Hepatorenal Syndrome: A Critical Update

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Abstract

Acute kidney injury (AKI) is common in cirrhotic patients with ascites. Although not the primary etiology of AKI in cirrhotic patients, hepatorenal syndrome (HRS) is a unique form of AKI that develops only in cirrhotic patients. Intense renal vasoconstriction is the hallmark of HRS. Different mechanisms contribute to renal vasoconstriction, with splanchnic vasodilatation and reduced effective blood volume playing a central role. Diagnostic criteria for HRS have been developed and were recently modified, but diagnosing HRS and differentiating it from other causes of AKI in cirrhotic patients continues to be a difficult task in some patients. Given its overall dismal prognosis, strategies to prevent HRS have been developed and proved to be effective in reducing HRS prevalence among cirrhotic patients. Liver transplantation is the ultimate treatment, but more than one treatment modality can be utilized as a bridge to transplantation. This review provides an update on our current understanding of HRS with emphasis on the underlying pathophysiological mechanisms involved, difficulties in diagnosis, and different treatment modalities.

Keywords

► acute kidney injury
► liver cirrhosis
► vasopressin analogues
► liver transplantation
► hepatorenal syndrome

Pathophysiology

HRS compromises the most advanced stage of hemodynamic dysfunction that starts early in the course of liver disease even before ascites is clinically detectable. These hemodynamic changes continue to progress as cirrhotic patients progress from the preascitic stage to diuretic-sensitive then diuretic-resistant ascites and finally HRS. These hemodynamic changes are characterized by (1) splanchnic vasodilatation,
(2) reduced effective arterial blood volume, (3) hyperdynamic circulation with increased cardiac output (CO), (4) reduced systemic vascular resistance, (5) vasoconstriction of various extrasplanchnic vascular beds including the renal and cerebral circulations, (6) increased activity of the renin-angiotensin-aldosterone system (RAAS), the sympathetic nervous system (SNS), and nonosmotic release of vasopressin. Figure 1 schematically summarizes the progression of these hemodynamic changes from the preascitic stage to type 2 HRS. In type 1 HRS similar pathophysiological changes occur, albeit at a faster pace than in type 2 HRS.

Arterial Vasodilatation

The key pathophysiological change responsible for the development of type 2 HRS in cirrhotic patients is arterial vasodilatation. Arterial vasodilatation occurs primarily in the splanchnic circulation and is mediated by the release of potent vasodilators, the most important of which is nitric oxide (NO). NO production is increased in the splanchnic circulation in cirrhotic patients due to shear-stress-induced upregulation of endothelial NO synthase (eNOS) activity as well as endotoxin-mediated eNOS activation. Increased inducible NOS (iNOS) activity has also been documented. Other vasodilator substances such as calcitonin gene-related peptide (CGRP), substance P, carbon monoxide, endocannabinoids, and adrenomedullin might also be involved in the splanchnic vasodilatation. Bacterial translocation plays a central role in splanchnic vasodilatation in decompensated cirrhosis, and the circulating level of bacterial DNA (a marker of bacterial translocation) is associated with lower systemic vascular resistance in cirrhotic patients compared with patients who do not have increased expression of this marker. Intense vascular neoformation in the liver and in the splanchnic circulation also develops due to the presence of high levels of proangiogenic substances such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), which are also involved in the formation of an extensive network of portosystemic collaterals. The end result is a reduction in systemic vascular resistance and a decrease in effective blood volume despite overall increase in total plasma and blood volumes. Indeed, studies that included large numbers of cirrhotic patients who underwent invasive hemodynamic monitoring confirmed the presence of low systemic vascular resistance and reduced effective circulating blood volume in cirrhotic patients. There is also evidence of altered blood volume distribution in cirrhotic patients with increased blood pooling in the splanchnic region supporting the role of splanchnic vasodilatation in reducing effective circulating blood volume. Reduced effective blood volume activates the RAAS, unloads the high-pressure baroreceptors in the carotid body and aortic arch with subsequent activation of the SNS, and induces nonosmotic release of vasopressin. These changes lead to intense renal vasoconstriction and reduced glomerular filtration rate (GFR). Other vascular beds show similar changes, and studies have demonstrated vasoconstriction in the cerebral, femoral, and upper extremities circulations that correlated with reduced renal blood flow in HRS patients. With worsening of the liver disease and progression of cirrhosis, further splanchnic vasodilatation occurs, creating a vicious cycle that favors further activation of the RAAS, SNS, and vasopressin release, and subsequent intensification of renal vasoconstriction. Indeed, HRS patients exhibit higher levels of circulating renin, aldosterone, norepinephrine, and other neurohormonal mediators compared with cirrhotic patients with normal kidney function. Despite the presence of high circulating levels of vasoconstrictor substances, the abundance of vasodilators in the splanchnic circulation precipitates a state of hyporesponsiveness in this vascular bed to the vasoconstrictive action of these mediators. Table 1 summarizes the changes in the splanchnic and systemic circulations occurring in HRS patients.

Renal Prostaglandins

In the kidney, renal vasoconstriction is counterbalanced by increased intrarenal production of vasodilating prostaglandins. Indeed, patients with liver disease and ascites exhibit increased renal vasodilating prostaglandins production as evidenced by increased urinary excretion of these substances compared with normal controls. In HRS, both urinary prostaglandin excretion and renal medullary cyclooxygenase activity are reduced, a finding that is not present in patients with other causes of AKI, indicating a role of reduced renal prostaglandin production in the development of HRS. Factors associated with lower renal prostaglandin production in HRS are unknown, but reduced renal blood flow from intense renal vasoconstriction may be the cause. It is important to mention that the administration of cyclooxygenase inhibitors to ascitic cirrhotic patients precipitates a syndrome similar to HRS; therefore, nonsteroidal antiinflammatory drugs (NSAIDS) should be strictly avoided in these patients.

