The Hepatorenal Syndrome

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The onset of renal failure in a patient with cirrhosis or acute liver failure (ALF, also known as “fulminant liver failure”) is alarming because it raises the possibility of the hepatorenal syndrome (HRS). HRS is a distinct form of renal failure that occurs in the setting of severe liver disease. HRS is the most frequently fatal complication of cirrhosis, because nearly half of patients die within 2 weeks of this diagnosis (Fig. 1) [1]. The annual incidence of HRS is estimated at 8% to 40% in cirrhosis [2,3]. The Model for End Stage Liver Disease (MELD) score [4–6] in patients with cirrhosis and ascites parallels the risk of developing HRS [3,7]. Onset of ascites in patients with MELD scores of about 10 is associated with an 8% and 11% risk of HRS at 1 and 5 years, respectively [7]. If the MELD score approaches 18, nearly 40% of patients develop HRS within 1 year [3]. The frequency of HRS in severe acute alcoholic hepatitis and in fulminant liver failure is about 30% and 55%, respectively [8,9]. Most episodes of renal failure in patients with liver disease, however, are not related to HRS. Common high-risk scenarios for HRS include diuretic-resistant tense ascites, severe hyponatremia or coagulopathy, and a MELD score greater than 18. Profound jaundice is often present, but HRS can develop in patients with minimal hyperbilirubinemia. Periodic surveillance of renal function is helpful in patients with severe liver disease to detect HRS early and to help correct reversible contributing factors. Once established, HRS responds relatively poorly to medical management, although recent advances have brought hope for an improved prognosis. In this article, the diagnosis,
Definition

HRS is a distinct form of acute or subacute renal failure characterized by severe renal vasoconstriction, which develops in decompensated cirrhosis or ALF. This definition, developed by expert consensus in 1996, has been recently updated to include albumin as a volume expander [10–12]. With greater understanding of HRS, the definition should be refined further to include more specific parameters and improved tests of renal injury [13,14].

Clinical presentation and classification

Patients with liver failure can develop two distinct clinical forms of HRS, designated as type 1 and type 2, based on the time course and precipitating factors. These syndromes reflect renal injury from circulatory disturbances caused by profound liver failure. Patients with HRS and underlying acute or chronic kidney disease do not fit into this classification, and are denoted as type 3 HRS (Box 1). The major diagnostic criteria of HRS are shown in Box 2.

Type 1 hepatorenal syndrome

In type 1 HRS the serum creatinine level doubles to greater than 2.5 mg/dL within 2 weeks [10–12]. The key features of type 1 HRS are its rapid progression and high mortality, with a median survival of only 1 to 2 weeks.
Common precipitating events in type 1 HRS include bacterial infections, particularly spontaneous bacterial peritonitis; variceal hemorrhage; major surgery; and acute alcoholic hepatitis. Sometimes acute hepatic injury, superimposed on cirrhosis, may lead to liver failure and HRS. The hepatic injury can occur from acute viral hepatitis; drug-induced liver injury (acetaminophen; idiopathic drug-induced hepatitis); hepatic

<table>
<thead>
<tr>
<th>Box 1. Classification of the hepatorenal syndrome</th>
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<tr>
<td>Type 1: cirrhosis with rapidly progressive acute renal failure(^a)</td>
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<td>Type 2: cirrhosis with subacute renal failure(^a)</td>
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<tr>
<td>Type 3: cirrhosis with types 1 or 2 HRS superimposed on chronic kidney disease or acute renal injury(^b)</td>
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<tr>
<td>Type 4: fulminant liver failure with HRS(^b)</td>
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The clinical characteristics, natural history, and laboratory features of types 3 and 4 HRS have not been studied.

\(^a\) As recently redefined by the International Ascites Club [12,95].

\(^b\) Chronic kidney diseases include diabetic nephropathy, chronic glomerulonephritis, hypertensive nephropathy, and others. Acute renal injury includes acute tubular necrosis and other causes.

(see Fig. 1) [7,11]. Common precipitating events in type 1 HRS include bacterial infections, particularly spontaneous bacterial peritonitis; variceal hemorrhage; major surgery; and acute alcoholic hepatitis. Sometimes acute hepatic injury, superimposed on cirrhosis, may lead to liver failure and HRS. The hepatic injury can occur from acute viral hepatitis; drug-induced liver injury (acetaminophen; idiopathic drug-induced hepatitis); hepatic

<table>
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<th>Box 2. Major diagnostic criteria for hepatorenal syndrome(^a)</th>
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<tr>
<td>1. Chronic or acute liver disease with advanced hepatic failure and portal hypertension</td>
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<td>2. Serum creatinine &gt;1.5 mg/dL, reflecting decreased glomerular infiltration rate</td>
</tr>
<tr>
<td>3. Absence of shock, bacterial infection, and current or recent treatment with nephrotoxic drugs; absence of gastrointestinal or renal fluid losses</td>
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<td>4. No sustained improvement in renal function (decrease in serum creatinine to (\leq 1.5) mg/dL) after diuretic withdrawal and plasma volume expansion with intravenous albumin (1 g/kg body weight up to a maximum of 100 g)(^b)</td>
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<tr>
<td>5. Proteinuria &lt; 500 mg/dL and no evidence of parenchymal renal disease by urinalysis, or of obstructive uropathy by ultrasonography(^c)</td>
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\(^a\) As defined by expert consensus [10–12].

\(^b\) Albumin favored over isotonic saline for plasma volume expansion [12,95].

