Hepatorenal Syndrome

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Abstract: Acute kidney injury (AKI) secondary to hepatorenal syndrome (HRS) is an ominous complication of end-stage liver disease (ESLD). In HRS, splanchnic and peripheral vasodilatation with reduction in effective arterial volume causes activation of mechanisms leading to intense renal vasoconstriction and functional AKI. HRS is a diagnosis of exclusion and all other causes of AKI (especially prerenal azotemia) have to be considered and excluded. Spontaneous bacterial peritonitis (SBP) frequently precipitates HRS and should be ruled out in all ESLD patients presenting with AKI. Prompt therapy of SBP with intravenous antibiotics and albumin lessens the risk of developing HRS. Combined use of intravenous albumin, splanchnic and/or peripheral vasoconstrictors, and renal replacement therapy (RRT) are only bridges to early liver transplantation (or combined liver-kidney transplantation in selected patients). Transplantation is the only definitive way of improving the long-term prognosis. Close collaboration between hospitalists/internists managing HRS patients and hepatology and nephrology consultants is critically important.

Key words: acute kidney injury, end-stage liver disease, hepatorenal syndrome

Hepatorenal syndrome (HRS) is a complication of end stage liver disease (ESLD) associated with a dismal prognosis for patient survival. It can develop in patients with advanced chronic liver disease (cirrhosis of any etiology) and in patients with acute fulminant hepatic failure of diverse causes. HRS is an entity encountered in the inpatient setting in ESLD patients. This article presents a review of the current concepts regarding HRS for hospitalists, internists, and primary care physicians.

HRS is defined as a unique functional form of acute kidney injury (AKI) in patients with advanced cirrhosis (almost always associated with ascites) or in patients with fulminant acute hepatic failure that cannot be explained by the common etiological factors that account for AKI in patients without underlying liver disease.1–3 HRS is thus a diagnosis of exclusion, requiring ruling out of other causes of AKI. It is a functional disorder because it is caused by intense renal vasoconstriction without structural changes in the kidneys. Prompt reversal of renal dysfunction caused by HRS in the majority of patients is achieved by successful liver transplantation, and prompt restoration of renal function in patients with end-stage renal disease following renal transplantation using a kidney from a donor with HRS proves that HRS is a functional disorder.4 Table 1 shows the current diagnostic criteria for HRS (proposed originally by the International Ascites Club in 1996 and revised in 2005).5,6

Two types of HRS are recognized based on the tempo of development of AKI:3 Type 1 HRS is characterized by rapid...
Table 1. Hepatorenal syndrome: currently recommended diagnostic criteria

| Presence of cirrhosis with ascites. |
| Serum creatinine >1.5 mg/dL (creatinine clearance <40 ml/min no longer included in the criteria). |
| Failure of serum creatinine to improve to <1.5 mg/dL after cessation of all diuretics + volume expansion with intravenous albumin 1 g/kg body weight/day up to maximum of 100 g/d for at least 48 h. Albumin infusion has replaced normal saline (1.5 L/d) that was included in older diagnostic criteria. |
| HRS can be diagnosed in the presence of infection if shock is absent. |
| No current or recent use of nephrotoxic drugs. |
| No evidence of parenchymal kidney disease: proteinuria <500 mg/d, RBCs in the urine sediment <50/high power field and normal renal ultrasonography. |
| Previously included minor diagnostic criteria (oliguria, low urine sodium level, and high urine osmolality) have been eliminated from current criteria. |

*HRS, hepatorenal syndrome.*

HRS can also complicate acute fulminant liver disease.

worsening of renal function (at least a doubling of serum creatinine to >2.5 mg/dL or a >50% drop in creatinine clearance or glomerular filtration rate (GFR) in 2 weeks or less. Renal functional decline is more gradual in type 2 HRS, which is seen mainly in patients with diuretic-refractory ascites.

The limitations of defining HRS on the basis of the serum creatinine level, glomerular filtration rate (GFR) estimated from the serum creatinine level (using the Cockroft-Gault or Modification of Diet in Renal Disease formulae), or measured 24 hour urinary creatinine clearance should be recognized. 

