Hepatorenal Syndrome: Physiology, Diagnosis and Management

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Semin Intervent Radiol 2018;35:194–197

Abstract

Keywords

- hepatorenal syndrome
- pathophysiology
- TIPS
- terlipressin

Individuals with end-stage liver disease are susceptible to a myriad of highly morbid complications, including hepatorenal syndrome (HRS). This specific type of renal dysfunction in patients with underlying liver disease occurs in pathophysiologically normal kidneys and is a result of renal vasoconstriction secondary to diminished renal blood flow in the setting of worsening hepatic dysfunction. Liver transplantation is curative; shortage of available organs limits access to this beneficial therapy. Medical management of HRS has demonstrated increasing promise. Transjugular intrahepatic portosystemic shunt creation has also been shown to be efficacious in enhancing transplant-free survival, although further study is advisable before widespread implementation of this strategy.

Objectives: Upon completion of this article, the reader will be able to identify the diagnostic criteria for hepatorenal syndrome, as well as the options for treatment of hepatorenal syndrome.

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Hepatorenal syndrome (HRS) is a variant of renal dysfunction in patients with end-stage liver disease, including cirrhosis and alcoholic hepatitis. Renal dysfunction in this patient population generally occurs in the setting of portal hypertension and may be related to prerenal, intrinsic, or postrenal etiologies. HRS, specifically, occurs in physiologically normal kidneys, often in the absence of an obvious precipitating factor and is categorized by two variants, type 1 and type 2 HRS. Type 1 HRS is characterized by faster disease progression, generally within 2 weeks and is associated with a poorer prognosis, with a 90-day survival rate of 10%.¹ In contrast, patients with type 2 HRS present with a more gradual decline in renal function, over a period of several weeks and have an improved prognosis, with a survival time of 6 to 8 months. Both variants are definitively rectified by transplantation, although there have been efforts over the past two decades for developing alternate management strategies.

Issue Theme Update on Portal Hypertension; Guest Editor, Bartley G. Thornburg, MD

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Tel: +1(212) 584-4662.

DOI <https://doi.org/10.1055/s-0038-1660797>.
ISSN 0739-9529.

Pathophysiology

Hepatorenal syndrome is characterized by renal vessel vasoconstriction in response to deteriorating liver function in patients with cirrhosis and ascites.²⁻⁶ The mechanism that leads to this vasoconstriction is not entirely apparent. In general, in patients with cirrhosis and portal hypertension, marked splanchnic arterial vasodilation occurs leading to a reduction in effective circulating blood volume. This reduction of blood volume leads to activation of the renin-angiotensin system, which causes an increase in salt retention and renal arteriole vasoconstriction. In the early phase, renal perfusion is maintained within the normal range due to increased synthesis of renal vasodilators (such as prostaglandins).⁷ However, as HRS progresses, renal perfusion worsens due to arterial under filling and further activation of vasoconstrictive systems. A simple schematic of the pathophysiologic process is shown in ►Fig. 1.

Fig. 1 Pathophysiology of hepatorenal syndrome

Despite this long-term restriction in perfusion to the kidneys, it is unlikely that renal damage is permanent. Notably, in 1969 cadaveric kidneys were transplanted from patients with HRS to patients with unrelated renal failure. Of seven recipients, four recovered significant renal function, suggesting renal impairment in HRS is reversible.⁸

Diagnosis

Diagnostic criteria for HRS were defined in 1994 by the International Ascites Club.³ Since then, the criteria have been updated as understanding of the pathogenesis has improved. The latest diagnostic criteria were published in 2015.⁹ The most recent definition incorporates currently accepted criteria for acute kidney injury, namely an increase in serum creatinine of greater than 0.3 mg/dL within 48 hours or a percentage increase in serum creatinine of greater than or equal to 50% of that from baseline within 7 days. Patients fulfilling this criteria, who then have nonresponse to plasma volume expansion with albumin (1 g/kg) after 2 consecutive days and have an absence of other competing etiologies (i.e., structurally normal kidneys and absence of proteinuria or hematuria) or other precipitating factors, are then deemed to have HRS. A full listing of these criteria is summarized in ►Table 1.

Medical Management

Despite improvements in the clinical management of patients with HRS over the past 20 years, current pharmacologic treatments offer minimal long-term benefit and are often only a bridge to transplant. The mechanism of action of currently available therapies is aimed at volume expansion and improving splanchnic arterial vasoconstriction. The later aims to increase effective blood volume to thus improve renal perfusion.