\(^c\) This criterion does not apply to patients with liver disease who also have intrinsic renal disease and develop HRS. No studies have been performed to characterize HRS in the presence of renal disease.
ischemia; flare of chronic hepatitis B virus infection caused by an emergent resistant viral strain or withdrawal of antiviral therapy; or superimposed acute delta virus hepatitis. Early identification of a precipitating event is clinically important because it is frequently preventable or treatable with specific medical therapy.

**Type 2 hepatorenal syndrome**

In type 2 HRS, the serum creatinine increases slowly and gradually during several weeks or months with a reciprocal gradual reduction in glomerular infiltration rate (GFR). This generally occurs without a precipitating factor. The median survival of type 2 HRS is about 6 months, significantly longer than for type 1 [15]. Nonetheless, type 2 HRS still has an extremely poor prognosis. Unless liver transplantation is performed, or a dramatic response to therapy of the underlying liver disease occurs (such as HBV-related cirrhosis responding to antiviral therapy), many patients with type 2 HRS eventually progress to type 1 HRS because of a precipitating factor.

The clinician should distinguish between type 1 and type 2 HRS. The former is associated with a rapidly fatal prognosis. Type 1 HRS must be urgently managed, with elimination of precipitating factors and evaluation for liver transplantation. In contrast, type 2 HRS permits less frantic evaluation and therapy [15]. Both types are part of a spectrum of renal dysfunction in the setting of severe liver disease. Patients may progress from type 2 to type 1 HRS without an obvious precipitating factor other than worsening liver failure. The mechanisms of this progression are unknown.

**Type 3 hepatorenal syndrome: coexistent kidney disease and hepatorenal syndrome**

Patients with advanced liver disease frequently have coexistent intrinsic renal dysfunction. A recent study found that 85% of end-stage cirrhotics had intrinsic renal disease on renal biopsy [16,17]. Patients with pre-existing renal disease do not meet the traditional diagnostic criteria for HRS [10–12]. They have not been included in therapeutic clinical trials. Because they can also develop HRS from circulatory derangements found in liver failure, patients with pre-existing kidney disease and HRS are best categorized separately (see Box 1). A cirrhotic patient with long-standing diabetic nephropathy, obstructive renal disease, or chronic glomerulonephritis can develop HRS from a precipitating event or worsening liver failure. Similarly, a patient may develop HRS simultaneous with acute tubular necrosis (ATN) because of the same precipitating factor, such as severe variceal hemorrhage. Given the absence of diagnostic markers for HRS, the evaluation of a cirrhotic patient with multiple causes of renal failure is complex. It is unclear whether a chronically reduced baseline GFR, from chronic intrinsic renal disease, predisposes cirrhotic patients to develop HRS. Patients presenting with multiple causes for renal failure should be carefully evaluated by
a hepatologist and a nephrologist. In selected cases renal histology may be necessary for the diagnosis and for selection of patients for liver transplant alone versus combined liver-kidney transplant (see later).

Type 4 hepatorenal syndrome: acute liver failure

More than half of patients with ALF develop HRS, although the frequency varies depending on the ALF etiology [8,9]. HRS complicating ALF is superimposed on the already poor prognosis of ALF, especially when acetaminophen-related. Nonetheless, both organ failures can be reversed by urgent liver transplantation. The pathophysiology of HRS in ALF is believed to be similar to that postulated for HRS occurring in cirrhosis. This contention remains speculative because of a lack of pathophysiologic studies. The clinical course, prognosis, and complications are very different for patients with cirrhosis than for patients with ALF. The mechanism of HRS may differ in the setting of ALF versus the setting of cirrhosis.

Diagnosis

A rising serum creatinine in a patient with cirrhosis or ALF is sufficient cause to investigate for possible HRS. In patients with advanced cirrhosis, the normal serum creatinine level is typically 0.6 to 0.8 mg/dL because of muscle wasting, and a serum creatinine above 1.4 mg/dL reflects a substantially decreased GFR [10–12]. Five major criteria must all be present for the diagnosis of HRS [11,12,18]. Minor additional criteria are supportive but not essential for the diagnosis (Box 3). Because of the lack of diagnostic markers or tests, HRS is diagnosed by the clinical method outlined in Box 2. Despite these straightforward diagnostic criteria, recent studies found that HRS was misdiagnosed in 60% to 70% of cases at a tertiary care center [19,20]. Misdiagnosed patients had intrinsic renal disease, active sepsis, drug-induced renal disease, and ATN. Greater adherence to the consensus guidelines for the diagnosis of HRS is necessary.

First, other causes of renal failure must be investigated in cirrhotics. Relatively common other causes include volume depletion; obstructive

<table>
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<th>Box 3. Minor diagnostic criteria for hepatorenal syndrome a</th>
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<tr>
<td>Urine volume &lt; 500 mL/24 h</td>
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<td>Urine sodium &lt; 10 mEq/L</td>
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<td>Urine osmolality greater than plasma osmolality</td>
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<tr>
<td>Urine red blood cells &lt; 50 per high power field</td>
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<td>Serum sodium &lt; 130 mEq/L</td>
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The minor criteria are supportive but not required for the diagnosis.

