# Hepatorenal Disorders

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Renal dysfunction is common in patients with end-stage liver disease (ESLD); it takes on many forms from acute to chronic renal injury and may involve a variety of mechanisms. Hepatorenal syndrome (HRS) is a specific type of hepatorenal disorder (HRD) with a unique pathophysiology. HRS is characterized by splanchnic arterial vasodilatation and decreased effective intravascular volume that leads to renal vasoconstriction and decreased renal blood flow. The incidence of HRS in relation to other forms of HRD is unknown; however, it is estimated that 35% to 40% patients with ESLD and ascites eventually develop the condition. Two subtypes of HRS have been described. Type 1 HRS is rapidly progressive, whereas the renal function in type 2 HRS deteriorates slowly over weeks or months. Type 1 HRS may be precipitated by sepsis or acute alcoholic hepatitis and occasionally develops in patients who already have type 2 HRS. The diagnosis of HRS is based on the exclusion of other causes of renal dysfunction because no specific test is available. The definitive treatment of HRS is liver transplant. As a bridge to liver transplant, medical management with volume expansion and the use of vasoconstrictors is often implemented. A transjugular intrahepatic portosystemic shunt has been attempted in treating HRS, although there is little evidence of its efficacy compared with standard therapy. Renal replacement therapy is often used if the patient is a liver transplant candidate. Artificial liver assist devices are in the research phase.

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**ABBREVIATIONS:** ADQI = Acute Dialysis Quality Initiative; AKI = acute kidney injury; AKIN = Acute Kidney Injury Network; ATN = acute tubular necrosis; CRRT = continuous renal replacement therapy; eGFR = estimated glomerular filtration rate; ESLD = end-stage liver disease; GFR = glomerular filtration rate; HDF = hemodiafiltration; HRD = hepatorenal disorder; HRS = hepatorenal syndrome; IAC = International Ascites Club; IHD = intermittent hemodialysis; MARS = molecular adsorbent recirculating system; RAAS = renin angiotensin-aldosterone system; RIFLE = Risk, Injury, Failure, Loss, End-Stage; RRT = renal replacement therapy; SBP = spontaneous bacterial peritonitis; SCr = serum creatinine; SNS = sympathetic nervous system; TIPS = transjugular intrahepatic portosystemic shunt

The term hepatorenal disorder (HRD) was proposed by the Acute Dialysis Quality Initiative (ADQI) and the International Ascites Club (IAC) and is used to encompass the full range of conditions in which liver and kidney disease coexist.<sup>1,2</sup> HRD is prevalent because the two organs are susceptible to many of the same insults (eg, toxins, certain infections) and because the conditions that cause kidney injury

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(eg, sepsis, hemorrhagic shock) are common in patients with end-stage liver disease (ESLD). However, the two organs also have a unique interaction resulting in a specific type of HRD known as the hepatorenal syndrome (HRS). The unique physiology of HRS may well occur to some extent in the majority of patients with ESLD; however, clinical criteria for the diagnosis of HRS (Table 1)<sup>3</sup> are specific. An understanding of the full range of pathophysiology of renal dysfunction in the setting of ESLD is necessary to care for these complex patients. This review covers the nomenclature, pathophysiology, and treatment of HRD.

# Acute Kidney Injury in Cirrhosis

The incidence of acute kidney injury (AKI) in patients with liver disease is difficult to determine. Systematic evaluation of the literature is hindered by the lack of a precise classification of the severity or cause of renal dysfunction, variations in the definitions used to describe renal dysfunction, the fact that underlying chronic kidney disease may be present, and the variability of the underlying causes of liver disease. In 2004, the ADQI developed a consensus definition and classification for AKI known as the Risk, Injury, Failure, Loss, End-Stage (RIFLE) criteria, which stratified acute renal dysfunction into grades of increasing severity based on changes in serum creatinine (SCr) level, urine output, or both.<sup>4</sup> Subsequently, it was recognized that even smaller increases in SCr (absolute increase in SCr level  $\geq 0.3 \text{ mg/dL}$ ) are associated with an adverse outcome.<sup>5</sup> As a result, the criteria were modified by the Acute Kidney Injury Network (AKIN)<sup>6</sup> to broaden the definition (Table 2),6 and these criteria were adopted by the international multidisciplinary