Role of Sympathetic Nervous System

Both human and animal studies demonstrate increased renal SNS activity which contributes to the renal vasoconstriction occurring in HRS. For example, Kostreva et al showed increased renal SNS activity following vena cava ligation in anesthetized dogs that was abolished only after severing the...
Table 1  Hemodynamic Changes That Occur in Liver Cirrhosis

<table>
<thead>
<tr>
<th>Hepatic and splanchnic circulation</th>
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<tr>
<td>Splanchnic vasodilatation</td>
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<tr>
<td>Hepatic vascular neoformation</td>
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<tr>
<td>Increased portal pressure with portosystemic collateral formation</td>
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<tr>
<td>Systemic circulation</td>
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<tr>
<td>Increased cardiac output</td>
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<tr>
<td>Hyperdynamic circulation</td>
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<tr>
<td>Decreased arterial blood pressure</td>
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<tr>
<td>Increased plasma and total blood volumes</td>
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<td>Reduced central blood volume</td>
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<tr>
<td>Vasocostriction of the renal, femoral, and cerebral vascular beds</td>
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Hepatic nerves. In humans, transjugular intrahepatic portosystemic shunt (TIPS) insertion was associated with improvement in renal blood flow and reduction of SNS activity that subsequently reversed following TIPS occlusion. Finally, lumbar sympathectomy increased glomerular filtration rate (GFR) in five patients with HRS, suggesting that increased renal sympathetic activity is implicated in HRS development. These studies suggest the presence of a hepatorenal reflex that contributes to renal vasoconstriction in HRS.

Myocardial Dysfunction

Hyperdynamic circulation with increased CO and heart rate is a characteristic feature of the hemodynamic changes occurring in cirrhotic patients. Both increased SNS activity and reduced effective blood volume are responsible for this hyperdynamic state, which may not be apparent in the early stages of cirrhosis or may be evident only in the supine position. With the progression of liver disease, there is close association between the severity of cirrhosis and the degree of hyperdynamic circulation. Multiple lines of evidence, however, indicate that a relative decline in CO develops prior to HRS diagnosis and contributes to renal hypoperfusion and renal vasoconstriction in HRS patients. For example, low baseline CO at the time of spontaneous bacterial peritonitis (SBP) diagnosis correlated with subsequent development of HRS. After the resolution of infection, CO further declined in those in the HRS group. Ruiz-del-Arbol studied the systemic and hepatic hemodynamics of 66 patients with cirrhosis and tense ascites who had normal serum creatinine at baseline, with repeat measurements in 27 patients who subsequently developed HRS. At baseline, arterial blood pressure (BP) and CO were significantly lower and RAAS and SNS activity were significantly higher in the group that later developed HRS with further reduction in CO at the onset of renal dysfunction. In another study that included 24 patients with cirrhosis and ascites, cardiac index below 1.5 L/min/m² was associated with lower GFR and increased risk of subsequent type 1 HRS development compared with those with higher cardiac indices. Although these studies do not establish causality, they do suggest that low CO and HRS are interrelated. It is noteworthy to mention that impaired cardiac function, which is now termed cirrhotic cardiomyopathy, is also responsible for the acute heart failure that manifests following TIPS insertion and the increased cardiovascular morbidity and mortality after liver transplantation. Cirrhotic cardiomyopathy is characterized by blunted systolic and diastolic contractile responses to stress in conjunction with evidence of ventricular hypertrophy or chamber dilatation. The end result is reduced renal perfusion and renal vasoconstriction following development of infections and other stressful conditions that lead to HRS.

A detailed discussion of the etiologies of cirrhotic cardiomyopathy is outside the scope of this review, but factors involved in impaired cardiac function may include (1) myocardial growth and fibrosis due to neurohumoral activation; (2) diminished myocardial β-adrenergic receptor signal transduction from chronic SNS activation; and (3) an inhibitory effect of circulating cytokines, including tumor necrosis factor-α (TNF-α) and NO, on ventricular function. In alcoholic patients, a variable degree of alcoholic cardiomyopathy may also be a contributing factor.

Adrenal Insufficiency

Two studies examined the role of adrenal dysfunction in HRS, especially in the intensive care setting. In the first study, adrenal insufficiency was detected in 80% of patients with HRS, but only in 34% with a serum creatinine below 1.5 mg/dL. Because normal adrenal function is essential for an adequate response of the arterial circulation to endogenous vasoconstrictors, adrenal insufficiency could be an important contributory mechanism of circulatory dysfunction associated with HRS, especially in patients with severe bacterial infections. Other features associated with adrenal insufficiency were severe liver failure, arterial hypotension, vasopressor dependency, and increased hospital mortality. The second study showed that treatment with hydrocortisone in cirrhotic patients with severe sepsis and adrenal insufficiency is associated with a rapid improvement in systemic hemodynamics, a reduction of vasopressor requirements, and a lower hospital mortality. The mechanisms of adrenal dysfunction in cirrhosis with severe sepsis have not been explored, but a reduction in adrenal blood flow secondary to regional vasoconstriction is a possible mechanism.

Abnormal Renal Autoregulation and Precipitating Factors

Under normal conditions, effective renal autoregulation maintains constant renal blood flow despite wide fluctuations in arterial blood pressure. In cirrhotic patients, the relationship between renal blood flow and perfusion pressure is altered due to the activation of the SNS and other vasoconstrictor stimuli with rightward deviation of the renal autoregulatory curve. Thus renal blood flow becomes increasingly dependent on the arterial blood pressure with the progression of liver disease (Figs. 2 and 3). Therefore, in patients with advanced cirrhosis, events that lead to the

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slightest change in perfusion pressure will translate into major drops in renal blood flow that might precipitate intense renal vasoconstriction and HRS. Identifiable precipitating events include intravascular volume depletion from aggressive diuretic use or following large-volume paracentesis without albumin infusion, also known as postparacentesis syndrome. The incidence of postparacentesis syndrome is very low when the volume of ascites removed is less than 5 L, but it progressively increases to involve up to 70% of cases when the amount of fluid removed is above this limit.45,46 Probably the most important precipitating event is bacterial infections, especially SBP. Twenty to 30% of patients with SBP develop HRS despite appropriate treatment and resolution of infection.47,48 SBP patients with preexisting hyponatremia or elevated serum creatinine or those with high plasma or ascitic fluid cytokine levels at the time of SBP diagnosis are predisposed to HRS.23,47 The reason why SBP is associated with high risk of HRS is related to the role of the inflammatory response to SBP in HRS development.23,47 Another possible explanation is the development of septic cardiomyopathy with secondary deterioration in renal function.33 Urinary tract infections can also precipitate HRS in 15% of cases but HRS is uncommon following other infections such as cellulitis and pneumonia.49,50 Twenty-five percent of patients presenting with acute alcoholic hepatitis eventually develop HRS.51,52 Although AKI following gastrointestinal hemorrhage occurs more frequently in cirrhotic patients compared with those without liver disease (8% vs 1%, p < 0.05), AKI develops almost exclusively in patients with hypovolemic shock and responds to fluid resuscitation making prerenal failure a more plausible diagnosis.53 As previously mentioned, NSAIDs do precipitate HRS by blocking vasodilating prostaglandin synthesis in the kidneys.54