a Defined by expert consensus [10–12].
uropathy; shock; drug-induced renal failure; and intrinsic renal disease (eg, hepatitis C–related chronic glomerulonephritis, diabetic nephropathy). It is critical to ensure an adequate intravascular volume by discontinuing diuretics and expanding the plasma volume. A significant improvement in renal function (serum creatinine) after these maneuvers is inconsistent with HRS. Plasma volume expansion was previously accomplished by intravenous administration of 1.5 L of normal saline [10], but sodium chloride can readily escape from the intravascular compartment, particularly in patients with severe hypoalbuminemia (<2–2.5 g/dL), and minimally expands the intravascular volume. Intravenous albumin (1 g/kg body weight up to 100 g) is now used (with packed erythrocytes if concomitant severe anemia is present) because of greater efficacy in volume expansion and in achieving a sustained reduction in serum creatinine [11]. In one study, 55% of patients with HRS who failed a trial of volume expansion with isotonic saline had reversal of HRS following albumin administration alone [21]. Patients who respond to volume expansion with albumin do not have HRS, but renal failure from hypovolemia. If renal failure persists after vigorous volume replacement with colloids, HRS is likely. A history of recent shock or administration of nephrotoxic agents, imaging evidence of urinary obstruction or scarred kidneys, and a urinary sediment consistent with glomerular disease suggest etiologies other than HRS. If intrinsic renal disease is identified, the dilemma consists of determining whether the kidney disease is the sole cause of the renal failure, or whether HRS is a contributing factor (type 3 HRS).

Infections (particularly spontaneous bacterial peritonitis, but also sepsis, cellulitis, urinary tract infection, or pneumonia) can cause transient renal dysfunction in cirrhotics that typically resolves with control of the infection. Infections can, however, precipitate type 1 HRS (see later). This scenario is suspected when the renal failure persists or worsens despite resolution of the infection. Nonoliguric HRS (urine volumes >500 mL per 24 hours) and HRS with urinary sodium excretion greater than 10 mEq/L can occasionally occur [22–24].

Pathophysiology

Type 1 hepatorenal syndrome

A series of clinical and experimental studies during the last two decades has considerably increased the understanding of the pathophysiology of HRS (Figs. 2, 3) [11,25–27]. Hepatic fibrosis, architectural distortion, and inflammation from hepatic injury result in portal hypertension that is generally progressive. Both chronic liver disease and ALF can cause portal hypertension. Portal hypertension leads to arterial vasodilatation and pooling of blood in the splanchnic bed, with a decrease in systemic vascular resistance. In response, a systemic hyperdynamic circulatory state develops. Eventually, activation of the renin-angiotensin-aldosterone system and the sympathetic
nervous system and stimulation of antidiuretic hormone release become necessary to maintain arterial blood pressure. As the liver disease worsens (ie, from chronic active hepatitis C virus infection), these circulatory changes gradually increase until systemic hemodynamic stability depends on vasoconstriction of the extrasplanchnic vascular beds (renal, hepatic, brain, muscle, skin, adrenal glands, and possibly other regional vascular territories). In very advanced liver disease, prolonged high-level activation of the renin-angiotensin-aldosterone system, sympathetic nervous system, and antidiuretic hormone leads to intense, sustained renal vasoconstriction, resulting in decreased renal perfusion, decreased GFR, rising serum creatinine levels, and ultimately to HRS (see Fig. 2). Intrarenal imbalance of vasoactive mediators, such as prostaglandins, kallicreine, adenosine, leukotrienes, F2-isoprostanes, and endothelin, may play an important role in this severe and sustained renal vasoconstriction [28–31].

Cardiac and adrenal dysfunction may contribute to the circulatory disturbances in type 1 HRS (Fig. 3) [11,32]. Unlike compensated cirrhosis without renal failure, the cardiac output is normal or even subnormal in patients with HRS [26,27]. Similarly, tachycardia is less prominent with HRS. Despite intense sympathetic nervous system activation, inotropic and chronotropic cardiac functions are depressed in HRS. A decreased cardiac preload and a cirrhotic cardiomyopathy may cause the decreased cardiac performance in patients with HRS. Additional studies are needed to ascertain the reason for this impaired cardiac function.

In a recent report, 80% of patients with HRS precipitated by sepsis had adrenal dysfunction [33]. Replacement therapy with hydrocortisone in
cirrhotics with sepsis and adrenal insufficiency improved systemic hemodynamics and in-hospital survival [34]. The arterial response to endogenous vasoconstrictors depends on adequate levels of adrenal corticosteroid hormones. Adrenal dysfunction may be important in the hemodynamic mechanism of type 1 HRS related to sepsis.

The precipitating event for type 1 HRS is believed rapidly to worsen the hemodynamic disturbances that led to acute renal failure. The magnitude and pace of circulatory derangement induced by this precipitating event may exceed a threshold beyond which the hepatic, brain, and adrenal vascular beds join with the renal vasculature in vasoconstriction, which results in multiorgan failure (see Fig. 3) [11]. Conceptual differences between HRS types 1 and 2 have clinical implications for the prevention of HRS and the management of precipitating events.

**Type 2 hepatorenal syndrome**

The hemodynamic and humoral abnormalities described previously for type 1 HRS also operate in type 2 HRS, but are present to a lesser extent. Type 2 HRS is related to gradually deteriorating liver function that results in circulatory dysfunction. In contrast to type 1 HRS, precipitating factors are generally not present in type 2 HRS. Many patients with type 2 HRS eventually progress to type 1 HRS, however, often because of a precipitating event.

