Accurate Diagnosis and Appropriate Treatment Beneficial for HRS and AIH

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Hepatorenal syndrome (HRS) and autoimmune hepatitis (AIH) are serious conditions that require accurate diagnosis and early treatment to achieve the best outcomes.

Florence Wong, MD, University of Toronto, Toronto, Canada, discussed the management of HRS, a form of renal failure in patients with end-stage liver disease. HRS is a potentially reversible syndrome that occurs in patients with cirrhosis, ascites, and liver failure, consisting of impaired renal function, abnormalities in cardiovascular function, and overactivity of endogenous vasoactive systems [Salerno F et al. *Gut*. 2007].

The characteristics of the 2 clinical types of HRS are defined in Table 1. Survival without treatment for type 1 is only days; survival for type 2 is better than that of type 1, but still lower than for cirrhosis without renal failure [Alessandria C et al. *Hepatology*. 2005].

HRS develops when cirrhosis-related shear stress on splanchnic vessels increases vasodilator production [Wong F. *Nat Review Gastro Hepatol*. 2012]. The presence of portal hypertension in cirrhosis also increases translocation of gut bacteria and stimulates the production of cytokines and chemokines, which themselves also have vasodilatory properties. These lead to splanchnic vasodilation and portal inflow increase. Angiogenesis further increases splanchnic capacitance. Increased vascular capacity leads to a relative decrease in circulatory volume, which in turn stimulates compensatory activation of various vasoconstrictor systems in an attempt to reduce the extent of the vasodilatation in the splanchnic and system circulations. The kidneys respond by undergoing renal vasoconstriction, leading to renal failure. The most common precipitant of HRS is infection, which can cause further vasodilatation of an already-dilated vascular system, exaggerating the cascade of vasoconstrictor activation and further renal vasoconstriction.

Table 1. Clinical Presentation of Hepatorenal Syndrome

Type 1 (acute)	Type 2 (chronic)
Rapid reduction in renal function in < 2 wk	Renal function slowly deteriorates over weeks to months
Doubling of initial serum creatinine to > 2.5 mg/dL OR 50% reduction of the initial 24 h creatinine clearance to < 20 mL/min	Serum creatinine > 1.5 mg/dL Usually occurs in cirrhotic patient with refractory ascites
Severely ill patient with jaundice, coagulopathy	Mild jaundice; some degree of coagulopathy

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Each treatment option for HRS aims at correcting one or more aspects of the pathophysiology: vasoconstrictors for splanchnic systemic arterial vasodilatation, volume replacement for decreased effective arterial blood volume, a transjugular intrahepatic portosystemic shunt for portal hypertension, and liver transplant for liver dysfunction and portal hypertension.

Vasopressin analogs act as splanchnic vasoconstrictors, redistributing the central blood volume, increasing systolic blood pressure, and improving renal perfusion pressure. Terlipressin is a vasopressin analog that, in combination with albumin, reverses HRS in about 35% of patients, although several studies showed no significant improvement in transplant-free survival [Sanyal AJ et al. AASLFD. 2014. Abstract 241].

In type 1 HRS, patients with baseline serum bilirubin < 10 mg/dL are more likely to respond to terlipressin plus albumin (OR, 0.901; 95% CI, 0.834 to 0.974; $P = .009$). Patients with a response of mean arterial pressure at day 3 ≥ 5 mmHg are also more likely to respond to terlipressin plus albumin (OR, 9.482; 95% CI, 1.007 to 89.316; $P = .049$) [Nazar A et al. *Hepatology*. 2010].

Terlipressin is currently not available in North America. In a study of norepinephrine (noradrenalin) versus terlipressin, both drugs resulted in similar improvements in serum creatinine, urine output, plasma renin activity, aldosterone levels, and survival [Singh V et al. *J Hepatology*. 2012]. Therefore, norepinephrine can be used as an alternative vasoconstrictor for patients with HRS.

Patients with type 1 HRS may have a response to treatment sufficient to allow them to wait for a liver transplant. Predictors of mortality include age > 65 years, serum bilirubin > 6 mg/dL, and lack of serum creatinine response after diagnostic volume expansion with albumin. The presence of all 3 predictors is associated with 100% mortality [Salerno F et al. *J Hepatology*. 2011].

Liver transplantation is the definitive treatment for HRS because it eliminates liver dysfunction and portal hypertension. Because it does not correct the abnormal hemodynamics immediately postoperatively, transient persistence of renal dysfunction may occur post-transplant, necessitating short-term dialysis.