**Epidemiology**

The prevalence of HRS has declined over the last 2 decades, probably reflecting better management of cirrhotic patients and the wide use of prophylactic antibiotics for SBP prevention. For example, Ginès et al.51 had previously estimated the 1- and 5-year probability of HRS at 18% and 39%, respectively. However, a recent study that included 263 cirrhotic patients followed for 41 ± 3 months from their first episode of ascites showed much lower risk of HRS development with a prevalence of type 1 and type 2 HRS of 2.6% and 5%, respectively.55 In this study, the cumulative 5-year probability of HRS development was only 11.4%.55 The prevalence of HRS increases with progression of liver disease. In early stages of

<table>
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<th>Table 2 Characteristics of Type 1 and Type 2 Hepatorenal Syndrome</th>
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<tr>
<td><strong>Course</strong></td>
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<tr>
<td>Type 1 HRS</td>
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<td>Type 2 HRS</td>
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Table 3  IAC Criteria for Hepatorenal Syndrome Diagnosis

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Details</th>
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<tr>
<td>Cirrhosis with ascites</td>
<td>Serum creatinine &gt; 1.5 mg/dL</td>
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<tr>
<td></td>
<td>No improvement of serum creatinine (a decrease in serum &lt; 1.5 mg/dL)</td>
</tr>
<tr>
<td></td>
<td>after 2 days of diuretics and volume expansion with albumin (1 g/kg body weight up to a maximum of 100 g/d)</td>
</tr>
<tr>
<td>Absence of shock</td>
<td>No current or recent treatment with nephrotoxic drugs</td>
</tr>
<tr>
<td>Absence of signs of parenchymal renal disease, as suggested by proteinuria (&gt; 500 mg/d) or hematuria (&gt; 50 red blood cells per high-power field) and/or abnormal renal ultrasound</td>
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Adapted from Salerno et al. 59

HRS Definition and Diagnostic Criteria

The criteria to diagnose HRS were initially developed in 1996 and were recently updated by the International Ascites Club (IAC) in 2007. 59,60 Type 1 HRS is defined as doubling of the serum creatinine to a level greater than 2.5 mg/dL in less than 2 weeks’ duration, whereas in type 2 HRS there is a gradual rise in serum creatinine to greater than 1.5 mg/dL. It is important to think of the two types of HRS as two different clinical entities rather than stages of progression of the same disease. Type 1 HRS is more acute, is more commonly associated with multiorgan failure, has a very grim prognosis, and overlaps with other causes of AKI. A precipitating event is identified in 70 to 100% of type 1 HRS patients, and more than one event can occur in a single patient. 61–64 Type 2 HRS can be considered the genuine form of renal failure in cirrhotic patients. It represents the extreme expression of cirrhosis-induced circulatory failure and is heralded by refractory ascites. Renal failure in type 2 HRS is slowly progressive and parallels the degree of deterioration in liver function. The median survival for patients with type 2 HRS is 6 months, whereas the survival for patients with type 1 HRS is only 10% at 90 days from diagnosis. 65 – Table 2 highlights the major differences between type 1 and type 2 HRS.

The new IAC criteria for HRS diagnosis are summarized in – Table 3. The main points of difference between the old and new criteria for HRS are as follows:

1. Creatinine clearance is no longer incorporated in the diagnosis.
2. Ongoing bacterial infection does not exclude the diagnosis of HRS, provided septic shock is not present.
3. Albumin is preferred to saline for plasma volume expansion.
4. Nonessential minor diagnostic criteria including low fractional excretion of sodium and oliguria have been omitted.

The IAC criteria, however, have been recently challenged for multiple reasons. First, these criteria cannot establish HRS diagnosis in anuric patients, and they cannot identify HRS superimposed on organic renal disease, which limits their clinical applicability. 66 A recent multicenter study examined the applicability of these diagnostic criteria in daily clinical practice. Of the 116 patients diagnosed with HRS only 64% met all diagnostic criteria as outlined by the IAC, whereas the remaining 36% with acute deterioration of serum creatinine to above 1.5 mg/dL could not meet one or more of the diagnostic criteria due to anuria, hematuria, or proteinuria. 67 Some of these urinary abnormalities were attributed to bladder catheterization or previous nephropathies. 67 Second, in the case of type 2 HRS, these criteria overlap with the definition of chronic kidney disease (CKD). CKD is defined as low GFR < 60 mL/min for more than 3 months’ duration. Therefore patients with type 2 HRS with a progressive rise in serum creatinine over 3 months or more can be misclassified as having CKD despite the absence of other CKD features such as proteinuria or hematuria. Lastly and probably most importantly, there is discrepancy between the IAC diagnostic criteria and the current AKI diagnostic classifications. For example, The Acute Kidney Injury Network (AKIN) defines AKI in the general population as an absolute increase in serum creatinine by 0.3 mg/dL within a 48-hour period and/or urine output below 0.5 mL/kg/h for 6 hours. 68 Cirrhotic patients who develop AKI and HRS with a rise in serum creatinine by more than 0.3 mg/dL in less than a 48-hour period whose creatinine does not exceed 1.5 mg/dL cannot be labeled as having HRS according to the IAC criteria. This scenario is common in patients with a low baseline serum creatinine from low muscle mass, which is common in cirrhotic patients. This may delay access to timely HRS treatment and may therefore adversely affect these patients’ prognosis, especially that two studies have already correlated the AKI staging system with the in-hospital mortality in cirrhotic patients. 69–71 A working party proposal suggested defining AKI in cirrhotic patients as a rise in serum creatinine by 0.3 mg/dL or more within a 48-hour period or an absolute 50% rise in serum creatinine. 66 Since AKI is diagnosed, all efforts should be made to differentiate organic AKI from functional HRS. The same group did not feel that the urine output criteria...
are applicable to cirrhotic patients.\textsuperscript{66} Overall, the current available criteria for HRS diagnosis still need modification to align HRS diagnosis with the current AKI staging system and to clearly separate type 2 HRS from CKD.