A better understanding of circulatory abnormalities associated with HRS has led to a combination of therapeutic interventions to correct these abnormalities (ie, the decreased intravascular effective arterial volume, the renal vasoconstriction, and the peripheral arterial vasodilatation).
Type 3 hepatorenal syndrome: pre-existing kidney disease and hepatorenal syndrome

Cirrhotics often have long-standing intrinsic renal disorders, such as diabetic nephropathy, chronic glomerulonephritis, and nephrolithiasis [16,17]. Such patients were traditionally excluded from HRS [10–12], and the presence of the renal vasoconstriction of HRS in the presence of intrinsic renal disease has not been analyzed. Without these data, specific diagnostic criteria have not been developed for type 3 HRS. Except for the absence of pre-existing kidney disease, clinicians use the other diagnostic criteria of HRS to assess whether patients with underlying renal disease have HRS. This approach, however, has not been validated. Patients with cirrhosis and pre-existing renal disease may be at higher risk to develop HRS. The pathophysiology is likely more complex than pure forms of HRS. Studies are needed to address this growing and complex group of patients at risk for HRS (see Box 1).

Type 4 hepatorenal syndrome: acute liver failure

ALF patients rarely develop refractory ascites or severe portal hypertension, with a hyperdynamic circulatory state. Acute renal failure in ALF may share certain pathways with HRS of cirrhosis, but little is known concerning the events and mechanisms leading to HRS in the setting of ALF.

Therapy

General management

Patients with types 1 and 4 HRS require monitoring in an intensive care unit. Patients with type 2 and 3 HRS may alternate between intensive care, monitored bed, or standard hospital care. Diuretics are discontinued when HRS is suspected. The status of the intravascular volume is assessed, and this volume is restored as needed. It may be difficult to assess the intravascular volume status in the presence of ascites and edema. Determination of the central venous pressure, and a trial of volume expansion with intravenous albumin may be helpful. If acidosis, hyperkalemia, uremic symptoms, or volume overload occurs, continuous hemofiltration or hemodialysis may be helpful. Discontinuation of nephrotoxic agents is essential, including nonsteroidal anti-inflammatory agents and aminoglycosides. Angiotensin-converting enzyme inhibitors, nitrates, and other vasodilators should be withheld during HRS. In a prospective study, administration of radiologic contrast media to cirrhotics did not precipitate renal failure [35].

Type 1 HRS should be diagnosed early, with vigorous treatment of the precipitating event, and management of any multiorgan failure. Because septic processes (spontaneous bacterial peritonitis, urosepsis, and
gastrointestinal or biliary infections) are the most common precipitating events, early systemic antibiotic therapy is critical in patients at high risk for, or with established, HRS [36,37]. In type 1 HRS, adrenal function should be tested with cosyntropin or another synthetic adrenocorticotropic hormone. If adrenal insufficiency is detected, administration of stress doses of intravenous hydrocortisone improves survival [33,34]. Likewise, control of esophagogastric variceal hemorrhage in a patient with type 1 HRS enhances the probability of reversal or bridging to liver transplantation. If a patient with type 1 HRS has severe or tense ascites, large-volume paracentesis with albumin replacement is performed as needed. It is unclear how much massive ascites impairs renal vein outflow and hinders recovery from HRS.

Specific therapy for the underlying liver disease is promptly initiated, as appropriate, such as antiviral therapy for HBsAg-positive cirrhosis (at doses adjusted for renal failure); alcohol abstinence and nutritional support for acute alcoholic hepatitis; and antidotes for toxic causes of ALF.

Patients with type 2 HRS often survive for several months. During this time patients should receive prophylaxis for spontaneous bacterial peritonitis (SBP) and avoid precipitating events that can lead to type 1 HRS, including volume depletion. This is particularly true during large-volume paracentesis, because patients with type 2 HRS often have recurrent severe ascites. Administration of intravenous albumin during large-volume paracentesis (approximately 10 g/L of ascites removed) is important to maintain the intravascular volume and minimize circulatory disturbances after paracentesis. Primary or secondary prophylaxis of variceal hemorrhage with variceal band ligation is important [38]. Many cirrhotics take nonselective beta receptor antagonists as prophylaxis against bleeding from esophagogastric varices [38]. The effects of adrenergic beta receptor antagonists in HRS are unstudied. Beta receptor antagonism in a patient with HRS may be undesirable because of a decrease in cardiac output, but may be desirable because of an antirenin effect of these agents. Duhamel and colleagues [39] suspected that propranolol therapy may have precipitated HRS in 3 of 12 analyzed patients. Responders to beta receptor antagonists had a lower risk of developing HRS in one study [40]. In an informal survey, most experts believed that beta receptor antagonists should be discontinued during HRS, but all considered that this issue should be investigated (P. Gines, V. Arroyo, F. Wong, F. Salerno, A. Gerbes, personal communications, 2007). Avoidance of hepatotoxic and nephrotoxic therapeutic agents, such as aminoglycoside antibiotics and nonsteroidal anti-inflammatory agents, is also essential during the course of type 2 HRS. Vasodilators, such as angiotensin-converting enzyme inhibitors, prazosin, and nitrates, should be discontinued.

No data on the optimal care of patients with type 3 HRS are available. The medical support for patients with type 4 HRS is similar to that for patients with type 1 HRS, but there are no studies specifically addressing the treatment of type 4 HRS.
Patients with types 1, 2, or 4 HRS should undergo prompt evaluation for liver transplantation. If a patient is on an active liver transplant waiting list, development of HRS prompts a high priority status. Patients with type 3 HRS should be evaluated for combined liver-kidney transplantation (see later). Specific treatments described next may be additionally considered in these desperately ill patients, with the understanding that knowledge about these therapies and their limitations is incomplete.

