major Criteria[b]
  Low GFR, as indicated by serum creatinine >1.5 mg/dl or 24-h creatinine clearance <40 ml/min
  Absence of shock, ongoing bacterial infection, fluid losses, and current treatment with nephrotoxic drugs
  No sustained improvement in renal function (decrease in serum creatinine to ≤1.5 mg/dl or increase in creatinine clearance to ≥40 ml/min) after diuretic withdrawal and expansion of plasma volume with 1.5 L of a plasma expander
  Proteinuria <500 mg/d and no ultrasonographic evidence of obstructive uropathy or parenchymal renal disease
Additional Criteria
  Urine volume <500 ml/d
  Urine sodium <10 mEq/L
  Urine osmolality greater than plasma osmolality
  Urine red blood cells <50/high-power field
  Serum sodium concentration <130 mEq/L

  [a]HRS, hepatorenal syndrome.
  [b]Only major criteria are necessary for diagnosis of HRS.

Table 2. Cause of acute renal failure in patients with cirrhosis

Prerenal causes
  intravascular volume depletion and hypotension
  gastrointestinal fluid loss (nasogastric suction) or pooling of fluid (pancreatitis, bowel disease)
  trauma, surgery, burns
Decreased effective intravascular volume
  congestive heart failure or other causes of myocardial failure
  nephrotic syndrome, infection caused by spontaneous bacterial peritonitis
HRS types 1 and 2
Anaphylaxis
Anesthetic agents
Renal artery or renal vein occlusion by thrombosis; atheroembolism
Intrinsic causes
  tubular necrosis
  ischemic (as a consequence of above-mentioned prerenal events)
  toxic as a result of drugs, organic solvents (carbon tetrachloride, ethylene glycol), heavy metals (mercury, cisplatin), heme pigments (rhabdomyolysis), myeloma light chain
Interstitial nephritis related to drugs, infection, cancer, or sarcoidosis
Postrenal causes
  upper urinary tract obstruction: Ureteral obstruction of one or both kidneys
  lower urinary tract obstruction: Bladder-outlet obstruction

Differentiation between HRS and other causes of ARF in liver disease, especially ATN, is usually difficult. Patients with prerenal azotemia and HRS are sodium avid, with a urine sodium concentration <20 mEq/L and fractional excretion of sodium <1%. In contrast, urine sodium is elevated in ATN. Nevertheless, a minority of patients with HRS may have high urine sodium values, especially if they previously were treated with diuretics (77,81). Conversely, urine sodium may be low early in the course of ATN or after radiocontrast agents. For these reasons, urinary indices are not needed for the diagnosis. Differentiation between these two causes of ARF on the basis of urine sediment may be confounded by the presence of granular casts associated with hyperbilirubinemia in patients with prerenal azotemia and HRS. The presence of proteinuria or hematuria or ultrasonographic evidence of parenchymal renal disease points toward other causes of renal failure. Table 2 lists the potential causes of ARF in patients with cirrhosis.

Prognosis

Untreated type 1 HRS carries a grim prognosis: Mortality is as high as 80% in 2 wk, and only 10% of patients survive >3 mo (74,81). The prognosis is particularly poor in patients with apparent precipitating factors. By contrast, patients with type 2 HRS have a much better median survival, approximately 6 mo (77). The second important determinant of survival is the severity of liver disease; patients with Child-Pugh class C disease have a worse outcome compared with those with class B disease (77). A recent study assessed the prognostic value of the model of end-stage liver disease (MELD) score, the system that currently is used for liver allocation, on outcome of HRS (82). MELD score was an independent predictor of death from HRS

with the median survival of patients with a MELD score of 20 or more being only 1 mo compared with 8 mo in those with a MELD score <20 ($P < 0.001$). It is interesting that patients with type 1 HRS had a very poor prognosis (median survival 1 mo), which was almost independent of the MELD score (82).