**HRS Diagnosis**

There is no test or investigation that is specific for the diagnosis of HRS. Therefore the diagnosis is mainly based on the exclusion of other causes of AKI, unresponsiveness to volume expansion and meeting the diagnostic criteria for HRS outlined earlier. As mentioned, type 2 HRS can be confused with CKD; however, the presence of diuretic-resistant ascites and the lack of other radiological and laboratory features of CKD (e.g., proteinuria or renal cortical thinning) can differentiate between the two conditions. The main differential diagnosis of type 1 HRS is ATN because both conditions are characterized by an acute onset and rapid progressive deterioration of kidney function. ATN may also develop following infectious complications, which are known to precipitate HRS. Traditional markers to differentiate ATN from HRS such as the presence of granular urinary casts, low fractional excretion of sodium, or elevated blood urea nitrogen are insensitive to differentiate between type 1 HRS and ATN.\textsuperscript{59,72} In one study that included 44 cirrhotic patients with renal dysfunction who underwent kidney biopsy as part of liver transplant evaluation, low fractional excretion of sodium (\( \text{FeNa} < 1 \)) was present in 92\% of cases despite biopsy evidence of ATN or glomerulonephritis.\textsuperscript{73} Multiple urinary biomarkers including interleukin-18 (IL-18), neutrophil gelatinase associated lipocalin (NGAL), and others are currently under investigation to differentiate between type 1 HRS and ATN. Despite these difficulties, pinpointing the etiology of AKI in cirrhotic patients is important for both prognostic and therapeutic purposes.

**Natural History and Prognosis**

HRS is a functional renal failure without significant histological changes and therefore is potentially reversible. Indeed kidney function recovers following liver transplantation or when kidneys from HRS patients are transplanted in healthy subjects.\textsuperscript{74,75} However, prolonged renal vasoconstriction may precipitate irreversible renal damage, which might explain why only two thirds of HRS cases recover kidney function following liver transplantation.\textsuperscript{76–79} HRS carries a grim prognosis. Ginès and others have previously reported a 2-week mortality rate as high as 80\% in untreated type 1 HRS patients with only 10\% of patients surviving for 3 months.\textsuperscript{51,60} Progression of type 2 HRS patients is slightly better, with a median survival of 6 months.\textsuperscript{65} In recent years, however, there is a trend toward a slight improvement in HRS prognosis. For example, in a multicenter study by Salerno et al that included 116 HRS patients, some of them did receive vasoconstrictor therapy, and the 3-month survival was 20\% and 40\% for type 1 and type 2 HRS, respectively.\textsuperscript{67} Another study showed a 38\% 1-year survival for type 2 HRS patients and a mean survival of only 7 days for type 1 HRS.\textsuperscript{55} Figures 4A, B outlines the historical and most recent survival rates for patients with type 1 and type 2 HRS.

It is noteworthy to mention that HRS carries the worst survival among all causes of AKI in cirrhotic patients as demonstrated in a study that included 562 cirrhotic patients with AKI.\textsuperscript{84} In this study, 3-month survival for HRS patients was 15\% compared with 31\% for patients with infection-induced AKI, 46\% for hypovolemia-induced AKI, and 73\% for AKI associated with evidence of parenchymal renal disease [e.g., proteinuria or hematuria (\( P < 0.0005 \))]. Therefore, determining the etiology of AKI in cirrhotic patients does not only determine the treatment plan but also foretells the prognosis in these patients.

**Treatment**

**Prevention**

Due to its overall poor prognosis, HRS is better prevented than treated, and preventive measures have been beneficial in some clinical scenarios. For example, following large-volume paracentesis (\( \geq 5 \text{ L} \)), albumin is superior to other plasma expanders in preventing postparacentesis circulatory dysfunction and renal impairment.\textsuperscript{45,80} In a double-blind,
controlled study pentoxyfylline use for 28 days in patients with alcoholic hepatitis was associated with lower risk of HRS development and lower mortality. Prophylactic antibiotics prevent bacterial translocation and suppress proinflammatory cytokine formation implicated in the pathogenesis of HRS. It is not therefore surprising that prophylactic antibiotic use in patients at risk of SBP was effective in reducing both SBP and HRS risks. In one study, daily norfloxacin was associated with lower 1-year SBP probability (7% compared with 61%, P < 0.001) and lower 1-year HRS probability (28% compared with 41%, p = 0.02).4 Once SBP has developed, treatment with intravenous albumin (1.5 g/kg of body weight at diagnosis followed by 1 g/kg 48 hours later) in addition to ceftriaxone reduced the incidence of HRS to 10%, compared with 33% in those who received ceftriaxone alone (p = 0.002). Hospital mortality (10% vs 29%) and 3-month mortality rates (22% vs 41%) were also lower in patients receiving albumin and an antibiotic compared with those who received an antibiotic alone. The mechanisms by which albumin prevents HRS are incompletely understood but may be related to albumin's positive effect on circulatory function and its antioxidant properties.

General Management of HRS Patients

Type 1 HRS patients need to be managed in an intensive care unit because these patients have multigorgan failure and they rapidly deteriorate. Type 2 HRS patients can be managed on an outpatient basis or in a non-intensive care setting. In either case, diuretic treatment should be stopped and ascites should be managed with paracentesis. Large-volume paracentesis (more than 5 L) should be followed by 8 g of albumin infusion for each liter of ascitic fluid removed. There is enough evidence to recommend early paracentesis to exclude the adverse effects of increased intraabdominal pressure (IAP) on renal hemodynamics. For example, Cade et al reported a significant increase in urine flow rate and creatinine clearance following reduction in IAP from 22 to 10 mm Hg following paracentesis in patients with cirrhosis and ascites. Umgelter and colleagues studied 12 patients with established HRS and showed improvement in GFR and urine output and Doppler ultrasound evidence of reduction in renal resistive indices following paracentesis. In another study, paracentesis with albumin infusion but not albumin infusion alone improved creatinine clearance and fractional excretion of sodium in 19 HRS patients. Type 1 HRS patients, assessing the intravascular volume status using central venous access or, preferably, global end-diastolic volume index (GEDVI) is essential to guide fluid resuscitation and albumin infusion. In accordance with the IAC criteria and due to its established beneficial effects in cirrhotic patients, albumin infusion should be aggressively used prior to labeling patients as having HRS. Synthetic plasma expanders are less effective than albumin and are not recommended. Precipitating or aggravating factors such as SBP or adrenal insufficiency should be diagnosed and aggressively treated. Many of these patients are bed bound and decondition rapidly; therefore early ambulation, rehabilitation, and adequate nutrition should be thought of early and adequately planned for.