ESLD patients have marked muscle wasting and decreased creatinine generation by skeletal muscles. Hepatic synthesis of creatine (the substrate for creatinine synthesis in skeletal muscles) may be impaired. There is also evidence that serum bilirubin levels >10 mg/dL may interfere with colorimetric methods of measuring serum creatinine. These extrarenal factors result in significant overestimation of GFR when the serum creatinine is used as the index of renal function in this population. However, despite its limitations, creatinine is currently the only readily available and easily measured test of renal function.

Incidence and Prognostic Significance of HRS

In a large cohort of initially nonazotemic cirrhotic patients with ascites at the start of the study, the incidence of HRS was reported as 18% at one year and 39% at 5 years of follow up. The incidence of HRS in acute fulminant liver disease has been reported to be between 20% to 30%.

Unless liver transplantation is performed without delay, the development of either type of HRS is associated with very poor patient survival. Type 2 HRS is associated with better patient survival than type 1. However, this is still significantly worse than that in ESLD patients without HRS (Fig.).

In addition to high mortality without liver transplantation, patients who are transplanted after developing HRS have significantly decreased survival, increased requirement for early postoperative intermittent or continuous renal replacement therapy (RRT), and increased risk of other posttransplant complications. There may also be incomplete recovery of renal function in some HRS patients following liver transplantation with greater risk of progression eventually to end-stage renal disease.

HRS: Pathogenesis

HRS is a functional form of AKI without irreversible structural renal damage. Severe renal vasoconstriction in the setting of generalized vasodilatation, especially in the splanchnic circulation, with blood pooling in areas of vasodilatation and consequent reduction of effective arterial volume (EAV) is the pathophysiologic basis of HRS. Splanchnic vasoconstriction is mediated by the production of potent vasoconstrictor substances, in particular nitric oxide. Increased nitric oxide synthesis in the splanchnic vasculature is believed to result from high endothelial shear stress as a result of portal hypertension complicating cirrhosis. There is also experimental evidence showing that the intestinal mucosal barrier is defective in the setting of advanced liver disease and portal hypertension. This permits increased bacterial migration from the intestinal lumen to mesenteric lymph nodes and leads to increased production of vasoactive cytokines, endotoxins, etc, which further increases nitric oxide production, thereby aggravating splanchnic vasoconstriction.

In ESLD, vasodilatation and decreased EAV antedate the development of HRS. Increased cardiac output initially offsets the decreased EAV and maintains renal blood flow. Decreased EAV also activates a variety of other compensatory mechanisms (the renin-angiotensin system (RAS), sympathetic nervous system, and increased release of antidiuretic hormone (ADH), endothelin, etc), which tend to cause renal vasoconstriction. Increased intrarenal synthesis of vasoconstrictors such as prostaglandins initially counters the renal...
vasoconstriction. HRS eventually develops when increased cardiac output and intrarenal vasodilators are no longer able to counter the decreased EAV and renal vasoconstriction, respectively, with resultant AKI due to decreased renal blood flow.

Intense renal vasoconstriction also results in avid renal tubular retention of sodium and water. This sodium retention further aggravates ascites and edema. In fact, HRS almost never develops in the cirrhotic patient who does not have ascites. Nonosmotic ADH release secondary to decreased glomerular filtration rate (GFR) results in increased renal tubular sodium and water reabsorption, which further aggravates ascites and edema. This sodium retention results from increased EAV and renal vasoconstriction. Reductions in EAV resulting from overdiuresis, vomiting, variceal hemorrhage, diarrhea (aggravated by lactulose use), or large volume paracentesis without concomitant albumin administration, etc may also precipitate HRS. Use of nonsteroidal anti-inflammatory agents (NSAIDs) may contribute to the development of HRS by inhibiting renal vasodilatory prostaglandin synthesis.

Clinical Presentation of HRS

HRS may present as de novo AKI in patients with previously good kidney function or as AKI superimposed on preexisting chronic renal dysfunction. By definition, AKI progresses more rapidly in type 1 compared to type 2 HRS. In both types of HRS, serum creatinine may increase progressively to a level which necessitates RRT. In other HRS patients, serum creatinine, after initially increasing steadily, may stabilize at a level not requiring immediate RRT. In general, type 1 HRS patients are more severely ill than those with type 2 HRS. Uremic encephalopathy secondary to HRS superimposed on preexisting hepatic encephalopathy may result in marked deterioration of mental status. HRS may occur spontaneously. However, the importance of SBP as a precipitating factor cannot be overemphasized: approximately one third of patients with SBP will develop HRS.