Specific treatments

Medical therapies that target the circulatory abnormalities of HRS have been developed during the last decade [11,12,22,23,41–47]. Although the results are generally promising, the total number of patients analyzed in prospective trials is small. Furthermore, some studies may have included patients without HRS or with potentially reversible renal failure. Because of these trial shortcomings, these treatments may have limitations and unappreciated toxicity. Despite these problems, the new therapies seem reasonably safe and possibly effective in sometimes reversing HRS [48]. Conventional renal replacement therapy (RRT) does not improve the prognosis of HRS, but can help manage specific complications of HRS, including fluid overload in anuric patients, acidosis, uremic symptoms, or severe hyperkalemia. Adjuvant therapy of these complications with RRT is appropriate in liver transplant candidates, or in patients with severe acute alcoholic hepatitis and HRS. RRT is unjustified, however, for HRS with terminal liver failure. RRT may be useful in patients with chronic renal disease who develop superimposed HRS (see Box 1), but these patients have been inadequately studied.

Renal vasodilator therapy with low-dose intravenous dopamine infusion or the prostaglandin E₁ analogue misoprostol did not prove efficacious and are rarely used for HRS [49,50]. Experimental therapy with N-acetylcysteine seems logical, but has not been evaluated in large studies [51,52]. Administration of the nonselective endothelin antagonist tezosentan was associated with further deterioration of renal function in patients with type 2 HRS [53]. As knowledge increases on the mechanisms of renal vasoconstriction, renal vasodilator therapy may be re-evaluated for HRS in the future.

Specific therapies for type 1 hepatorenal syndrome

Vasoconstrictors plus plasma volume expansion

Use of vasoconstrictors in HRS is intended to increase renal perfusion caused by vasoconstriction of the splanchnic vascular bed. Intravenous albumin is simultaneously infused to support the effective plasma volume. These simultaneous interventions presumably reduce renal vasoconstriction and improve renal perfusion (Table 1). Vasoconstrictor therapy for HRS is inappropriate in the setting of terminal liver failure, intractable hepatocellular carcinoma, or when otherwise contraindicated (Box 4).
About 12 pilot studies conducted during the last decade have suggested that vasopressor therapy plus intravenous albumin improves the prognosis of HRS. The total number of studied patients is less than 250, however, and the results may be subject to sampling bias because of inconsistent study inclusion criteria [54,55]. Nevertheless, prudent use of this combined therapy seems justified in type 1 HRS given the consistently reported benefits in the context of the otherwise rapidly fatal outcome of type 1 HRS. In some reports, responders to vasoconstrictor plus albumin therapy had improved survival, and a significant proportion of patients were successfully bridged to liver transplantation [56–60]. Patients with type 1 HRS typically have

### Table 1

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<tr>
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<th>Noradrenaline and albumin (N = 10)</th>
<th>Terlipressin and albumin (N = 12)</th>
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<tr>
<td></td>
<td>Baseline</td>
<td>End of therapy</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>2.3 ± 0.2</td>
<td>1.3 ± 0.1a</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>71 ± 2</td>
<td>84 ± 2a</td>
</tr>
<tr>
<td>Central venous pressure (mm H2O)</td>
<td>11 ± 1</td>
<td>12 ± 1</td>
</tr>
<tr>
<td>Urine volume (mL/d)</td>
<td>788 ± 84</td>
<td>1583 ± 243a</td>
</tr>
<tr>
<td>MELD score</td>
<td>26 ± 1</td>
<td>24 ± 2</td>
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<tr>
<td>Plasma renin (ng/mL/h)</td>
<td>15 ± 3</td>
<td>9 ± 3</td>
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*Abbreviation:* MELD, Model for End Stage Liver Disease.

a *P* < .05 with respect to baseline.


### Box 4. Contraindications to vasoconstrictor therapy in hepatorenal syndrome

- Coronary artery disease
- Cardiomyopathies
- Cardiac arrhythmias
- Cardiac or respiratory failure
- Arterial hypertension
- Cerebrovascular disease
- Peripheral vascular disease
- Bronchospasm, asthma
- Terminal liver disease
- Advanced hepatocellular carcinoma
- Age >70 years
actual or impending multiorgan failure. Use of vasoconstrictors and plasma volume expansion should be closely monitored, with continuous monitoring of central venous and arterial blood pressures.

The effect of these therapies on the probability of liver transplantation is controversial. In countries where organ allocation is determined by the MELD score, such as the United States, the significant improvement in MELD score, induced by vasoconstrictor therapy, can reduce the chances of receiving a liver transplantation, particularly for type 1 HRS patients. Whether improvement of HRS induced by vasopressor therapy is better than liver transplantation is debatable. HRS often recurs after discontinuation of vasoconstrictor therapy and then has a high mortality. These patients should be maintained at a high level on the waiting list, despite their reduced MELD score secondary to vasoconstrictor therapy, by an exception request to the regional review boards.

Therapies with a vasoconstrictor plus albumin are very promising for type 1 HRS, an entity with nearly universal mortality without urgent liver transplantation, but the risks of noradrenaline infusions require further study.