Assessment for liver transplantation should start as soon as possible. In type 1 patients not candidates for liver transplantation realistic expectations should be set and aggressive treatment modalities should be avoided. Pharmacological treatment and other interventions can be offered to selected type 2 HRS patients not suitable for liver transplantation on a case by case basis. In many cases, transplant candidacy is unclear. In these patients all therapeutic options should be attempted until suitability for liver transplantation becomes clearer. The ideal goals of treatment for HRS are to prolong survival until a liver transplant becomes available and to optimize conditions for successful liver transplantation.

Vasoconstrictor Therapy

Intravenous terlipressin and albumin infusion constitute the treatment of choice for HRS patients in Europe. However, terlipressin has not yet been approved for the treatment of HRS in the United States and Canada. Terlipressin is a long-acting synthetic vasopressin analogue composed of one molecule of lysine vasopressin and three glyline residues. It exerts its vasoconstrictive action through binding to the vasopressin (V1) receptor, which is preferentially expressed on the vascular smooth muscle cells within the splanchic circulation. It is metabolized through exopeptidases to release small amounts of lysine vasopressin over a sustained period, allowing it to be administered by bolus injection rather than by continuous infusion. Yet continuous infusion of terlipressin is associated with a higher HRS reversal rate compared with bolus injections. Multiple studies have demonstrated improvement in clinical parameters (including arterial blood pressure, urine output, and hyponatremia) and amelioration in the neurohormonal abnormalities in 50 to 70% of HRS patients following terlipressin and albumin infusions. Even in patients with cirrhosis and ascites but not HRS, terlipressin infusion has been associated with improvement in renal function and increased nephriuresis. Renal blood flow also improved following terlipressin infusion in 19 patients with cirrhosis and portal hypertension as evidenced by reduction in renal arterial resistive index. The median time to HRS reversal is 7 days with faster recovery in patients with lower serum creatinine at presentation. Other factors that predict favorable response to terlipressin include lower serum bilirubin level (< 171 µmol/L) and more than 5 mm Hg increase in mean arterial blood pressure following terlipressin initiation. Terlipressin has an acceptable side effects profile, with ischemic events occurring in 5 to 30% of cases, but most studies have excluded patients at high risk of ischemic events. Following completion of therapy, HRS recurred in up to 50% of cases. Factors associated with HRS recurrence are unknown, but renal function responds to the reintroduction of terlipressin. The benefits of terlipressin also seem to extend to type 2 HRS, with a slightly better response rate and longer survival than in type 1. All studies used terlipressin until serum creatinine decreased to less than 1.5 mg/dL or for a maximum of 15 days; therefore, it...
is unclear if longer duration of therapy will be of any benefit in increasing the HRS reversal rate.

The beneficial effects of albumin infusion on HRS reversal are well established.\textsuperscript{90,100} Because the majority of previously published studies concerning terlipressin use in HRS included both terlipressin and albumin infusions, it was unclear if HRS reversal was related to terlipressin or related to the albumin infusion. Two recent prospective, randomized studies evaluated the effect of terlipressin and albumin infusions versus albumin alone in type 1 HRS patients. The first of these studies was a double-blinded, multicenter study conducted in the United States and included 112 patients with type 1 HRS randomized in 1:1 fashion to either terlipressin plus albumin or placebo plus albumin. Reversal of HRS (as defined by a serum creatinine of $\leq 1.5$ mg/dL on two separate occasions 48 hours apart) occurred in 34% of cases in the terlipressin arm compared with 13% in the placebo arm ($p = 0.008$).\textsuperscript{101} The most important predictor of HRS reversal was a low serum creatinine at initiation of therapy. In fact, none of the HRS cases with a serum creatinine $\geq 5.6$ mg/dL responded to terlipressin.\textsuperscript{101} Importantly, HRS reversal was associated with improved 90-day patient survival ($p = 0.025$), but no survival benefit was demonstrated 180 days from terlipressin ($p = 0.07$).\textsuperscript{101} The second study was an open-label study conducted in Spain and included 46 patients with either type 1 or type 2 HRS randomized to receive either terlipressin and albumin or albumin alone.\textsuperscript{98} There was a significant difference in favor of terlipressin in the likelihood of HRS reversal (44% in the study group vs 8.7% in the control group, $p = 0.017$), but 3-month survival was not different between those who did or did not receive terlipressin (27% in the terlipressin arm vs 19% in the albumin arm, $p = 0.7$).\textsuperscript{98} Again, a lower baseline serum creatinine at initiation of therapy predicted a favorable response to terlipressin, suggesting that earlier initiation of therapy might confer the best probability of improvement in kidney function. Other predictors of favorable response to terlipressin include young age and a Child-Pugh score of less than 13.\textsuperscript{58,62}

From these two studies, terlipressin appears to have an independent beneficial effect on HRS reversal. However, neither study confirmed a survival advantage of terlipressin use even in patients who responded to therapy with the exception of improved 90-day (short-term) survival in the study by Sanyal et al.\textsuperscript{101} A recent meta-analysis confirmed that terlipressin and albumin infusions are associated with improvement in short-term (90-day) survival.\textsuperscript{102}