Prof Wong presented data for all patients with type 1 HRS who had liver transplants at her institution, including patients who had reversal of HRS after transplant (HRS–; n = 47) and those who did not have reversal (HRS+; n = 15) [Wong F et al. *Transplantation*. 2014 in press]. Resolution of HRS was associated with lower serum creatinine at the time of transplant ($P = .0285$), shorter duration of HRS pre-transplant ($P = .0005$), and shorter duration of dialysis pre-transplant. The current recommendation for patients with HRS is 6 to 8 weeks of pre-transplant dialysis before they are considered for a combined liver and kidney transplant. Patients who had 30 days of pre-transplant dialysis had persistent HRS after transplant. Most of the patients who were HRS– had received < 14 days of dialysis (HR for reversal = 9.2). The survival for HRS– versus HRS+ is significantly better ($P = .0045$).

For patients with HRS type 2 with ascites, liver transplant lowered serum creatinine, although renal function remained impaired even 12 months after transplant. Survival was similar to that of patients undergoing liver transplant who did not have HRS [Tan HK et al. *Transplantation*. 2014 in press].

Autoimmune hepatitis (AIH), a disorder of immune regulation, presents different diagnostic and therapeutic challenges, which were discussed by Michael A. Heneghan, MD, MRCP, King's College Hospital, London, United Kingdom. AIH can be triggered in genetically susceptible individuals by viral infections, antibiotics, or other agents.

The International Autoimmune Hepatitis Group (IAHG) Scoring System was originally designed as a research tool, but it may be useful in clinical practice for a differential diagnosis and to score response to treatment [IAHG. *J Hepatology*. 1999]. AIH is no longer classified by type, but it is one of the few remaining liver diseases in which liver biopsy is mandatory at the time of diagnosis and at follow-up to assess the degree of fibrosis, lymphoplasmacytic infiltrate, and inflammation. Simplified diagnostic criteria for AIH are presented in Table 2.

Patients with AIH require appropriate treatment. Current treatment paradigms are derived from old studies, which showed improved survival with treatment with corticosteroids and azathioprine. Adult induction regimens are summarized in Table 3.

The European Association for the Study of the Liver (EASL) draft guidelines for remission induction and maintenance base the prednisone initial therapy on weight (0.5 to 1 mg/kg), followed by the addition of azathioprine (50 mg/dL, increased depending on toxicity and response up to 1 to 2 mg/kg per day after 2 weeks) for first-line treatment of AIH. Children may be more likely to present with more advanced disease and require liver transplant; treatment is similar to that for adults.

Table 2. Simplified Diagnostic Criteria for Autoimmune Hepatitis

Feature/Parameter	Discriminator	Score
ANA or SMA +	≥1:40	+1
ANA or SMA +	≥1:80	+2
Or LKM +	≥1:40	
Or SLA +	Any titer	
IgG or immunoglobulin level	> Upper limit of normal	+1
	> 1.1 upper limit	+2
Liver histology	Compatible with AIH	+1
	Typical of AIA	+2
Absence of viral hepatitis	No	0
	Yes	+2

Score: > 6 probably AIH; > 7 definite AIH.

AIH, autoimmune hepatitis; ANA, antinuclear antibodies; IgG, immunoglobulin G; LKM, liver-kidney microsomal (antibody); SLA, soluble liver antibodies; SMA, smooth muscle antibody.

Adapted from Hennes EM et al. Simplified criteria for the diagnosis of autoimmune hepatitis. *Hepatology*. 2008;48:169–176. Copyright © 2008 American Association for the Study of Liver Diseases.

Table 3. Adult Induction Regimens

Prednisone 40–60 mg/d	Prednisone 40 mg/d + Aza	Budesonide 6–9 mg/d
Reduce 2 mg weekly.	Reduce steroids 2 mg weekly.	Not for patients with cirrhosis.
Maintain remission at 7.5–10 mg/d and add Aza when bilirubin < 6 mg/dL.	Escalate Aza.	Reduce according to response.
		Add Aza.

Aza, azathioprine.

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When AIH is unresponsive to treatment, the diagnosis should be questioned. Adherence to azathioprine therapy can be determined using metabolite monitoring. Alternative therapies (eg, mycophenolate, tacrolimus, or cyclosporine) can be considered, based on the side effect profile and comorbidities, for patients for whom standard steroids are contraindicated. Some patients will need transplantation for unresponsive disease. The definition of remission is being debated, as is whether treatment can be discontinued. Prof Muir believes most patients need to be on continuous treatment.

Management of both HRS and AIH require early diagnosis and treatment, which should be individualized for patients. Liver transplant, the definitive therapy for HRS, should not be delayed for a long course of dialysis. Patients with AIH need treatment to induce and maintain remission, and some may also require liver transplant.