#### TABLE 1 Diagnostic Criteria for Hepatorenal Syndrome<sup>3</sup>

(> 50 RBC per high power field) and/or a normal renal ultrasonography Kidney Disease Improving Global Outcomes (KDIGO) in their 2012 clinical practice guideline.<sup>7</sup>

In critically ill patients with cirrhosis, AKI defined by RIFLE criteria has been shown to be a predictor of hospital survival.8-10 In 2010, the ADQI workgroup, together with several members of the IAC, recommended adaptation of the modified RIFLE criteria to define AKI in patients with cirrhosis, instead of the traditional definition using a fixed SCr cutoff value of >1.5 mg/dL.<sup>1,2</sup> These criteria are used irrespective of whether the presumed cause of the acute deterioration in renal function is related to a functional or a structural disorder. Fagundes et al<sup>11</sup> proposed a classification that combines the AKIN criteria and the classic criteria of kidney failure in cirrhosis that provided a better risk stratification than did the AKIN criteria alone. Three risk groups were identified: (1) patients with AKI stage 1 with peak  $c_{reatinine} \leq 1.5 \text{ mg/dL}$ , (2) patients with stage 1 with peak creatinine > 1.5 mg/dL, and (3) patients with stage 2 or 3 (survival 84%, 68%, and 36%, respectively, and this was statistically significant). Piano et al<sup>12</sup> also suggested that conventional criteria are more accurate than AKIN criteria in the prediction of in-hospital mortality in patients with cirrhosis and ascites. The addition of either the progression of AKIN stage or the cutoff of SCr  $\geq$  1.5 mg/dL to the AKIN criteria improves their prognostic accuracy.12

# Definition of HRS

Conceptually, HRS is a "functional" (ie, no parenchymal injury) renal failure in the setting of ESLD, characterized by renal vasoconstriction without significant histologic renal abnormalities.<sup>13</sup> In 1996, the IAC proposed a definition and diagnostic criteria for HRS<sup>3</sup> that was revised in 2007 (Table 1).14 The main difference between the two definitions was the removal of minor criteria, which included a low urine sodium level, the use of albumin instead of saline for plasma volume expansion, and the removal of creatinine clearance. HRS is divided into two types, type 1 and type 2. HRS type 1 is defined as a doubling of SCr to a value > 2.5 mg/dL or a 50%reduction in creatinine clearance to < 20 mL/min in < 2 weeks. It frequently follows a precipitating event, and survival without treatment is usually in the order of weeks. HRS type 2, by contrast, is characterized by a slower deterioration of renal function; survival without treatment is usually in the order of months and it mainly presents as diuretic-resistant ascites.15,16

The diagnosis of HRS is mainly one of <u>exclusion</u> (Table 1). Differentiating HRS from other forms of AKI can be quite

#### TABLE 2 Modified RIFLE Criteria for Acute Kidney Injury

Stage	Serum Creatinine	Urine Output
1	1.5-1.9 times baseline	<0.5 mL/kg/h for 6-12 h
	OR	
	$\geq\!0.3$ mg/dL (>26.5 $\mu\text{mol/L})$ increase	
2	2.0-2.9 times baseline	$<$ 0.5 mL/kg/h for $\ge$ 12 h
3	3.0 times baseline	$<$ 0.3 mL/kg/h for $\ge$ 24 h
	OR increase in serum creatinine to ${\geq}4.0$ mg/dL (353.6 ${\mu}\text{mol/L})$	OR
	OR initiation of renal replacement therapy	Anuria for $\geq$ 12 h
	OR, in patients aged ${<}18$ y, decrease in eGFR to ${<}35$ mL/min per 1.73 $m^2$	