Midodrine and norepinephrine are two $\alpha_1$-adrenergic receptor agonists that are readily available and have been shown to be effective in the treatment of HRS. Continuous norepinephrine infusion in association with albumin and furosemide has been shown to be beneficial in reversing HRS.\textsuperscript{103} In a study that included 12 type 1 HRS patients, norepinephrine dose was titrated to achieve 10 mm Hg increase in mean blood pressure and/or increase in urine output by $> 200$ mL every 4 hours. Norepinephrine was infused either until serum creatinine decreased to less than 1.5 mg/dL or for a maximum of 15 days. The mean norepinephrine dose was 0.8 mg/h for a mean duration of 10 days. Ten of the 12 patients (83%) achieved HRS reversal; two of these had previously failed terlipressin therapy. Ischemic events were observed in two patients (17%).\textsuperscript{103} Improvement of kidney function was associated with improvement in patient survival, and four of the responders did not require liver transplantation 6 to 18 months after recovery of renal function.\textsuperscript{103}

Midodrine is a prodrug that is metabolized in the liver into an active metabolite, desglymidodrine, which is later eliminated in the urine. The pharmacokinetics of midodrine and desglymidodrine in HRS patients have not been studied. When given as monotherapy, oral midodrine slightly improved systemic hemodynamics but failed to improve renal function in patients with HRS or with refractory ascites.\textsuperscript{104–106} When combined, however, with the glucagon inhibitor octreotide (glucagon mediates splanchic vasodilatation) and in combination with albumin infusion, improvement in renal function, mean arterial pressure, and plasma renin activity was observed. Unfortunately, there are no randomized trials that evaluate the effect of midodrine and octreotide on HRS reversal, but two nonrandomized studies that included 19 type 1 HRS patients demonstrated reversal of HRS in 70 to 100% of cases treated with this protocol.\textsuperscript{63,107} Doses of midodrine and octreotide varied between these two studies, and in one study the octreotide dose was titrated according to the central venous pressure measurement.\textsuperscript{107} In both studies no significant treatment-related side effects were reported, and therapy was well tolerated.\textsuperscript{63} In the largest study to date that included 162 HRS patients, 75 patients received octreotide, midodrine, and albumin, and outcomes were compared with a historical cohort of 87 patients who did not receive any therapy. Octreotide, midodrine, and albumin were associated with improvement in kidney function, survival, and greater likelihood for liver transplantation compared with the no treatment arm.\textsuperscript{108}

**Effect of Different Vasoconstrictors on HRS Reversal and Patients’ Survival**

Although there are limited head to head studies comparing terlipressin to other vasoconstrictor agents, studies so far have not demonstrated an advantage of any vasoconstrictor agent over the other on HRS reversal. One study suggested that terlipressin-treated patients have a higher HRS recovery rate, longer survival, and greater likelihood of receiving a liver transplant compared with those treated with an octreotide–midodrine combination, but this study was nonrandomized, and the results could have been affected by selection bias.\textsuperscript{109} A meta-analysis has also confirmed that terlipressin and norepinephrine were equivalent in terms of efficacy and side effect profile in reversing HRS.\textsuperscript{110}

Apart from the rate of HRS reversal, a recent meta-analysis has shown no difference between various vasoconstrictors and patient survival.\textsuperscript{111} This meta-analysis included 10 trials comprising 376 patients with either type 1 or type 2 HRS who received terlipressin alone or with albumin, octreotide plus albumin, or norepinephrine plus albumin. Mortality was the primary outcome measure. Overall, vasoconstrictors used alone or with albumin reduced short-term mortality.
compared with no intervention or albumin alone (74% vs 58%, RR: 0.82, 95% CI: 0.70 to 0.96). In subgroup analyses, the survival benefit was apparent at day 15 of therapy (RR: 0.60, 95% CI: 0.37 to 0.97), but not at 30, 60, 90, and 180 days.\(^{111}\) Although this seems to be a dismal survival advantage, these few days of increased life expectancy might be sufficient for liver transplantation to become available, especially given that there are emerging reports of more prolonged vasoconstrictor use as a bridge to liver transplantation.\(^{112}\)

**Transjugular Intrahepatic Portosystemic Shunt**

The effect of TIPS insertion on improving urinary sodium excretion and renal function in cirrhotic patients with refractory ascites is well documented.\(^{26,113,114}\) Recently, Stadlbauer and colleagues demonstrated improvement in renal blood flow following TIPS insertion, which was attributed to leftward shift of the renal blood flow/renal perfusion pressure curve.\(^{44}\)

Two studies evaluated the effect of TIPS insertion in patients with type 1 HRS and preserved liver function as evidenced by a Child-Pugh score < 12.\(^ {115,116}\) Reversal of HRS occurred in almost 50% of cases within 3 months from TIPS insertion.\(^ {115,116}\) These clinical changes paralleled amelioration in renal hemodynamics and reduction of the plasma levels of different mediators of vasoconstriction. Patients’ survival ranged from 10 to 570 days, with 30 days survival achieved in five patients (71%).\(^ {115}\) An important observation from these two studies is the slow and delayed recovery of renal function following TIPS (within 2 to 4 weeks), unlike vasoconstrictor therapy, in which responders have faster recovery of renal function (1 to 2 weeks). Hepatic encephalopathy was a common complication but was controlled with medical therapy. Another drawback of TIPS insertion in type 1 HRS patients is the fact that most of these patients have advanced liver disease with a serum bilirubin level above 5 mg/dL, a known absolute contraindication for TIPS, limiting the utility of TIPS in this group of patients.\(^ {117}\) Nevertheless, the results of these studies suggest that TIPS insertion is a reasonable alternative in patients not candidates for vasoconstrictive therapy.

Two pilot studies also assessed the effect of TIPS insertion on type 2 HRS reversal.\(^ {116,118}\) Almost all patients had reversal of HRS and 70% of the patients were still alive 1 year post-TIPS. The results of these studies demonstrate that in a selected group of HRS patients, TIPS insertion might prolong survival long enough either to receive a liver transplant or, if they are not candidates, to stay off dialysis. It is noteworthy to mention that a recent study has demonstrated that TIPS insertion improves post-liver transplant outcomes, probably through improving kidney function.\(^ {119}\)

**Combination Therapy**

Vasoconstrictor therapy in conjunction with TIPS was evaluated in two studies. The first study included 14 type 1 HRS patients who received oral midodrine, octreotide, and albumin, followed by TIPS insertion in stable patients who responded to the vasoconstrictor therapy and were at low risk of hepatic encephalopathy.\(^ {63}\) All five patients who received combination therapy were alive 6 to 30 months following TIPS, with only one patient requiring liver transplantation 13 months later. On the other hand, responders to vasoconstrictors who did not receive TIPS either died (three patients) or required a liver transplantation (two patients). The second study, which included 11 type 2 HRS cases managed with sequential terlipressin and TIPS, also showed further improvement of kidney function following TIPS insertion.\(^ {94}\) However, due to the small number of cases and the limited applicability of TIPS in patients with advanced cirrhosis, it is hard to utilize this combination therapy on a large number of patients.