Treatment

General Measures

Patients with type 1 HRS usually require hospitalization, whereas those with type 2 HRS can be treated on an outpatient basis. In hospitalized patients, central venous access is helpful to assess the intravascular volume status and guide fluid and albumin infusion. Diuretics should be stopped, and tense ascites can be managed with paracentesis. If >5 L of ascitic fluid will be removed, then albumin seems to be superior to other plasma expanders in preventing circulatory dysfunction after paracentesis (83,84). Every effort should be made to exclude other causes of ARF and to look for precipitating factors, especially SBP. Special consideration should be given to nutrition because these patients usually are malnourished; however, a high-protein diet may precipitate hepatic encephalopathy and aggravate the metabolic abnormalities. A low-salt diet should

be reinforced in all cases as well as free water restriction in those who develop hyponatremia (85). Once the patient is stabilized, realistic assessment of the patient's overall prognosis and concurrent medical condition will determine future management plans. Given the dismal prognosis of patients with type 1 HRS, aggressive therapy usually is indicated only for patients who are waiting for a liver transplant or undergoing evaluation to determine candidacy for transplantation. There are four major therapeutic interventions for the patient with HRS: Pharmacologic treatment, TIPS, RRT, and liver transplantation.

Pharmacologic Treatment

The goal of pharmacologic therapy is to reverse renal failure and prolong survival until candidates undergo liver transplantation. Pharmacologic agents can be grouped into two broad categories: Renal vasodilators and systemic vasoconstrictors.

Renal Vasodilators. Because the immediate cause of HRS is renal vasoconstriction, it was sensible to hypothesize that the changes in renal hemodynamics could be reversed either by using direct renal vasodilators (dopamine, fenoldopam, and prostaglandins) or by antagonizing the endogenous effect of renal vasoconstrictors (saralasin, angiotensin-converting enzyme inhibitors, and endothelin antagonist). Unfortunately, none of the studies that used renal vasodilators showed improvement in renal perfusion or GFR. Relevant among these are the studies by Barnardo et al. (86) and Bennett et al. (87), who demonstrated that low-dose dopamine infused for up to 24 h improved cortical blood flow and angiographic appearance of renal cortical vasculature without improvement in GFR or urine flow. Subsequent studies that used low-dose dopamine consistently showed the same response both in refractory ascites and in HRS (88,89). Attempts to use dopamine in combination with vasoconstrictors conferred a better success rate, but this could be attributed to vasoconstrictor therapy (90,91). Similarly, the oral prostaglandin-E1 analog misoprostol or intravenous prostaglandin infusion did not induce significant changes in GFR or sodium excretion (92,93). Improvement in renal function occurred in one report but could be explained by volume expansion (94). The endothelin-A antagonist BQ-123 demonstrated a dose-dependent renal improvement in three treated patients, but there still is controversy over the role of endothelin blockers in HRS because subsequent studies showed a paradoxic vasodilating effect of endothelin in patients with cirrhosis (95,96). Because of adverse effects and lack of benefit, the use of renal vasodilators in HRS largely has been abandoned.

Systemic Vasoconstrictors. Systemic vasoconstrictors are the most promising pharmacologic agents in the management of HRS. They rely on the assumption that interrupting the splanchnic vasodilation will subsequently relieve the intense renal vasoconstriction. Studied vasoconstrictors include vasopressin analogues (ornipressin and terlipressin), somatostatin analogue (octreotide), and the α-adrenergic agonists (midodrine and norepinephrine).

Vasopressin analogues have marked vasoconstrictor effect through their action on the V1 receptors that are present in smooth muscles of the arterial wall. They are used extensively for the management of acute variceal bleeding in patients with cirrhosis and portal hypertension. Ornipressin infusion combined with volume expansion or low-dose dopamine is associated with a remarkable improvement in renal function and an increase in RPF, GFR, and sodium excretion in almost half of the treated patients (90,97,98). Despite its efficacy, ornipressin use largely has been abandoned because of significant ischemic adverse effects that develop in almost 30% of treated patients (97).