**Terlipressin plus albumin**

Terlipressin is the most studied vasopressor agent, given its efficacy and better safety profile [56,58–68]. This synthetic vasopressin derivative is believed to have a much greater effect on vascular receptors (V1) than renal vasopressin receptors (V2) [48]. A recent meta-analysis of 10 clinical trials of terlipressin reported that this therapy was well tolerated and reversed HRS in 52% of cases [48]. About 29% of treated patients experienced side effects, including abdominal pain, self-limited cardiac arrhythmias, cutaneous necrosis, finger ischemia, bronchospasm, and diarrhea. Most side effects did not mandate treatment discontinuation and responded to lowering the dosage [48]. Terlipressin therapy is associated with improved serum creatinine, urinary output, urinary sodium excretion, and plasma renin and aldosterone levels (see Table 1) [56]. The terlipressin dose schedules used in the prospective randomized studies are shown in Box 5. A randomized, prospective, placebo-controlled clinical trial completed in the United States used terlipressin at doses of 1 mg intravenously every 6 hours until the serum creatinine level decreased to less than 1.5 mg/dL on two measurements 48 hours apart, or for up to 14 days [60,61]. If after 3 days the serum creatinine did not decline by at least 30% from baseline, the dose of terlipressin was increased to 2 mg every 6 hours. In this clinical trial, terlipressin was significantly more effective than placebo in reversing type 1 HRS with a similar safety profile [60,61]. A later report from the same group demonstrated that earlier therapy with terlipressin increases the probability of HRS reversal, whereas patients with a baseline serum creatinine greater than 5.6 mg/dL had no reversal of HRS in this study [61]. The minimum duration for successful therapy is 3 to 5 days [56,61].
For patients whose HRS reversed with terlipressin and albumin, the prognosis after liver transplantation is excellent and similar to that of transplanted patients without HRS [57]. The rate of postoperative hemodialysis, severe infections, bleeding complications, recurrence of renal failure, and survival and the mean hospital length of stay are similar to recipients transplanted without HRS [57]. Limitations of terlipressin therapy include a failure to reverse HRS in 40% to 45% of patients, high cost, and a high rate of HRS recurrence after treatment discontinuation. Terlipressin cannot be used in patients with vascular disorders (see Box 4). It is presently unavailable in the United States. Where available, terlipressin plus albumin therapy seems relatively safe, well tolerated, and able to reverse the renal failure in about half of treated patients. Additional studies are necessary to optimize this therapy [54,55].

**Noradrenaline plus albumin**

Intravenous noradrenaline plus albumin has been evaluated as a therapy for HRS in countries where terlipressin is unavailable. Alessandria and
colleagues [56] recently reported a prospective randomized comparison of noradrenaline versus terlipressin for HRS, according to the protocol outlined in Box 5. Both study groups received volume expansion with albumin. Therapy with noradrenaline led to a complete response in 75% of type 1 HRS patients, similar to the 80% response achieved with terlipressin. Eighty-three percent of the patients responding to noradrenaline were successfully bridged to liver transplantation, with improved survival (Fig. 4). No significant ischemic complications occurred in either group. HRS recurred after discontinuation of therapy, however, in 33% to 50% of patients [56]. The costs of terlipressin therapy are about 15-fold greater than the costs of noradrenaline therapy [56]. This study confirms previous observations and suggests that noradrenaline plus albumin may be a useful alternative to terlipressin. Patients included in this clinical trial, however, had early, moderately severe HRS (mean baseline serum creatinine, 2.4 mg/dL). Half of the patients had baseline serum creatinine levels less than 2 mg/dL, and substantial urinary output (see Table 1). Whether these favorable results apply to patients with severe or advanced HRS (creatinine > 4 mg/dL, or severe hepatic decompensation with bilirubin > 10 mg/dL, and INR > 3) is unknown.

Fig. 4. Response of hepatorenal syndrome to vasoconstrictor plus albumin therapy results in improved probability of survival. Solid line, responders; broken line, nonresponders. (From Alessandria C, Ottobrelli A, Debernardi-Venon W, et al. Noradrenaline vs terlipressin in patients with hepatorenal syndrome: a prospective randomized unblinded pilot study. J Hepatol 2007;47:499–505; with permission.)
**Midodrine and octreotide**

An oral α-adrenergic agonist (midodrine) in combination with octreotide has been shown in three clinical trials, using variable dose regimens, to improve type 1 HRS with results comparable with those reported for terlipressin [22,50,69,70]. Midodrine is a direct vasoconstrictor, whereas octreotide inhibits endogenous vasodilators. In two of the studies the intravascular volume was supported with albumin [22,50]. In a recent report of 81 patients treated with midodrine-octreotide (without concurrent albumin), 40% of patients responded with sustained reduction in serum creatinine, and the 30-day survival was 57%, significantly superior to the 30% survival of controls [69]. The combination of oral midodrine and subcutaneous octreotide is appealing because of its suitability for outpatient use. The protocol of midodrine-octreotide in the most recent study is summarized in Box 6 [69].

**Transjugular intrahepatic portosystemic shunt**

Transjugular intrahepatic portosystemic shunt (TIPS) is a theoretically attractive therapy because it dramatically lowers both the portal pressure and the pooling of blood in the splanchnic vascular bed, key pathogenetic factors in HRS. The increased venous return produced by TIPS may be inappropriately handled, however, and even aggravate the cardiac dysfunction observed in HRS. Furthermore, patients with HRS often have contraindications for TIPS, such as hepatic encephalopathy, severe jaundice, or very advanced liver disease. TIPS in these circumstances may lead to liver failure.

