# Hepatorenal syndrome: Are we doing better?

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**ARTICLE**

Watt K, Uhanova J, Minuk GY. Hepatorenal syndrome: Diagnostic accuracy, clinical features, and outcome in a tertiary care center. Am J Gastroenterol 2002;97:2046-50.

This is a retrospective study assessing the accuracy of diagnosis, clinical features and outcome of patients coded with a medical record diagnosis of hepatorenal syndrome (HRS) between 1988 and 1998 in a tertiary care centre in Canada. The authors found that, of the 46 patients whose medical records revealed a diagnosis of HRS, only 27 patients (59%) fulfilled the criteria for the diagnosis of HRS defined by the International Ascites Club (IAC) (1). Most patients with HRS were middle-aged men with decompensated alcoholic cirrhosis, jaundice and hepatic encephalopathy. Infection (48%), gastrointestinal bleeding (33%) and overly aggressive paracentesis (27%) were the major precipitants of renal failure. Once HRS developed, the mortality rate was high (93%), with multiorgan failure being the most common cause of death. The authors concluded that diagnostic accuracy is paramount for studies of HRS. In addition, decompensated alcoholic cirrhosis remains the main predisposing factor for HRS, with various other factors precipitating its development.

## COMMENTARY

Renal dysfunction often complicates cirrhosis. HRS is a functional renal disorder that frequently occurs in very ill patients with liver failure and refractory ascites. Until the IAC created guidelines for the definition of HRS in 1996 (1), HRS was generally defined as the development of renal failure in patients with advanced liver failure (acute or chronic) in the absence of any other identifiable cause. Despite the fact that HRS is a diagnosis of exclusion, it is often incorrectly diagnosed in patients with cirrhosis. The study by Watt et al (2) illustrates this fact. In their cohort of 46 patients, more than 40% of patients with a medical record diagnosis of HRS did not actually have HRS. In fact, 11 of the 46 patients (24%) had organic renal disease. Therefore, there is a need for physicians to recognize that not all cases of renal disease in cirrhosis are HRS. There are many organic renal diseases that occur as a result of liver disease, and there are many systemic diseases that can affect the liver and the kidney simultaneously (3). An inaccurate diagnosis of HRS may lead to inappropriate treatment and an undesirable outcome.

In 1996, the IAC established criteria for the diagnosis of HRS (1). The major criteria, which must be fulfilled before a diagnosis of HRS can be made, are listed in Table 1. The minor criteria are used as supportive evidence (Table 1) but are not absolutely necessary for diagnosis, because there are cases of HRS that do not exhibit avid renal sodium retention (4). To date, there have been no other studies assessing the accuracy of the diagnosis of HRS since the publication of the IAC criteria. Presumably, use of the IAC criteria has led to improved diagnostic accuracy and has facilitated the clinical investigation of HRS, but the accuracy of the diagnosis of HRS in the non-research setting is unknown.

Can we predict which patient with decompensated cirrhosis will develop HRS? In order to answer this question, we need to understand the pathophysiology of HRS. Patients with advanced cirrhosis and liver failure have a hyperdynamic circulation, with reduced systemic vascular resistance and increased cardiac output (5). As a result of splanchnic and systemic arterial vasodilation, there is relative underfilling of the systemic circulation and a reduction in mean arterial pressure (6). Consequently, renal perfusion pressure is diminished, leading to decreased renal blood flow. There is compensatory

**TABLE 1**
**Diagnostic criteria for hepatorenal syndrome (1)**

| **Major criteria** |
|---|
| • Chronic or acute liver disease with liver failure and portal hypertension |
| • Low glomerular filtration rate, as indicated by a serum creatinine >1.5 mg/dL or a creatinine clearance of <40 mL/min |
| • Absence of shock, ongoing bacterial infection or recent treatment with nephrotoxic drugs. Absence of excessive fluid loss, including gastrointestinal loss |
| • No sustained improvement in renal function following expansion with 1.5 L of isotonic saline |
| • Less than 0.5 g of proteinuria per day |
| • No ultrasonographic evidence of renal tract disease |
| **Minor criteria** |
| • Urine volume < 500 mL/day |
| • Urine sodium < 10 mmol/day |
| • Urine osmolality < plasma osmolality |
| • Urine red cell count < 50 per high power field |
| • Serum sodium < 130 mmol/L |

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activation of various vasoconstrictor systems to maintain hemodynamic stability. Vasoconstriction occurs in some nonsplanchnic vascular beds, including the kidneys, thereby further reducing renal perfusion and glomerular filtration rate (7). Therefore, one would expect that patients with the most arterial vasodilation to develop HRS. Indeed, Gines et al (8) found that a low serum sodium (which reflects inadequate effective arterial blood volume) and high plasma renin activity were two important predictive factors for the development of HRS.