In each stage, fulfillment of either serum creatinine level or urine output is required. eGFR = estimated glomerular filtration rate; RIFLE = Risk, Injury, Failure, Loss, End-Stage. (Adapted with permission from Mehta et al.<sup>6</sup>)

challenging. Although urine sodium and fractional excretion of sodium have been used to help differentiate HRS from acute tubular necrosis (ATN), a study using renal biopsies to determine cause in patients with cirrhosis revealed similar urine indexes in patients with HRS and ATN.<sup>17</sup>

Most forms of AKI in critically ill patients are associated with very subtle histologic abnormalities (at least early on), but perturbations are found at the cellular or molecular level.<sup>18</sup> Conversely, patients with the clinical phenotype of HRS may have cellular injury that is subclinical and may indeed have urine chemistry indistinguishable from ATN.<sup>17</sup> HRS affects approximately 18% of patients with ESLD at 1 year and 35% at 5 years.<sup>15</sup> Independent risk factors for developing HRS include hyponatremia, high serum renin activity, the absence of hepatomegaly, a low cardiac output, and an elevated resistive index on renal Doppler.<sup>15,19,20</sup>

A major limitation of the HRS criteria is that they do not allow for the coexistence of other forms of acute or chronic kidney disease, such as underlying diabetic nephropathy or other glomerular diseases often associated with patients with liver disease (eg, IgA, membranous or membranoproliferative disease). However, patients with underlying kidney disease can still develop "hepatorenal physiology." As a result, the ADQI/IAC members proposed that the term HRD be used to describe all patients with advanced cirrhosis and concurrent kidney dysfunction who fulfill the diagnostic criteria of AKI, chronic kidney disease, or HRS (Fig 1).<sup>4,5</sup> Such a definition would allow patients with cirrhosis and renal dysfunction to be properly classified and treated while maintaining the term HRS.

# Pathophysiology

Several proposed mechanisms contribute to the development of HRS (Fig 2).<sup>21</sup> However, alternative explanations have been suggested recently.<sup>22</sup> <u>Splanchnic arterial vasodilation</u> caused by increased production of endogenous vasodilators such as nitric oxide, prostacyclin, endogenous opiates, cannabinoids, and other molecules that are present in patients with portal hypertension<sup>3,23,24</sup> plays an important role in the development of HRS. The splanchnic arterial vasodilatation and <u>low effective</u> <u>circulating volume triggers</u> the activation of <u>vasoconstrictor systems</u> such as the renin angiotensin-aldosterone system (<u>RAAS</u>), the sympathetic nervous system (<u>SNS</u>), and the <u>arginine-vasopressin</u> system, which help maintain acceptable arterial pressure.<sup>3,21</sup>

In addition to intrarenal vasoconstriction with resulting decreased renal blood flow and glomerular filtration rate (GFR), these vasoconstrictor systems cause the retention of sodium and solute-free water, which may worsen ascites, hyponatremia, and systemic edema. In the early stage of cirrhosis, increased activity of systemic and renal vasodilators preserves renal perfusion despite the activation of the RAAS, the arginine-vasopressin system, and the



Figure 1 – Classification of hepatorenal disorders. Spectrum of hepatorenal disorders in patients with advanced cirrhosis. Three distinct scenarios are shown (1-3) based on the background renal function. AKI = acute kidney injury; CKD = chronic kidney disease; HRS = hepatorenal syndrome; KD = kidney disease. (Reprinted with permission from Wong et al.<sup>2</sup>)



Figure 2 – <u>HRS pathophysiology</u>. \*The exact mechanisms responsible for activation of systemic vasoconstrictors have not been established. The prevailing theory includes systemic vascular "underfilling" related to a failure of the liver to clear vasoactive compounds. \*\*Control of glomerular pressure is achieved by regulation of both efferent and afferent arteriolar tone. Therefore, glomerular filtration can be preserved for a time despite a fall in renal blood flow. See Figure 1 legend for expansion of abbreviation.