Terlipressin is the most currently studied vasopressin analogue. The administration of terlipressin and albumin is associated with significant improvement in GFR, increase in arterial pressure, near normalization of neurohumoral levels, and reduction of serum creatinine in 42 to 77% of cases (14–19). Despite the lack of a control group in all published studies, survival is constantly improved compared with historic cases, yet the median survival still is reduced at 25 to 40 d. Nonresponders tended to have more severe cirrhosis (Child-Pugh score >13) and marked reduced survival (14). The benefits of terlipressin seem to extend to type 2 HRS with slightly better response rate and longer survival than in type 1 (15,17). Ischemic adverse effects are less common, with terlipressin averaging between 10 and 25%; however, most studies excluded patients with a history of ischemic events. There is a 50% recurrence rate of HRS, but in all cases, HRS was reversed with reintroduction of therapy. The question still remains whether volume expansion, rather than terlipressin, is the mediator of improvement. Indeed, a recent study reported improved survival and reversal of HRS in 11 (55%) of 20 patients who were treated with intravenous albumin and diuretics (71). Also, the optimum duration of therapy is not clear. All studies used terlipressin until serum creatinine decreased to <1.5 mg/dl or for a maximum of 15 d. Whether extending the therapy beyond this preset duration will add any benefit is not known. Finally, the survival advantage of terlipressin is short lived, and 80% of patients who do not receive a transplant will succumb to their liver disease within 3 mo of therapy. Nonetheless, terlipressin and albumin infusion is a good alternative to those who are waiting for transplantation especially because pretransplantation normalization of kidney function in patients with HRS using vasopressin analogues confers similar posttransplantation outcomes to those who receive a transplant with normal renal function (99).

A drawback of terlipressin is its unavailability in many countries, including the United States. In these countries, vasopressin, not its analogue, often is used (100). Octreotide, an inhibitor of glucagon and other vasodilator peptide release, and α-adrenergic agonists such as midodrine and norepinephrine also are reasonable alternatives. Octreotide with albumin infusion proved to be ineffective for the treatment of HRS, whereas oral monotherapy with midodrine slightly improved systemic hemodynamics but failed to improve renal function in eight patients with type 2 HRS (101,102). However, when both agents were given in combination with albumin infusion, a significant improvement in renal function and survival was observed in five patients with type 1 HRS (103). It still is unclear whether

vasopressin analogues or combined therapy with octreotide and midodrine is more efficacious in reversing HRS. Kiser *et al.* (100) compared vasopressin and octreotide therapy in 43 patients with type 1 HRS. Patients who were treated with vasopressin had a significantly higher HRS recovery rate and improved survival and were more likely to receive a liver transplant (100). Finally, the administration of intravenous norepinephrine in association with albumin and furosemide resulted in reversal of HRS in 10 (83%) of 12 patients with type 1 HRS, and ischemic episodes were observed in only two (104). It is interesting that two of the responders to norepinephrine had previously failed terlipressin therapy. Regression of renal failure was associated with improvement in patients' survival, and four of the responders did not require liver transplantation 6 to 18 mo after recovery of renal function. Although norepinephrine use seems to be paradoxic because its level is already elevated in patients with HRS, the results are encouraging and deserve further confirmation in prospective studies.

TIPS

The association between the reduction of portal pressure that is induced by TIPS insertion and beneficial changes in neurohumoral factors and renal function in patients with cirrhosis and refractory ascites, a forerunner of HRS, is well documented (105–109). The mechanism by which TIPS exerts this effect still is speculative but could be the result of reduction of portal pressure, suppression of a putative hepatorenal reflex, improvement of the circulating volume, or amelioration of cardiac function (27,110). In an elegant study, Guevara *et al.* (111) prospectively investigated the biochemical, hemodynamic, and neurohumoral changes after TIPS insertion in seven patients with type 1 HRS. One month after TIPS, renal function improved in six (86%) patients, with significant reduction in serum creatinine and increase in urine volume. These clinical changes paralleled amelioration in renal hemodynamics with a significant rise in GFR and RBF. Moreover, the plasma levels of different vasoconstrictor mediators were significantly reduced. Patients' survival ranged from 10 to 570 d, with 30-d survival achieved in five (71%) patients (111). Another prospective, nonrandomized study evaluated the effect of TIPS on long-term outcome of 31 patients who had type 1 and type 2 HRS and were not candidates for liver transplantation (112). After TIPS, the 3-, 6-, 12-, and 18-mo survival was 81, 71, 48, and 35%, respectively. Importantly, the survival at 10 wk of patients who had type 1 HRS and were treated with TIPS was 53%, a significant improvement compared with historical cases and better than the one reported after terlipressin and albumin infusion (15,74). A novel finding was the ability to discontinue dialysis in four of the seven dialysis-dependent patients after TIPS insertion. Moreover, liver transplantation was performed in two patients 7 mo and 2 yr after TIPS, when the medical condition that precluded transplantation has abated. Although the results of these studies are encouraging and compatible with a beneficial effect of TIPS on reversal of HRS and improvement in patient survival, there still are unanswered observations. First, the clinical, biochemical, and neurohumoral parameters, although improved, still do not normalize after TIPS,