HRS: Diagnostic Approach

As previously stated, the diagnosis of HRS is one of exclusion: all causes of AKI that are not unique to ESLD must be considered in the differential diagnosis (Table 2). HRS is unlikely to be the cause of AKI if ascites, features of advanced parenchymal liver dysfunction, oliguria, hypotension, and hyponatremia, are lacking. Typically, urine examination in a patient with HRS reveals high specific gravity/osmolality, low urine sodium concentration, and low fractional excretion of sodium without significant proteinuria, hematuria, or sediment abnormalities. However, in two other functional forms of AKI that may occur in the ESLD patient, prerenal azotemia and abdominal compartment syndrome (ACS), urinary findings are the same as in HRS. Prerenal azotemia is caused by EAV depletion, hypotension, and/or low cardiac output. The difference between prerenal azotemia and HRS is that only in the former volume repletion, correction of hypotension, and/or improvement of cardiac output rapidly improves renal function. This is the basis for recommending diuretic withdrawal and volume expansion with intravenous albumin for at least 48 h. Rule out abdominal compartment syndrome (if tense ascites are present) by large volume paracentesis + intravenous albumin. Rule out spontaneous bacterial peritonitis by diagnostic paracentesis for ascitic fluid cell count, gram stain, and culture. Renal ultrasonography to rule out hydronephrosis/obstructive uropathy. Monitor blood urea nitrogen, serum creatinine, electrolytes, and liver function tests daily to assess evolution of renal and hepatic status. Early hepatology and nephrology consultations.

Table 2. Acute kidney injury in the patient with liver disease: diagnostic approach

| Careful history and physical examination: |
| Vomiting, diarrhea, gastrointestinal bleeding, marked recent weight loss and rapid decrease in ascites and edema: suspect prerenal azotemia due to gastrointestinal losses or overdiuresis. |
| Recent exposure to nephrotoxic agents such as nonsteroidal anti-inflammatory agents, aminoglycosides, sulfadiazine/trimethoprim, iodinated radiocontrast, etc: suspect nephrotoxic AKI. |
| If features of advanced liver disease (especially ascites) are not present, hepatorenal syndrome (HRS) is unlikely. |
| Urinalysis looking for proteinuria, hematuria, and other sediment abnormalities; random urine protein/creatinine ratio or 24 h urine collection to quantitate proteinuria; urine sodium/osmolality/fractional excretion of sodium. |
| Differentiating prerenal azotemia from HRS: discontinuation of diuretics and any nephrotoxic medications, and trial of volume expansion with intravenous albumin for at least 48 h. |
| Rule out abdominal compartment syndrome (if tense ascites are present) by large volume paracentesis + intravenous albumin. |
| Rule out spontaneous bacterial peritonitis by diagnostic paracentesis for ascitic fluid cell count, gram stain, and culture. |

Abdominal compartment syndrome (ACS), defined as increased intraabdominal pressure (IAP) of >20 mm Hg of any etiology, may lead to AKI by increasing renal venous pressure and causing renal arterial vasoconstriction. Intraabdominal pressure (measured by placing a Foley catheter connected to a manometer) is used as the surrogate for IAP. ACS (due to tense ascites), although rare, has been reported to cause AKI in ESLD patients. Renal function may improve dramatically in cirrhotics when tense ascites are relieved by large volume therapeutic paracentesis with concomitant intravenous albumin administration. Even if ACS is unlikely, all patients with HRS must have at least a diagnostic paracentesis to rule out SBP, a common precipitating factor for HRS.

The presence of significant proteinuria, hematuria, and sediment abnormalities in an ESLD patient with AKI suggests diagnoses other than HRS. Heavy proteinuria and RBC casts suggest glomerular disease. Common glomerular dis-
eases in patients with liver disease include cryoglobulinemic glomerulonephritis in patients with hepatitis C or hepatitis B and glomerulopathy in association with IgA deposits. Numerous granular casts suggest ischemic or nephrotic acute tubular necrosis. Tubular cell and/or white blood count casts suggest acute interstitial nephritis. However, it should be remembered that the development of HRS in a patient with preexisting kidney disease, proteinuria, hematuria, and/or sediment abnormalities secondary to the antecedent renal disorder can present a diagnostic difficulty. Therefore, it is important to review any available past test results to rule out preexisting urinary abnormalities. Renal ultrasonography should be performed to rule out hydronephrosis/obstructive uropathy as the cause of AKI.