SNS. As the cirrhosis advances, renal perfusion cannot be maintained, and HRS occurs.<sup>21</sup> Bacterial translocation in patients with advanced cirrhosis may trigger an inflammatory response that leads to the release of proinflammatory cytokines (tumor necrosis factor- $\alpha$ and IL-6) and vasodilator factors (nitric oxide), resulting in further splanchnic vasodilatation and the associated hemodynamic changes.<sup>25,26</sup> Bacterial products (endotoxin or DNA) can translocate to extraintestinal sites and promote an immunologic response similar to that produced by viable bacteria. Bacterial DNA detection and species identification in serum or ascitic fluid have been proposed as a potential marker of bacterial translocation.<sup>27</sup> A study of selective intestinal decontamination using norfloxacin revealed partial reversal of the hyperdynamic circulatory state associated with liver cirrhosis, which implicates bacterial translocation as part of the pathogenesis of HRS.28

Evaluation of Renal Function, Damage, and Stress

In the setting of cirrhosis, <u>SCr tends to overestimate renal</u> <u>function</u><sup>29</sup> because of <u>decreased creatine production</u> by

the liver, protein calorie malnutrition, an enlarged volume of distribution, and muscle wasting.<sup>29,30</sup> In addition, in the setting of AKI, SCr can lag by several hours to days, despite a decrease in the GFR. Serum cystatin C has been suggested as a more sensitive marker of renal function<sup>31-35</sup>; however, some studies have shown that like SCr, cystatin C is affected by muscle mass and liver disease and overestimates renal function in patients with cirrhosis.<sup>31,36</sup> GFR is considered the best estimate of renal function, although there is no universally accepted gold standard for its measurement. The Cockcroft equation<sup>37</sup> can overestimate GFR in patients with liver cirrhosis because it uses weight as a reflection of lean body mass, which is not applicable to patients with cirrhosis, in whom edema and ascites may account for a portion of their weight.<sup>29,38,39</sup> The Modified Diet in Renal Disease40 was best able to calculate the estimated GFR (eGFR) in comparison radionuclide GFR assessment; however, the precision of all GFR equations was poor.<sup>41,42</sup> Other eGFR equations, such as the Chronic Kidney Disease Epidemiology Collaboration and the cystatin C-based eGFR, have been proposed and used in patients with liver disease.43,44

The presence of "hepatorenal physiology" superimposed on existing kidney disease (acute or chronic) is not addressed by the current taxonomy for HRS. As diagnostics in this space mature, we expect to see significant changes in how these diseases are classified.

#### Prevention

In patients with cirrhosis and low protein ascitic levels (<15 g/L) with advanced liver failure (Child-Pugh score  $\geq$  9 points with serum bilirubin level  $\geq$  3 mg/dL) or impaired renal function (SCr level  $\geq$  1.2 mg/dL, blood urea nitrogen level  $\geq 25 \text{ mg/dL}$ , or serum sodium level  $\leq 130 \text{ mEq/L}$ ), primary prophylaxis with norfloxacin reduces the incidence of spontaneous bacterial peritonitis (SBP), delays the development of HRS, and improves survival.<sup>45</sup> These beneficial effects could be related to the prevention of bacterial translocation, a decreasing proinflammatory cytokine burden, and its deleterious effects on hemodynamics and renal perfusion.<sup>28,46</sup> In patients with SBP, the administration of IV albumin (1.5 g/kg) at the time of diagnosis of infection and another dose of albumin (1 g/kg) on day 3 of antibiotic treatment reduces the incidence of both renal impairment and mortality.<sup>47</sup> Nonselective β-blockers should be avoided once the diagnosis of SBP is established because their use has been associated with HRS and a reduction of transplant-free survival.48

A meta-analysis evaluated the impact of albumin infusion (in addition to antibiotics) on renal impairment and mortality in patients with SBP. Albumin infusion was associated with a significant decrease in the incidence of renal impairment and a significant reduction in mortality.<sup>49</sup>