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**Box 6. Typical protocol of midodrine plus octreotide for therapy of type 1 hepatorenal syndrome**

**Octreotide**

Initial dose: 100 μg tid subcutaneous

Goal to increase dose up to 200 μg tid

**Midodrine**

Initial doses: 5 mg, 7.5 mg, or 10 mg tid orally

Goal to increase dose up to 12.5 mg or 15 mg tid if necessary

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Doses of both agents are increased to induce a 15 mm Hg increase in mean arterial pressure.

During diagnostic phase of HRS: volume expansion with 1.5 L normal saline plus 120 g albumin. Discontinue albumin once HRS is established, and start midodrine plus octreotide.

or intractable hepatic encephalopathy. Three studies have evaluated the efficacy of TIPS in type 1 HRS in a combined total of only 35 patients [22,71,72]. Improved serum creatinine and reversal of HRS was observed in some patients who later became long-term survivors. The hazards and irreversible nature of TIPS have prevented broad application of this modality for type 1 HRS. Many patients with type 1 HRS do not meet the criteria for TIPS insertion (ie, serum bilirubin <5 mg/dL, INR <2, and Childs-Pugh score <12). Further studies are needed to determine if and when TIPS is helpful for HRS. TIPS is currently considered an experimental therapy for HRS, that can be considered in a Childs-Pugh class A or B patient, who meets the criteria for TIPS insertion, and who fails to respond to vasoconstrictor therapy and plasma volume expansion.

Specific therapy for type 2 hepatorenal syndrome

Type 2 HRS is more commonly seen in clinical practice than type 1 HRS. All patients with type 2 HRS should be evaluated for liver transplantation. Transplantation can potentially permanently reverse HRS and other complications of chronic liver failure. Severe ascites and hyponatremia are often associated with type 2 HRS. Treatment expectations include HRS reversal and survival improvement, and control of ascites and hyponatremia. The available therapies for type 2 HRS are summarized in Box 7.

Vasoconstrictor therapy in type 2 hepatorenal syndrome

In four small pilot studies of therapy with terlipressin and albumin [47,63,65] and one prospective controlled trial of therapy with noradrenaline plus albumin [56], the combined reversal rate of type 2 HRS was about 80%. HRS, however, frequently recurred after discontinuation of therapy. Further studies are needed on vasoconstrictor therapy and plasma volume expansion for type 2 HRS to determine the optimal vasoconstrictor and the optimal dosing schedules. Currently, intravenous vasoconstrictor therapy can be cautiously considered in selected patients with type 2 HRS. A liver transplant is substantially more beneficial if HRS is reversed by vasoconstrictor and albumin therapy before transplantation [57]. The effect of oral midodrine plus subcutaneous octreotide in type 2 HRS has not been studied. This combination is appealing because a significant proportion of type 2 HRS patients are ambulatory.

Box 7. Available treatments for type 2 hepatorenal syndrome

| Terlipressin plus albumin |
| Noradrenaline plus albumin |
| Liver transplantation |
| Transjugular intrahepatic portosystemic shunt |
Transjugular intrahepatic portosystemic shunt for type 2 hepatorenal syndrome

Several studies on the use of TIPS in type 2 HRS noted improvement in ascites control, serum creatinine level, and GFR, but no firm conclusions can be made on reversal rate, effect on survival, or bridging to transplantation [47,71,73–75]. Given the potential hazards of TIPS in patients with very advanced liver disease, it should be cautiously applied as therapy for type 2 HRS. Refractory ascites often precedes development of type 2 HRS. A recent meta-analysis concluded that refractory ascites treated with TIPS was associated with better survival and less portal hypertensive complications, including HRS, than large-volume paracentesis [76].

Specific therapies for type 3 and type 4 hepatorenal syndrome

No specific therapies have been investigated for these types of HRS because of their exclusion from the traditional HRS classifications and the low frequency of ALF. Controlled therapeutic trials with vasoconstrictors and albumin are needed. Terlipressin has been evaluated in patients with ALF to treat arterial hypotension, but the effects on HRS were not reported [77,78]. One report found that terlipressin caused a slight increase in intracranial pressure in ALF [77], but a more recent study found that terlipressin increased cerebral perfusion without increasing intracranial pressure [78]. Patients with ALF and HRS may require dialysis. Continuous venovenous hemofiltration is preferred over intermittent hemodialysis because of enhanced hemodynamic and intracranial pressure stability [79].

Artificial liver support

Liver-assist technology may help in HRS by eliminating circulating mediators of splanchnic vasodilatation and renal vasoconstriction. Several systems have been tested in pilot studies of patients with acute or chronic liver failure, with and without HRS [80–83]. Hemodynamic benefit and improvement of hepatic encephalopathy have been observed and lowered serum creatinine. The latter effect is predictable in systems that include standard dialysis or continuous venovenous hemofiltration [81,82]. ALF patients treated with a porcine hepatocyte-based bioartificial liver developed renal failure at half the rate of controls [80]. No details were provided, however, regarding the specific types of renal failure observed in this prospective randomized, controlled study. Recently, selective plasma hemofiltration liver-assist devices have been used in HRS with acute-on-chronic end-stage liver disease [83,84]. Currently, liver-assistance therapies cannot be advocated for HRS.