Watt et al found that events that disturb the balance between the intravascular volume and the intravascular capacity, such as gastrointestinal bleeding or large volume paracentesis, are the most frequent precipitants of HRS. This suggests that decompensated cirrhotic patients, because of hemodynamic instability, are at risk of developing renal impairment if their circulation is further compromised. The corollary from this observation is that such patients should be subjected to as little disturbance of their circulatory volume as possible. Therefore, patients who have clinical evidence of significant arterial vasodilation, such as low arterial blood pressure or tachycardia, should be assessed to receive intravascular volume replacement if they undergo large volume paracentesis. Likewise, patients with gastrointestinal bleeding should receive complete fluid resuscitation. It is interesting to note that Watt et al found that bacterial infections are also important precipitants of HRS. This is because infections induce endotoxin and cytokine production, which exacerbates systemic vasodilation (9). This might explain the renal protective effects of volume expanders like albumin in patients with spontaneous bacterial peritonitis (10).

With better understanding of the pathophysiology of HRS, much progress has recently been made in the treatment for HRS. For example, terlipressin, a vasopressin analogue, is used to counteract the systemic arterial vasodilation and improve renal perfusion, and has been shown to decrease serum creatinine in approximately two-thirds of patients with HRS (11). Midodrine, an alpha agonist, and octreotide, a nonspecific inhibitor of the systemic vasodilation, have also been shown to improve renal function in HRS (12). A transjugular intrahepatic portosystemic shunt returns a significant portion of the splanchnic volume to the systemic circulation, thereby augmenting arterial blood volume and increasing glomerular filtration rate in HRS patients. Many of these therapeutic modalities serve as bridges to liver transplantation, the definitive treatment for HRS (13). Consequently, the dismal prognosis (median survival of 1.7 weeks [8]) has been dramatically improved. In the near future, we can expect to see combination treatments that address various aspects of the pathophysiology of HRS. Therefore, the onus will be on clinicians to recognize HRS early, so that appropriate and timely treatment could be given.

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## REFERENCES

1. Arroyo V, Gines P, Gerbes AL, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. International Ascites Club. Hepatology 1996;23:164-76.
2. Watt K, Uhanova J, Minuk GY. Hepatorenal syndrome: Diagnostic accuracy, clinical features, and outcome in a tertiary care center. Am J Gastroenterol 2002;97:2046-50.
3. Wong F. Liver and kidney diseases. Clin Liver Dis 2002;6:981-1011.
4. Dudley FJ, Kanel GC, Wood LJ, Reynolds TB. Hepatorenal syndrome without avid sodium retention. Hepatology 1986;6:248-51.
5. Blendis L, Wong F. The hyperdynamic circulation in cirrhosis: An overview. Pharmacol Ther 2001;89:221-31.
6. Schrier RW, Arroyo V, Bernardi M, Epstein M, Henriksen JH, Rodes J. Peripheral arterial vasodilation hypothesis: A proposal for the initiation of renal sodium and water retention in cirrhosis. Hepatology 1988;8:1151-7.
7. Moore K. The hepatorenal syndrome. Clin Sci 1997;92:433-43.
8. Gines A, Escorsell A, Gines P, et al. Incidence, predictive factors, and prognosis of the hepatorenal syndrome in cirrhosis with ascites. Gastroenterology 1993;105:229-36.
9. Guarner C, Soriano G, Tomas A, et al. Increased serum nitrite and nitrate levels in patients with cirrhosis: Relationship to endotoxemia. Hepatology 1993;18:1139-43.
10. Sort P, Navasa M, Arroyo V, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. N Engl J Med 1999;341:403-9.
11. Moreau R, Durand F, Poynard T, et al. Terlipressin in patients with cirrhosis and type 1 hepatorenal syndrome: A retrospective multicenter study. Gastroenterology 2002;122:923-30.
12. Angeli P, Volpin R, Gerunda G, et al. Reversal of type 1 hepatorenal syndrome with the administration of midodrine and octreotide. Hepatology 1999;29:1690-7.
13. Brensing KA, Textor J, Perz J, et al. Long term outcome after transjugular intrahepatic portosystemic stent-shunt in non-transplant cirrhotics with hepatorenal syndrome: a phase II study. Gut 2000;47:288-95.