## Management

Several interventions, including avoidance of nephrotoxins, adequate volume resuscitation, paracentesis, and the use of vasoconstrictors, have been used in an effort to prevent or manage HRS.<sup>50</sup> In patients with HRS, intravascular volume depletion should be reversed; however, the choice of IV fluids is controversial. IV administration of albumin (initially 1 g of albumin/kg of body weight, up to a maximum of 100 g, followed by 20-40 g/d) for a maximum of 15 days in combination with terlipressin was shown to be effective in one study enrolling 46 patients.<sup>51</sup> The question arises as to whether the beneficial effect observed with albumin is primarily a result of volume expansion or whether albumin has additional effects compared with other colloids. In one randomized unblinded pilot study, albumin was compared with hetastarch in patients with SBP.52 Treatment with albumin was associated with a significant increase in arterial pressure and a suppression of plasma renin activity, whereas no significant changes were observed in the hetastarch group.<sup>52</sup> However, the current evidence suggest that the use of hydroxyethyl starch increases the risk of AKI and mortality.53-55

Vasoconstriction of the splanchnic vascular beds is used to treat HRS by increasing the effective arterial blood volume, thereby suppressing activation of the RAAS and SNS, reversing compensatory renal vasoconstriction, and increasing renal perfusion. Using an early and substantial increase in mean arterial pressure as a therapeutic target was associated with better short- and long-term overall survival in patients with HRS type 1.<sup>56</sup>

Several pharmacologic agents have been used in the management of HRS.<sup>50</sup> Midodrine is an oral  $\alpha$  agonist that is widely used in combination with octreotide to treat HRS, despite relatively limited data.<sup>57-62</sup> The use of midodrine at doses of 7.5 mg po tid titrated up to 12.5 mg tid, along with octreotide 100 µg subcutane-ously tid titrated up to 200 µg tid has been evaluated in small numbers of patients, and the data suggest improvement in kidney function and survival when mean arterial pressure is increased by 15 mm Hg.<sup>60,63</sup> Although not approved for use in the United States, terlipressin has been used in managing HRS.<sup>64</sup> An initial pilot study demonstrated that, when compared with placebo, terlipressin improved GFR in patients with HRS type 1.<sup>65</sup> A retrospective study has demonstrated

a survival benefit, particularly as a bridge to liver transplant.66 These preliminary studies led to three randomized prospective trials that supported the use of terlipressin in combination with albumin to increase renal function in patients with type 1 HRS.<sup>51,67,68</sup> These trials looked at the resolution of HRS, partial reversal of HRS, survival, and improvement in hemodynamics and hormonal profiles. Although there were no effects on long-term survival, short-term mortality was reduced in part because of a reversal of HRS in patients treated with terlipressin. Norepinephrine has been used successfully in patients with HRS.<sup>69,70</sup> A meta-analysis that included patients with type 1 HRS compared therapy with terlipressin plus albumin with therapy with norepinephrine plus albumin.<sup>71</sup> The efficacy of terlipressin and norepinephrine was similar; however, adverse events (abdominal pain, chest pain, or arrhythmia) were significantly more common with terlipressin. In addition, the <u>cost</u> of <u>terlipressin</u> therapy was more than three times the cost of norepinephrine therapy.72

Other agents such as vasopressin<sup>69,73-76</sup> and N-acetylcysteine<sup>77,78</sup> may play roles in the management of HRS. Dopamine, prostanoids, natriuretic peptides, and endothelin antagonists have been shown to be ineffective.<sup>78-82</sup> Uncontrolled studies demonstrated an improvement in renal function in patients with HRS following paracentesis,<sup>83-85</sup> likely caused by increased venous return and cardiac function and reduced renal venous pressure and intrarenal pressure.

The use of nonpharmacologic therapies such as a transjugular intrahepatic portosystemic shunt (TIPS), renal replacement therapy (RRT), and extracorporeal liver support therapy in the treatment of HRS are not well established. One uncontrolled study that looked at the long-term effects of a TIPS in nontransplantable patients with HRS suggested an improvement in renal function and a possible survival advantage.<sup>86</sup> Using a TIPS in addition to pharmacotherapy has been investigated in small trials, and data suggest that a TIPS enhances the improvement of renal function, helps with ascites, and helps in cases in which patients relapsed after medical therapy.87-89 A TIPS carries operative morbidity and mortality and its postprocedure complications may include intraabdominal bleeding, shunt thrombosis and infection, hemolytic anemia, and, most importantly, an increase in the hepatic encephalopathy rate; therefore, the balance between risks and benefits should be taken into consideration.