suggesting that TIPS does not correct all of the underlying mechanisms of HRS. Second, the maximum renal recovery is delayed to 2 to 4 wk after TIPS insertion, and the renal capacity to excrete sodium still is impaired. The cause of this delay and the inability to normalize salt excretion are not clear. Third, patients with advanced cirrhosis are at risk for worsening liver failure and/or hepatic encephalopathy and are not candidates for TIPS. Fourth, TIPS has the potential for worsening the existing hyperdynamic circulation or precipitating an underlying acute heart failure; therefore, careful attention to the cardiac status is required (107). Nevertheless, there is a group of patients who have HRS and for whom TIPS insertion might prolong survival enough either to receive a liver transplant or, if they are not candidates, to stay off dialysis.

Combination Therapy

As previously mentioned, vasoconstrictor therapy and TIPS insertion improve but do not normalize renal function, neurohumoral, and hemodynamic changes in HRS. The explanation for this lack of normalization is not clear but possibly is the result of either the existence of a component of renal failure that is not related to circulatory dysfunction or the persistence of reduced effective circulating blood volume despite either of these therapies. A recent prospective study by Wong *et al.* (70) supported the second hypothesis. Fourteen patients with cirrhosis and type 1 HRS were treated with oral midodrine and intravenous octreotide with albumin infusion followed by TIPS insertion in selected patients with preserved liver function. The exciting finding was the persistent improvement in serum creatinine, RPF, GFR, and natriuresis after TIPS insertion. Similarly, plasma renin and aldosterone levels were significantly reduced 1 mo after TIPS. All five patients who received combined therapy were alive 6 to 30 mo after TIPS, with only one patient requiring liver transplantation 13 mo afterward. Conversely, patients who responded to vasoconstrictors and did not receive TIPS either died (three patients) or required a liver transplant (two patients). Considering the small number of patients and that those with advanced cirrhosis were inherently not candidates for TIPS, this study suggests that combination therapy may preclude the need for future liver transplantation and improve survival compared with vasoconstrictor therapy alone. Similarly, a beneficial effect of combination therapy was observed in 11 patients who had type 2 HRS and were treated with sequential terlipressin and TIPS insertion (17). These results are very encouraging and require future prospective assessment.

RRT

Initiation of RRT is controversial in untreated patients who have type 1 HRS and are not candidates for liver transplantation because of the dismal chance of survival and the high morbidity and mortality rates that are associated with RRT (113,114). However, mortality is even higher in patient who have HRS and do not receive RRT. In a retrospective study by Keller *et al.* (115), seven (44%) of 16 patients who had HRS and received RRT survived compared with only one (10%) of 10 who did not receive RRT. However, prolonged patient survival

is incurred at the cost of increased morbidity and hospital stay, with 33% of the days gained spent in the hospital (116). Therefore, the decision to initiate RRT in these patients should be individualized.

