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TOPIC HIGHLIGHT

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Hepatorenal syndrome

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Abstract

Hepatorenal syndrome (HRS) is a "functional" and reversible form of renal failure that occurs in patients with advanced chronic liver disease. The distinctive hallmark feature of HRS is the intense renal vasoconstriction caused by interactions between systemic and portal hemodynamics. This results in activation of vasoconstrictors and suppression of vasodilators in the renal circulation. Epidemiology, pathophysiology, as well as current and emerging therapies of HRS are discussed in this review.

Key words: Acute renal failure; End stage liver disease; Hepatorenal syndrome; Transjugular intrahepatic portosystemic shunts; Dialysis; Liver transplantation

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INTRODUCTION

The association between liver disease and renal dysfunction was reported more than a century ago when patients with chronic liver disease and normal renal histology were found to develop oliguric renal failure (Flint A, *Am J Med Sci* 1863). This led to proposed links between renal dysfunction and the derangement in systemic circulation secondary to the liver failure[1].

Renal failure in patients with liver disease may be caused by several factors, including shock, sepsis, nephrotoxic medications, intrinsic renal diseases, or volume depletion secondary to diuresis or large-volume paracentesis. However, renal failure may also occur in patients with liver disease in the absence of the above factors and in the absence of major renal histological changes. This is referred to as hepatorenal syndrome (HRS). HRS is considered a "functional" and reversible form of renal failure[2-6]. The International Ascites Club defined HRS as: "a syndrome that occurs in patients with advanced chronic liver disease and advanced hepatic failure and portal hypertension characterized by impaired renal function and marked abnormalities in the arterial circulation and activity of the endogenous vasoactive systems. In the kidney, there is marked renal vasoconstriction that results in low glomerular filtration rate (GFR). In the extrarenal circulation, there is a predominance of arterial vasodilation, that results in reduction of total systemic vascular resistance and arterial hypotension". The incidence of HRS in patients with chronic liver disease is not well studied. In one study of 234 non-azotemic patients with liver disease who had ascites and cirrhosis, 18% developed HRS at 1 year, and 39% by 5 years[7]. Although HRS usually occurs in patients with advanced cirrhosis, it has also been described in patients without ascites in the setting of acute fulminant hepatic failure[8].

PATHOPHYSIOLOGY

Approximately 80% of hospitalized patients with cirrhosis and ascites have decreased renal perfusion due to moderate vasoconstriction in the renal circulation, which predisposes them to develop HRS[7-9]. In 10%-17% of these patients, renal vasoconstriction becomes intense enough to cause significant renal hypoperfusion, resulting in HRS[7,10]. This intense renal vasoconstriction is the distinctive hallmark feature of HRS[11,12]. The mechanisms of renal vasoconstriction are complex and multifactorial, and are incompletely understood. There appear to be interactions between changes in systemic hemodynamics, portal hypertension, activation of vasoconstrictors, and suppression of vasodilators in the renal circulation[13,14]. In contrast, significant vasodilation occurs in the splanchnic arterial bed secondary to increased production of local vasodilators, predominantly nitric oxide[15]. Other vasodilators hypothesized to play a role in splanchnic arterial vasodilation include prostacyclin, prostaglandin E2, atrial natriuretic peptide, kallikreins, and kinins[10,16,17]. This splanchnic vasodilation is believed to lead to compensatory responses by activating vasoconstrictors including the renin-

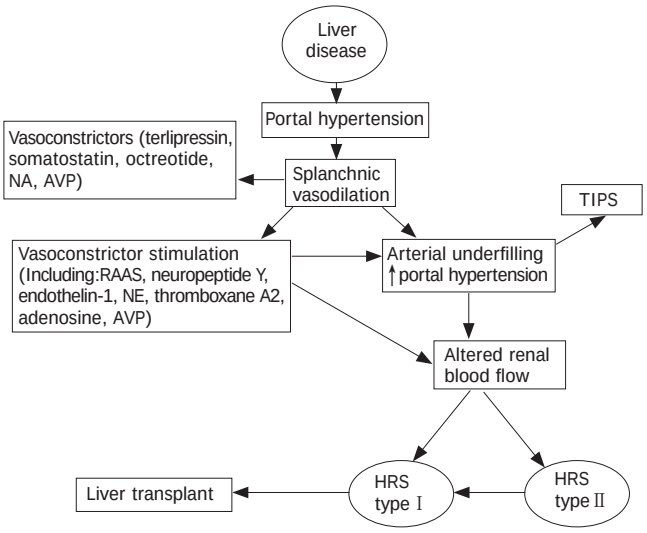

Figure 1 Pathophysiology of HRS and potential therapeutic interventions. NA: noradrenalin; AVP: arginine vasopressin; RAAS: renin-angiotensin system; NE: norepinephrine; TIPS: transjugular intrahepatic portosystemic shunt.

angiotensin-aldosterone system (RAAS), neuropeptide Y, endothelin-1, norepinephrine, thromboxane A2, adenosine, and antinatriuretic agents such as arginine vasopressin (AVP). This leads to retention of sodium and water in addition to renal vasoconstriction[15,18,19]. Other factors such as the absence of or decrease in glomerulopressin or other liver-borne diuretic factors (factors that are released by the liver and target the kidney) could also contribute to renal failure[20]. In recent years, the potential role of cirrhotic cardiomyopathy has been postulated in the pathogenesis of HRS. Ruiz-del-Arbol *et al* have demonstrated that HRS is due to decreased cardiac output in the setting of a severe arterial vasodilation[21]. Similar circulatory events were also shown in cirrhotic patients who developed spontaneous bacterial peritonitis[22].