Since the differential diagnosis of AKI in patients with ESLD is extensive and complex, early nephrology consultation is appropriate. A renal biopsy may be required if the cause of AKI is unclear. Patients with significant chronic, irreversible changes (glomerulosclerosis and/or tubular atrophy/interstitial fibrosis) on renal biopsy may require combined liver-kidney transplantation.18

Prevention of HRS

The following measures are effective in decreasing the incidence of HRS. Long-term, once a week, oral quinolone antibiotic suppression for the prevention of SBP which is recommended in selected cirrhotics with ascites (patients with low protein ascitic fluid, Child-Pugh scores >9, early renal dysfunction, history of variceal bleeding, prior history of SBP, etc) also decreases the incidence of HRS.25 In patients with SBP, two doses of intravenous albumin (1.5 gm/kg body weight upon diagnosis and 1.0 gm/kg 48 hours later) have been shown in a randomized controlled study to significantly reduce the incidence of HRS to 10% compared to 33% in patients not given albumin (both groups treated with cefotaxime).25 Minimizing EAV depletion by judicious use of diuretics to avoid excessive weight loss, prompt replacement of gastrointestinal fluid or blood loss, and concomitant administration of intravenous albumin (6 to 8 gm/liter of ascitic fluid removed) when performing large volume paracentesis for refractory ascites, may also decrease the risk of developing HRS.26 It is also judicious to avoid the use of potentially nephrotoxic medications such as nonsteroidal anti-inflammatory drugs and aminoglycoside antibiotics in cirrhotics with ascites.

Treatment of Established HRS

In established HRS, therapy is aimed at correcting the causative hemodynamic abnormalities. Various direct renal vasodilators (“low-dose” or “renal dose” intravenous dopamine, RAS blocking drugs, oral [misoprostol] or intravenous prostaglandin-E, endothelin antagonists, etc) have been evaluated in the treatment of HRS with uniformly negative re-
sults.27–29 Renal vasodilator therapy is not currently recommended in patients with HRS.

Reversing splanchnic and peripheral vasodilatation combined with expansion of EAV with albumin infusion is currently the cornerstone of the treatment of HRS.30–35 Agents used include octreotide31 (available in the United States) or the arginine-vasopressin analog terlipressin32,33 (not yet approved in the United States) as splanchnic vasoconstrictors and oral midodrine33 or intravenous norepinephrine34 as peripheral vasoconstrictors. The combination regimens that have been used in clinical trials of HRS are shown in Table 3. In these trials, reversal of HRS has been reported in 25% to 83% of patients treated with pressor agents plus albumin compared to 8.7% to 12.5% of patients treated with albumin alone.31–35 However, long-term patient survival without liver transplantation did not improve in these trials. The typical duration of vasoconstrictor therapy is 14 days. If HRS recurs, retreatment with the same regimen may again be successful. It should be noted that the use of intravenous albumin and splanchnic and/or peripheral vasoconstrictors has not been shown to be effective in hepatorenal syndrome complicating acute liver disease with fulminant hepatic failure. “Liver-dialysis/hemofiltration,” which combines dialysis technology with absorbents (albumin or charcoal) and/or hepatocytes (“bioartificial liver”) in the extracorporeal circuit to remove putative toxins resulting from liver failure, has been used in this setting in Europe but is currently unavailable in the United States.31–35

If SBP is documented, antibiotic therapy with an intravenous third generation cephalosporin or fluoroquinolone should be continued for 10–14 days followed by indefinite weekly oral fluoroquinolone suppressive therapy.25