For those who are waiting for a liver transplant and did not respond to vasoconstrictors or TIPS or developed volume overload, intractable metabolic acidosis, or hyperkalemia, RRT may be a reasonable option as a bridge to transplantation, yet the efficacy, safety, and best modality of RRT in HRS has not been studied appropriately. Davenport *et al.* (117–119) and Detry *et al.* (120) demonstrated that continuous RRT (CRRT) is better tolerated than intermittent hemodialysis (HD) in patients with liver failure as evidenced by better cardiovascular stability, gradual correction of hyponatremia, and less fluctuation in intracranial pressure. Furthermore, CRRT has the potential advantage of removing inflammatory cytokines, including TNF-α and IL-6, both of which have been implicated in the development of HRS and the exacerbation of hepatic injury (66,75,121–123). Despite these presumed advantages, in a prospective study by Witzke *et al.* (124), CRRT did not confer a survival benefit in 30 patients who had HRS and were waiting for liver transplantation. Patients were subjected to either CRRT when they were mechanically ventilated or HD when they were not. Eight (53%) patients who were treated with HD survived for 30 d, whereas none of the CRRT patients survived for the same duration. At 1 yr, only three were still alive; all received either liver (two patients) or combined liver/kidney transplantation (LKT; one patient), and none required posttransplantation HD. The author concluded that CRRT in patients who have HRS and are on mechanical ventilation is futile (124). In contrast to this experience, the group from Baylor in Dallas reported on their experience in patients who underwent RRT before liver transplantation (125). From 1985 to 1995, 10 patients received preoperative RRT (all HD) and their 1-yr survival after transplantation was 89.5%. From 1996 to 1999, a total of 19 patients also received preoperative RRT: One HD and 18 CRRT; the 1-yr patient survival in this group was lower, at 73.6%, possibly reflecting the more serious nature of their illness. Another recent study of 102 patients who had cirrhosis and ARF, 48% of them with HRS, and were awaiting a liver transplant and receiving RRT showed increased mortality for those who were maintained on CRRT compared with HD (78 *versus* 50%; $P = 0.02$) (80). Nevertheless, those who received CRRT had greater severity of illness and lower BP than those who received HD. The authors concluded that RRT still is justifiable in HRS as the high mortality rate is comparable to similarly ill patients who have ARF without cirrhosis (80). Although the best modality of RRT in HRS is not well defined, patients who have HRS and receive RRT can be treated with either HD or CRRT before transplantation with similar outcomes.

The molecular adsorbent recirculating system (MARS) is a cell-free, modified dialysis technique that is able to remove both albumin-bound and water-soluble substances by using a combination of albumin-enriched dialysate and CRRT (126). The advantage of using MARS in HRS relies on the assumption that removing albumin-bound toxins (*e.g.*, bile acids), which have a detrimental effect on hepatocytes and other organs,

including the kidney, will stabilize liver function and improve other end-organ damage (127,128). Furthermore, MARS has the ability to remove both water-soluble cytokines (TNF-α and IL-6) and albumin-bound vasoactive agents (*e.g.*, NO), both of which have been implicated in the pathogenesis of HRS (60,129). In a prospective, randomized, controlled study, Mitzner *et al.* (126) showed that MARS improved clinical and biochemical parameters as well as survival in eight patients who had type 1 HRS and were not candidates for TIPS insertion compared with a well-matched group of patients who were treated with volume expansion and CRRT. Survival was better in the MARS group, with a mean survival of 25 d compared with 4.6 d in the control group. Despite improved survival, the overall survival still was low, with 7-d survival of 37% and 30-d survival of 25%. In another uncontrolled study, eight patients with type 1 HRS and alcoholic hepatitis were treated with MARS and showed improvement in urine volume, mean arterial BP, encephalopathy grade, and Child-Pugh score (130). Five patients survived >12 mo, with only one patient requiring a liver transplant 18 mo after therapy. In both studies, patients received five to six MARS treatments, and MARS therapy was well tolerated. Although promising, the results of MARS require further evaluation to be considered as a bridge to transplantation. Until then, MARS should not be used in the treatment of HRS outside of clinical trials.