Liver transplantation

Because a failing liver and portal hypertension are the key initial events in the development of HRS, liver transplantation is the ultimate treatment of
choice for either type of HRS. Indeed, many reports have demonstrated resolution of HRS and long-term survival following liver transplantation. Patients with HRS undergoing liver transplantation, however, have a slightly increased perioperative morbidity and mortality compared with transplanted patients without HRS [85–88]. Nevertheless, HRS is not a contraindication to liver transplantation. Allocation of liver donors is now primarily guided by the MELD score, an index of disease severity and indicator of short-term prognosis [4–6]. Serum creatinine is the highest weighted factor in calculating the MELD score. Patients with HRS, particularly type 1, frequently achieve the highest priority for donor organ allocation. Despite their generally high priority, patients with HRS often are not transplanted. The precipitating event, such as SBP or sepsis, may prevent transplant surgery [36,37]. Additionally, type 1 HRS patients are often extremely ill, with multiorgan failure, in whom the risks of transplant surgery may be prohibitive. In regions with a severe shortage of liver donors, the progression of type 1 HRS within several weeks may provide insufficient time to receive a donor liver. In contrast, liver transplantation may be more practical and successful in type 2 HRS, because of an absence of precipitating events, its longer clinical course, and the relatively less severe renal failure. Patients with any type of HRS have a very poor short-term prognosis without liver transplantation [15]. They should have the highest priority for liver allocation, even if this requires requesting an exception to upgrade the MELD score.

With MELD scores governing liver allocation, more patients with simultaneous liver and renal failure are achieving a high priority for transplantation. An important dilemma is whether to transplant both the liver and the kidney in these extremely ill patients. Some patients have HRS, whereas others have coexisting intrinsic renal disease (type 3 HRS; see Box 1). These mixed clinical syndromes include chronic renal failure plus HRS, and non-HRS acute renal failure (ATN) plus simultaneous HRS. Determining the diagnostic category in a specific patient is complex and requires urgent consultation by a team consisting of a hepatologist, nephrologist, and liver transplant surgeon because of the poor short-term prognosis of HRS. This determination should be done as expeditiously and as precisely as possible given the time constraints. Liver transplantation without renal transplantation is the best choice for patients with pure forms of HRS, and perhaps in those with HRS and ATN, given the prospects of recovery with postoperative RRT. Two recent reports found a possible benefit of combined liver-kidney transplantation in HRS patients selected on the basis of requirement for RRT for longer than 8 weeks [89,90]. Simultaneous liver-kidney transplantation may be the preferred approach for HRS in a patient with chronic renal failure or with ATN superimposed on chronic renal failure. Unfortunately, little data are available on these combined clinical scenarios. Several large studies have reported the outcomes of patients with elevated serum creatinine undergoing liver transplantation, but these
studies did not report the proportion of patients with HRS, chronic renal failure, ATN, or combinations thereof [91]. Cohorts with elevated serum creatinine include different types of renal dysfunction [89].

The success of vasoconstrictor therapy for HRS in liver transplant candidates is important. Reversal of HRS before liver transplantation lowers the postoperative risks of severe infections, bleeding complications, need for hemodialysis, and recurrence of renal failure, while improving survival and shortening postoperative hospital length of stay [57].

After liver transplantation, patients with HRS slowly recover renal function. The persistent postoperative renal impairment frequently requires decreasing the dosage of calcineurin inhibitors (cyclosporine A, tacrolimus), or renal-sparing immunosuppressive protocols.

**Prevention of hepatorenal syndrome**

Sepsis, variceal hemorrhage, shock, severe acute alcoholic hepatitis, or use of nephrotoxic drugs often precipitate type 1 HRS. The risk of HRS may be lowered by following standard guidelines to prevent these events, particularly SBP or variceal bleeding [18,38]. Infections other than SBP should be promptly identified and vigorously treated to minimize the risk of HRS. Debilitated patients with advanced cirrhosis often have chronic leukopenia and may not develop leukocytosis or fever, even with severe infections. A high index of suspicion is necessary to identify infections early in decompensated cirrhotics.

Prevention of type 1 HRS has been demonstrated in three prospective randomized clinical trials [3,92,93]. In the most recent trial, administration of norfloxacin for primary prophylaxis for SBP reduced the 1-year probability of HRS to 28%, compared with 41% in controls not administered antibiotic prophylaxis (Fig. 5) [3]. This study strongly suggested that HRS can be prevented in patients with advanced cirrhosis and ascites with a low protein content (<1.5 g/dL). In another study, the administration of albumin (1 g/kg intravenously) at diagnosis and at day 3 in patients with SBP significantly reduced the incidence of type 1 HRS and the 3-month mortality [92]. Administration of pentoxifylline, 400 mg three times a day, to patients with severe acute alcoholic hepatitis was associated with a marked reduction in HRS incidence and in-hospital mortality [93]. A recent prospective controlled trial, however, failed to confirm these benefits [94]. Prevention of HRS by use of antibiotic prophylaxis for SBP [3], or of albumin for SBP [92], in patients with liver failure or acute alcoholic hepatitis [94] has not yet been confirmed by subsequent large studies. The magnitude of these effects in the context of the otherwise poor prognosis of HRS, however, has led to broad acceptance of these prophylactic measures.

Specific preventive measures for type 2 HRS have not been identified. Patients developing this variant of HRS do not usually have precipitating events. Because type 2 HRS is often associated with tense refractory ascites
or severe hyponatremia, optimal management of refractory ascites or severe hyponatremia could reduce the risk of developing type 2 HRS [7,76]. Further research is necessary to determine how to prevent type 2 HRS in patients with advanced cirrhosis.

References