- **Table 4** summarizes the 30- and 90-day survival of untreated HRS patients and those who received therapy with different vasoconstrictor agents, TIPS, or a combination of vasoconstrictor and TIPS. The important observations are that (1) compared with no treatment, 30-day survival of HRS did improve with different treatment modalities, and (2) 90-

<table>
<thead>
<tr>
<th>Treatment Modality</th>
<th>Number of Patients</th>
<th>30-Day Survival (%)</th>
<th>90-Day Survival (%)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>No treatment</td>
<td>25</td>
<td>10</td>
<td>10</td>
<td>Ginès et al(^{21})</td>
</tr>
<tr>
<td>Octreotide + midodrine</td>
<td>5</td>
<td>80</td>
<td>33</td>
<td>Angeli et al(^{107})</td>
</tr>
<tr>
<td>NE</td>
<td>12</td>
<td>50</td>
<td>NA</td>
<td>Duvoux et al(^{103})</td>
</tr>
<tr>
<td>Terlipressin</td>
<td>21</td>
<td>61</td>
<td>12</td>
<td>Ortega et al(^{92})</td>
</tr>
<tr>
<td>TIPS</td>
<td>99</td>
<td>40</td>
<td>22</td>
<td>Moreau et al(^{58})</td>
</tr>
<tr>
<td>NE</td>
<td>23</td>
<td>NA</td>
<td>27</td>
<td>Martín-Llahi et al(^{98})</td>
</tr>
<tr>
<td>Terlipressin + NE</td>
<td>14</td>
<td>81</td>
<td>64</td>
<td>Guevara et al(^{115})</td>
</tr>
<tr>
<td>Vasoconstrictor + TIPS</td>
<td>5</td>
<td>100</td>
<td>100</td>
<td>Wong et al(^{83})</td>
</tr>
</tbody>
</table>

NE, norepinephrine; TIPS, transjugular intrahepatic portosystemic shunt; NA, not available.

*Patients with advanced cirrhosis were not candidates for TIPS insertion.
day survival of HRS remains dismal, irrespective of the treatment offered.

Renal Replacement Therapy

The indications for renal replacement therapy (RRT) initiation in HRS patients are no different from those with other non-cirrhotic patients with AKI and include volume overload, intractable metabolic acidosis, and hyperkalemia. In one study the most common reason for RRT initiation in HRS patients was volume overload.64 However, given the dismal prognosis of HRS patients, most nephrologists will offer RRT only to liver transplant candidates or those undergoing liver transplant evaluation. The decision to initiate RRT in HRS patients is further complicated by the presence of hepatic encephalopathy, hypotension, and coagulopathy, which have been associated with increased risks of hemorrhage and hypotension and which directly contributed to mortality in some cases.120,121 However, delaying RRT in HRS patients is associated with a mortality rate as high as 90%.122 Predictors of mortality following RRT initiation have been studied in 82 cirrhotic patients with AKI, 26 of them with HRS. In general, patients with advanced liver disease as evidenced by the presence of hepatic encephalopathy, malignancy, or thrombocytopenia had a 2.8- to 8.2-fold increased mortality rate.122 Therefore, in HRS patients waiting for a liver transplant, RRT is justifiable as a bridge to transplantation but is associated with increased morbidity and mortality compared with patients with other forms of AKI. In HRS patients who are not candidates for liver transplantation, initiation of RRT is controversial and can be offered only to a selected group of patients who have the potential of recovering kidney function after a short duration of dialysis.

There is still controversy regarding the best modality of RRT in orthotopic liver transplant (OLT) candidates. Continuous RRT (CRRT) is better tolerated than intermittent hemodialysis (HD) in HRS patients as evidenced by better cardiovascular stability, gradual correction of hyponatremia, and less fluctuation in intracranial pressure.123–126 However, prospective studies showed that the dialysis modality utilized in 30 HRS patients waiting for liver transplantation did not affect their survival.127 Other studies have also shown no advantage of CRRT over intermittent HD in HRS patients waiting for liver transplantation.128 A single-center trial that included 102 liver transplant candidates with AKI requiring RRT (48% of them with HRS) showed higher mortality with CRRT compared with HD (78% vs 50%, p = 0.02).56 As expected, cirrhotic patients with AKI who were maintained on CRRT were much sicker as evidenced by higher APACHE (acute physiology and chronic health evaluation) II score and lower blood pressure and were more likely to be mechanically ventilated and on vasopressor support.56 Hence, although the best modality of RRT in HRS is not well defined, OLT candidates in need of RRT can be managed with either HD or CRRT before transplantation with similar outcomes. The choice of best modality is dictated by hemodynamic stability and severity of illness and should be tailored to individual patients. One clear indication for CRRT is in patients with fulminant hepatic failure and increased intracranial tension due to the adverse effect of intermittent HD on intracranial pressure.125 One drawback of CRRT is the need for continuous systemic anticoagulation, which might increase the risk of bleeding; however, cirrhotic patients are often coagulopathic, and anticoagulation may be safely avoided. Other alternatives include regional citrate or regional heparin/proteam anticoagulation; both have been used in cirrhotic patients and provided filter lifespan similar to those obtained using systemic anticoagulation.129 However, caution should be exercised with citrate anticoagulation because hepatic citrate metabolism is impaired in cirrhotic patients increasing the risk of citrate toxicity.130

The ultimate dialysis dose and timing for RRT initiation have not been studied in cirrhotic patients with HRS, but data can be inferred from other studies of AKI in critically ill patients, which suggests that early RRT initiation and maintenance of negative fluid balance improve patient survival.131,132 Two recent randomized studies that included a large number of critically ill patients with AKI (many of them with concomitant liver cell failure) showed no clear benefit of higher dialysis dose on hospital mortality or the probability of renal function recovery.133,134 However, other studies demonstrated an improvement in gas exchange, lower noradrenaline dose, earlier weaning from mechanical ventilation, shorter intensive care unit stay, and better survival in septic patients with AKI who received early high-dose isovolemic hemofiltration (45 mL/kg/h for 6 hours), followed by conventional CRRT at 20 mL/kg/h, compared with a similar group of patients who received conventional-dose CRRT.135 Currently, it remains unclear whether critically ill patients with HRS will benefit from higher RRT dose. A randomized study specifically addressing this question is needed.