Liver Transplantation

Liver transplantation remains the best treatment for suitable candidates with HRS because it offers a cure to both the diseased liver and the renal dysfunction. Indeed, subsequent to liver transplantation, renal sodium excretion and hemodynamic abnormalities normalize within 1 mo, and renal resistive indices decrease to normal values during the first posttransplantation year (131,132). Survival of patients with type 2 HRS is sufficiently prolonged to enable them to receive a liver transplant; however, the clinical applicability of transplantation in patients with type 1 HRS is limited by their shortened survival expectancy and long waiting times. Currently, the liver allocation in the United States is based on the MELD score. In the study by Alessandria *et al.* (82), patients with HRS seemed to be disadvantaged by this system because they had worse survival compared with matched liver transplant candidates without HRS for any given MELD score. This highlights the need to allocate livers differently to patients with HRS to give them priority for transplantation.

Renal function before liver transplantation is an independent predictor of both short-term and long-term posttransplantation patient and graft survival (133). Gonwa *et al.* (134,135) studied the effect of HRS on posttransplantation outcomes. Although the 2-yr patient and graft survival was similar in those with or without HRS, the actuarial 5-yr patient and graft survival rates were decreased in those with HRS. After transplantation, patients with HRS were sicker and required longer hospitalizations, prolonged stays in the intensive care unit, and more dialysis treatments. It is interesting that pretransplantation treatment of HRS with vasopressin analogues confers a slightly better 3-yr survival than those without HRS (100 *versus* 83%)

(99). However, a longer follow-up period still is needed to determine whether pretransplantation treatment of HRS actually will have an impact on posttransplantation outcomes.

After transplantation, renal failure still persists at 6 wk and is more pronounced than those without pretransplantation HRS (135). The reported rate of posttransplantation complete renal function recovery is variable. In the study by Gonwa *et al.* (135), 7% of patients with HRS ultimately developed ESRD compared with 2% in those without HRS. With pretransplantation vasopressin analogue therapy, the incidence of renal failure at 6 mo was similar in patients with HRS to those with normal kidney function at transplantation (22 *versus* 30%; $P = 0.7$) (82). Despite these encouraging recovery rates, a recent study estimated the posttransplantation reversal of HRS to be only 58% (136). Predictors of renal recovery included younger recipients, nonalcoholic liver disease, and low posttransplantation bilirubin. The age of the donor also affected renal recovery, suggesting that marginal livers should not be used in patients with HRS. It is interesting that the duration of dialysis before liver transplantation did not have an impact on the chance of renal recovery. The low recovery rate in this study highlights the difficulty of assessing the need for combined LKT and diagnosing HRS with reasonable accuracy and that ATN might complicate HRS and make renal recovery less likely (137). Although United Network for Organ Sharing data seem to favor LKT for patients with HRS (5-yr patient survival of LKT is 62.2% compared with 50.4% for patients who have serum creatinine >2 mg/dl and receive liver transplant alone; $P = 0.0001$), single-center results suggested otherwise, indicating that with different management strategies, a similar transplant outcome can be achieved with transplantation of liver only (138). Nevertheless, LKT still is not justifiable in patients with HRS because of their reasonable chance of renal recovery and the increasing number of patients who are placed on the waiting list for kidney transplantation (138,139). LKT may be justifiable in those with prolonged duration of RRT pretransplantation, history of previous renal failure, or biopsy findings consistent with chronic kidney disease (139,140). The introduction of the MELD has increased both the number of liver patients who receive a transplant with elevated serum creatinine and the number of LKT being performed (139,141). This trend needs to be followed carefully.

Conclusions and Future Directions

During the past century, important progress has been made in the pathogenesis and treatment of HRS. More important, the prognosis has improved from a terminal one to one with a reasonable chance of recovery with various therapeutic options. Yet there still are unanswered questions, mainly related to the best modality of therapy and the predictability of the need for LKT *versus* a liver-only transplant. Until now, it has not been clear how vasoconstrictors compare with TIPS and MARS, which vasoconstrictor is best to use, and whether there is an independent beneficial effect of albumin in the treatment of HRS. The recovery rate of renal function after liver transplantation still is variable between centers, reflecting difficulties in HRS diagnosis and probably underutilization of kidney biopsies. Studies to compare the impact of various pretransplanta-

tion therapeutic modalities on outcomes after liver transplantation are deeply needed and still are awaited.

Acknowledgments

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