Table 3. Combination therapy regimens used in hepatorenal syndrome6,31–35

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<th>Treatment</th>
<th>Initial Dose</th>
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<td>Intravenous terlipressin</td>
<td>(not yet approved for use in the United States) initial dose 0.5–1.0 mg every 4 to 6 h, increased on day 4 to 2 mg intravenously every 4–6 h, if serum creatinine has not decreased by &gt;30% from baseline + intravenous albumin (initial dose 1 g/kg followed by 20 to 40 g/d).</td>
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<td>Oral midodrine</td>
<td>(initial dose 7.5 mg orally TID with an increase to 12.5 to 15 mg TID as needed to increase mean arterial pressure by 15 mm Hg) + octreotide SQ 100 µg TID, titrated 200 µg TID on day 2, if renal function has not improved + intravenous albumin (initial dose 1 g/kg followed by 20 to 40 g/d).</td>
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<td>Intravenous norepinephrine</td>
<td>(0.5–3.0 mg/h as continuous intravenous infusion adjusted to increase mean arterial pressure by 10 mm Hg even in the absence of hypotension or shock) + intravenous albumin (initial dose 1 g/kg followed by 20 to 40 g/d).</td>
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*Above measures have not been shown to be effective in hepatorenal syndrome complicating acute liver disease with fulminant hepatic failure.

**Use of octreotide alone without midodrine has not been shown to be effective. When using vasoconstrictor drugs such as midodrine, norepinephrine or terlipressin, the patient must be monitored closely for coronary, cerebrovascular, mesenteric, and/or digital ischemic complications.**
Transjugular intrahepatic portosystemic shunt (TIPS) placement ameliorates portal hypertension. TIPS has improved renal function in carefully selected patients with HRS.\(^\text{30}\) TIPS may, however, increase the risk of hepatic encephalopathy. The decision to use TIPS will have to be made in conjunction with the hepatologist who should be consulted early in the care of HRS patients.

In patients who are candidates for liver transplantation, if AKI progresses despite the above therapies, intermittent or continuous RRT will have to be initiated. RRT is futile in patients who are not candidates for liver transplantation, given the dismal prognosis of refractory HRS without transplantation.

It should be remembered that all of the above treatments are only temporizing measures. The only definitive way of improving the long term survival of HRS patients is liver transplantation.\(^\text{11}\) The development of HRS is an urgent indication for liver (+/- kidney) transplant evaluation or for expediting transplantation in patients already on the transplant waiting list.

**Conclusion**

HRS is a serious complication of chronic or acute ESLD. It is a functional form of AKI caused by intense renal vasoconstriction in the setting of splanchnic and peripheral vasoconstriction with pooling of blood in the vasodilated areas with consequent reduction in EAV. All other causes of AKI will have to be ruled out before diagnosing HRS. SBP, a common precipitant of HRS, will have to be excluded by ascitic fluid studies. Use of splanchnic and peripheral vasoconstrictors in combination with intravenous albumin may improve renal function in HRS. However, these regimens and RRT (if indicated) are only bridges to liver (+/- kidney) transplantation which is the only definitive way of improving long term outcomes.

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**References**


Hepatorenal Syndrome

July 2010 CME Questions

1. Which of the following features distinguishes prerenal azotemia from hepatorenal syndrome?
   A. Random urine sodium level < 10 mEq/L
   B. Random urine osmolality > 500 mosm/L
   C. Prompt improvement in renal function following intravenous albumin
   D. Random urine protein/creatinine ratio < 500 mg/gram
   E. Unremarkable urine sediment

2. Which of the following hemodynamic patterns is typical of hepatorenal syndrome?
   A. Splanchnic vasoconstriction, renal vasodilatation and increased effective arterial volume
   B. Splanchnic and renal vasoconstriction and decreased effective arterial volume
   C. Splanchnic, peripheral and renal vasodilatation with increased effective arterial volume
   D. Splanchnic and peripheral vasodilatation, renal vasoconstriction and decreased effective arterial volume

3. Which of the following measures have been reported to improve renal function in patients with hepatorenal syndrome?
   a. Direct renal vasodilatation using low-dose dopamine infusion
   b. Combination therapy with octreotide (or terlipressin), midodrine (or norepinephrine infusion) and intravenous albumin
   c. Renal vasodilatation using a combination of drugs blocking the renin-angiotensin system and endothelin antagonists
   d. Combination therapy with octreotide (or terlipressin) and low-dose dopamine infusion

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“Hepatorenal Syndrome” Objective: Upon completion, participants should be able to recognize the diagnostic criteria for hepatorenal syndrome, outline the pathophysiologic changes responsible for this disease, workup renal failure in cirrhotic patients and initiate appropriate therapy.

Evaluate these statements as they relate to this article.

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