The Molecular Adsorbent Recirculating System (MARS, Gambro Americas, Lakewood, CO) is an albumin-based form of RRT that combines a conventional CRRT circuit to an albumin-enriched dialysate that is then regenerated by passage through a charcoal and ion exchange cartridge. The assumption is that, by removing albumin-bound toxins (e.g., bile acids and nitric oxide) and water-soluble cytokines (TNF-α and interleukin-6) (both have been implicated in HRS pathogenesis), liver function will stabilize and end-organ damage will improve.136–138 Although studies have demonstrated improved survival with MARS compared with conventional CRRT, the overall survival is still low, with 7-day survival of 37% and 30-day survival of 25%.136,139 Other albumin-based dialysis techniques include single-pass albumin dialysis, which can be performed using a standard CRRT circuit and fractionated plasma separation, adsorption, and dialysis (Fractional Plasma Separation Adsorption and Dialysis System (Prometheus, Fresenius Medical Care, Bad Homburg, Germany)).140 MARS is currently approved by the U.S. Food and Drug Administration (FDA) for the treatment of drug overdose but not for HRS, whereas the Prometheus system is not FDA approved.

Intraoperative complications, including hemodynamic instability and hyperkalemia, are more prevalent in HRS patients undergoing liver transplantation. Townsend et al141 described their experience with intraoperative CRRT in 41
patients at the time of liver transplantation. Indications for
the procedure were preoperative CRRT in almost 50% of the
cases and hyperkalemia, dysnatremia, and metabolic acidosis
in the rest of the group. Despite the presence of elevated
international normalized ratio (INR) in all the patients, filter
circuit clotting occurred in 40% of the cases. However, heparin
or regional citrate anticoagulation was not used except in
three patients for fear of bleeding diathesis. Nevertheless,
CRRT was administered for almost 50% of the operative time,
and filter clotting did not affect the duration of CRRT. This
study demonstrates that intraoperative CRRT is feasible and
useful in providing negative or even intraoperative fluid
balance, despite the large number of blood transfusions in
this cohort.

Liver and Liver-Kidney Transplantation

Liver transplantation is the ultimate treatment of HRS patients.
Renal sodium excretion and serum creatinine and neurohor-
monal levels normalize within 1 month of liver transplan-
tation in the majority of patients. Renal artery resistive
indices, however, take up to 1 year to return back to their
normal values. However, recovery of renal function follow-
ing successful liver transplantation is not universal. For example,
Marik and colleagues studied renal function recovery follow-
ing successful liver transplantation in 28 HRS patients. Com-
plete recovery of kidney function occurred in only 58% of cases
within 4 to 110 days of OLT, whereas another 15% partially
recovered function. Importantly, kidney function never re-
covered in 25% of cases. In another study from China, 30 of 32
(94%) HRS patients recovered kidney function within a median
of 24 days after liver transplant. Reasons for lack of recovery
of kidney function can be only speculated due to the limited
number of studies addressing this question, but shorter HRS
duration, younger recipients’ age, and immediate liver allograft
function as evidenced by lower posttransplantation day 7
bilirubin level are factors that favor renal recovery. One
important predictor of post–liver transplant dialysis require-
ment in HRS cases is prolonged RRT for more than 8 weeks
prior to liver transplant. Therefore, although there is no
survival advantage of liver-kidney transplantation compared
with liver transplant alone in patients with HRS, liver-kidney
transplantation is recommended in HRS patients who have
been on RRT for 8 weeks or more. It is important to
mention that unexpected post–liver transplant events such as
primary allograft nonfunction, reoperation, infection, and
hemorrhage are associated with increased risk of AKI in the
immediate post–liver transplant period and can adversely
affect HRS recovery.

HRS affects post–liver transplant outcomes. HRS patients
have lower post–liver transplant survival and a higher risk of
postoperative complications compared with those without
HRS. Patients who do not recover kidney function and
remain on RRT post–liver transplant have a dismal
prognosis, with a 1-year mortality rate of around 70%. Kidney
after liver transplantation does provide a survival
advantage compared with staying on RRT. Those who
recover kidney function remain at high risk of developing
chronic kidney disease and end-stage renal disease compared

with those with normal kidney function at the time of liver
transplant. The effect of successful pre–liver transplant
treatment of HRS on post–liver transplant outcomes has
revealed mixed results. In a study by Restuccia and colleagues,
post–liver transplant outcomes were similar between nine
successfully treated HRS patients and 27 matching controls
who did not have HRS. Another study, however, showed no
advantage of pre–liver transplant HRS treatment on post–
liver transplant outcomes.

Our approach has been to provide OLT in the majority of
HRS patients, with the exception of those who have been on
RRT for 8 weeks or more. In cases where the etiology of renal
failure is unclear, or if there are overlapping features of
chronic kidney disease (proteinuria, hematuria, etc.) and
HRS, we rely on histological information to direct the trans-
plant options.

Conclusions and Future Directions

In summary, HRS is a drastic complication of liver cirrhosis.
Recent reports suggest a trend toward lower prevalence and
improved outcomes of HRS reflecting better understanding of
the underlying pathophysiological mechanisms and the avail-
ability of preventive and therapeutic strategies. Nevertheless,
HRS is still associated with significant morbidity and mortal-
ity, and it does adversely affect post–liver transplant out-
comes. Liver transplantation is the ultimate treatment for
HRS, but vasoconstrictor agents, TIPS, and/or RRT can be
utilized as a bridge to transplantation. The current HRS
classification needs to be revisited to incorporate HRS under
the general umbrella of AKI and to lower the threshold for
HRS diagnosis.

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