No prospective randomized trials have demonstrated a survival advantage in patients with HRS treated with RRT.<sup>16</sup> Continuous RRT (CRRT) would be a suitable RRT modality in patients with HRS because it does not cause intradialytic hypotension episodes as frequently as does intermittent hemodialysis (IHD); the changes in solute concentration in CRRT are gradual and are not as rapid as in IHD. The latter helps minimize changes in solute gradient across the blood-brain barrier, which decreases the risk of both brain edema and worsening intracranial pressure. Because of slow solute clearance, CRRT is optimal in cases in which patients with liver failure have chronic hyponatremia, by avoiding the rapid correction of serum sodium concentration seen with IHD. However, data are lacking to support a survival advantage with CRRT in patients with liver failure who are not candidates for liver transplant.90,91 Chronic dialysis in patients with HRS, who are not candidates for liver transplant, has been a controversial topic, primarily because of the increased burden of morbidity and in-hospital stay in these patients when kept alive on dialysis. Thus, in nontransplant candidates, the decision to provide RRT should be made on a case-bycase basis.<sup>92,93</sup> The use of the molecular adsorbent recirculating system (MARS) in the treatment of HRS has been investigated in few small trials. Treatment with MARS may play a role in improving renal function in patients with HRS.94,95

In a prospective controlled trial of 13 patients with liver failure and type 1 HRS, eight patients were treated with MARS and medical therapy; in addition, hemodiafiltration (HDF) was used when indicated, and five were treated with HDF and medical treatment alone.<sup>95</sup> The results of this trial suggested improvement in survival, serum sodium, and bilirubin. SCr decreased in the study; however, it is difficult to determine the effects of MARS and HDF on SCr because both treatment modalities clear creatinine from blood without a true effect on GFR.

## Prognosis

The onset of complications related to ESLD defines the transition from a compensated to decompensated state.<sup>96</sup> Without a liver transplant, patients who develop HRS have a median survival time of approximately 3 months, and the longer a patient has had HRS prior to transplantation, the less likely he or she is to recover normal renal function after the transplant.<sup>16</sup> A high Model for End-Stage Liver Disease score,<sup>97</sup> type 1 HRS,<sup>98</sup> and a systemic inflammatory response<sup>99</sup> are the major prognostic factors of mortality in patients with HRS. Generally, renal dysfunction in patients with advanced liver failure carries a poor prognosis, with an overall survival of about 50% and 20% at 1 and 6 months, respectively. Survival appears to be

particularly worse in patients with HRS, with a median survival of 1 month and 6 months in HRS type 1 and 2, respectively. Hence, the cause of renal dysfunction appears to influence survival; in two prospective studies,98,100 both HRS type 1 and the Model for End-stage Liver Disease score were found to be independent predictors of poor outcome. In contrast, HRS type 2 outcomes were similar to those of patients with liver failure with renal dysfunction from other causes.<sup>100</sup> It is still unclear whether vasoconstrictor therapy improves outcome in patients with HRS, but patients who respond to such a therapy appear to live longer. Ultimately, liver transplant is the only proven therapy to improve survival in patients with HRS, but we have to keep in mind that severe renal dysfunction is predictive of a poor outcome after liver transplant, which includes an increase in the incidence of postoperative sepsis, prolonged ICU length of stay, an increased use of pre- and postoperative dialysis, and reduced survival.101,102

# Conclusions

HRS is a unique abnormality that occurs in patients with ESLD and is under the umbrella of HRD. HRS is usually triggered by an event such as sepsis or GI bleeding. HRS is a diagnosis of exclusion, and type 1 HRS can rapidly lead to death without aggressive support, which consists of volume resuscitation, vasoconstrictors, RRT, and liver transplant.

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