Splanchnic arterial vasoconstriction can be enhanced by agents such as terlipressin. Although not currently available within the United States, it is the preferred pharmacologic therapy when available and is administered either with continuous intravenous (IV) infusion or IV bolus dosing, although the former has shown increased benefit. Moreover, a recent pooled analysis has shown added benefit when terlipressin is used in conjunction with albumin.¹⁰

Table 1 Diagnostic criteria for hepatorenal syndrome

1	Diagnosis of cirrhosis and ascites
2	Diagnosis of AKI
3	No response after 2 consecutive days of diuresis withdrawal and plasma volume expansion with albumin (1 g/kg)
4	Absence of shock
5	No current or recent use of nephrotoxic agents
6	No macroscopic evidence of structural kidney injury defined as: <ul style="list-style-type: none"> • Absence of proteinuria (>500 mg/d) • Absence of microhematuria (>50 RBCs per high-power field) • Normal findings on renal ultrasound

An alternate to terlipressin therapy within the United States is norepinephrine. This therapy is generally reserved for critically ill patients, as patients require close cardiac monitoring within an intensive care unit during treatment administration. Similar to terlipressin, norepinephrine is administered intravenously by continuous infusion in conjunction with albumin.¹¹

A therapeutic regimen that is more widely used and more readily available within the United States is the combination of midodrine and octreotide. The recommended dose of midodrine is 7.5 mg thrice daily titrated to 12.5 mg three times daily in conjunction with 100 to 200 µg of subcutaneous octreotide. These agents are also used in combination with albumin administration. Although survival benefit has not been shown to differ with this regimen when compared with terlipressin, improvement in renal dysfunction has been observed more often with terlipressin-based therapy.¹²

Transjugular Intrahepatic Portosystemic Shunt

Transjugular intrahepatic portosystemic shunt (TIPS) creation is most often employed in patients with cirrhosis and portal hypertension that present with uncontrolled variceal bleeding or ascites refractory to medical management. In patients with HRS, TIPS offers several benefits, including improved renal function through reduction in portal pressure and decreased activity of the renin-angiotensin-aldosterone system as well as reduction in ascites.¹³ There have been few publications regarding the role of TIPS in patients with HRS. In a 1997 study of patients with HRS revealed an approximate doubling of renal creatinine clearance 2 weeks after TIPS.¹³ In a meta-analysis of nine studies (128 patients) from 1998 to 2012, the 1-year survival rates post-TIPS were 47% in type 1 and 64% in type 2 HRS. In these studies, 49% of patients developed hepatic encephalopathy. Renal function improved in 93% of patients with type 1 HRS and in 83% of patient overall.¹⁴ A more recent meta-analysis of six studies including 390 patients showed that TIPS creation improved liver transplant-free survival as well as decreased the incidence of liver disease-related death, ascites, and HRS, at the cost of an increased risk of hepatic encephalopathy.¹⁵ A significant limitation of TIPS for this condition, however, is that many patients with HRS may not be able to tolerate the procedure, specifically those with decompensated liver disease with associated hyperbilirubinemia and/or cardiac dysfunction. Moreover, the need for contrast administration with risk of further renal injury needs to be considered prior to widespread implementation of this modality.

Hemodialysis

Indications for hemodialysis in patients with HRS are the same as with patients with acute renal insufficiency without cirrhosis. The goal of hemodialysis is not to reverse the causes of HRS, but rather to support the patient until other therapies can be initiated, most notably liver transplantation. There appears to be little long-term benefit to dialysis in these patients, as this does not facilitate recovery of hepatic

dysfunction.¹⁶ Additionally, patients may have significant hypotension precluding traditional hemodialysis and are at a higher risk of bleeding, infection, and an increased mortality while on hemodialysis.^{17,18} Because of these factors, the decision to initiate therapy may be more difficult.

Liver Transplant

Liver transplant continues to be the treatment of choice for patients with HRS. However, due to the quick progression of type 1 HRS, it is not uncommon for patients to die while awaiting transplant. Patients with HRS are more susceptible to posttransplant complications and have a shorter overall survival when compared with all liver transplant recipients.¹⁹ Notably, renal recovery is not guaranteed. In a 2005 study of 28 patients, complete recovery of renal function was seen in only 58% of liver transplant patients, with partial recovery in 17% and no recovery seen in 25% at 110 days posttransplant.²⁰ Furthermore, renal recovery is even less likely in patients who require renal replacement therapy before liver transplantation.²⁰ Although liver transplantation alone is recommended in patients with HRS rather than simultaneous liver kidney transplantation given organ shortages, those patients who do not have full renal recovery may be eligible for renal transplantation based on UNOS safety net policies.²¹

Conclusion

Hepatorenal syndrome is a highly morbid complication of cirrhosis. It results from a cascade of complex hemodynamic and neurohormonal changes related to the decompensated liver disease. This condition has a poor prognosis, quick progression, and high morbidity and mortality. Over the past two decades, strides have been made to improve short-term and long-term outcomes through a better understanding of the pathophysiology, improving diagnostic criteria, and advances in therapeutic strategies. Treatment of this syndrome includes medical management, TIPS, and dialysis. Despite advances, these solutions do not guarantee complete resolution of the disease. Transplant continues to be the most definitive method to resolve both liver and renal dysfunction. However, given that organs remain a limited resource, further research into alternate therapeutic options will need to be explored.

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