In the early stages of cirrhosis, the activation of local vasodilators may overcome the renal vascular effects of systemic vasoconstrictors, maintaining adequate renal perfusion[23]. As liver disease progresses, the renal vasodilators are no longer able to antagonize the circulating vasoconstrictors, and this results in severe renal vasoconstriction and impaired renal blood flow. In addition, the hypoperfusion itself may lead to further intrarenal vasoconstriction. Figure 1 summarizes the complex pathways involved in the development of HRS and potential therapeutic interventions.

CLASSIFICATION OF HRS

There are two types of HRS (Table 1). Type 1 is characterized by a rapid elevation in blood urea nitrogen (BUN) and creatinine, often defined as a 100% increase in serum creatinine, reaching a level higher than 2.5 mg/dL in less than two weeks[2]. The mortality of patients with type 1 HRS has been reported to be 80% at two weeks[7]. Type 2 HRS, on the other hand, generally follows a slower course and has a better prognosis. It is usually characterized by recurrent, diuretic-resistant ascites[10,14], and is thought to be due to significant activation of anti-natriuretic systems[2].

Table 1 Clinical types of HRS

Type 1
(1) 100% increase in serum creatinine to a level higher than 2.5 mg/dL or a 50% reduction of the initial 24-h creatinine clearance to a level lower than 20 mL/min in less than 2 wk
(2) Very poor short-term outcome
Type 2
(1) Serum creatinine > 1.5 mg/dL, without meeting the criteria for type 1 HRS
(2) Refractory ascites is usually present
(3) Prognosis is not as poor as with type 1

PRECIPITATING FACTORS

HRS may develop spontaneously without known precipitating factors, but there are known triggers[14,24]. Spontaneous bacterial peritonitis (SBP) has been associated with type 1 HRS in approximately 20% of cases[21,25], even with treatment and resolution of the infection. These patients have a very poor outcome. HRS may also occur after therapeutic paracentesis without plasma expansion[26,27]. Gastrointestinal bleeding has also been identified as a precipitant of HRS, but this usually occurs in patients with hypovolemic shock. In this setting, acute renal tubular ischemic injury or necrosis is more likely to be the cause of acute renal failure than HRS[28]. There is no clear evidence to support diuretic-induced volume depletion as a precipitating factor of HRS[14]. Other factors that have been associated with an increased risk of developing HRS in patients with ascites and cirrhosis include severe urinary sodium retention, spontaneous dilutional hyponatremia, and a mean arterial blood pressure less than 80 mmHg. There is not a direct linear association between the severity of liver failure and the incidence of HRS, but HRS is usually seen in patients with advanced liver disease and portal hypertension[14,23].

DIAGNOSIS OF HRS

There are no specific clinical or laboratory findings for the diagnosis of HRS. The diagnosis is established based on predefined criteria in the appropriate clinical setting (Table 2). Patients with advanced liver disease may develop renal failure from a number of causes other than HRS, and these causes must be excluded before making a diagnosis of HRS. Common causes of renal failure in patients with cirrhosis include volume depletion (which could be secondary to over-diuresis, diarrhea, or poor fluid intake), nephrotoxic medications (commonly non-steroidal anti-inflammatory agents and aminoglycosides), allergic interstitial nephritis, acute tubular necrosis (from various factors including shock), contrast nephropathy, and intrinsic renal diseases such as glomerulonephritis. A renal biopsy may rarely be necessary if the diagnosis is unclear, mainly to exclude other treatable renal diseases. It is also important to note that there are significant limitations in using serum creatinine as a marker of renal function in patients with liver disease. Patients with advanced liver disease usually have reduced muscle mass and hence low endogenous production of creatinine. When creatinine clearances in cirrhotic patients were compared with inulin clearances, the

glomerular filtration rates were significantly overestimated[29]. Alternative diagnostic approaches have been applied in order to overcome the limitation of serum creatinine values in this population. Platt *et al*[9] examined the utility of Doppler ultrasonography to assess the resistive indices of the renal vasculature. In their study of 180 patients with liver disease without azotemia, 42% of the patients were found to have an increase in renal vascular resistive indices. Of those patients, 55% subsequently developed renal failure as compared to 6% of those with normal resistive indices. The sensitivity and specificity of the resistive index in detecting renal failure were estimated at 71% and 80% respectively in a group of cirrhotic patients[30]. However, this technique is operator-dependent and is still under investigation, and therefore is not currently recommended as a standard method to diagnose HRS.

PROGNOSIS

The prognosis of HRS is extremely poor. The median survival time of patients with type 1 HRS is less than 2 wk, with less than 10% surviving their hospital stay[7]. The survival time of patients with type 2 HRS, although still short, is significantly longer, with a median survival time of approximately 6 mo[14].

MANAGEMENT

Prevention of HRS

Prevention of HRS is potentially possible in some high-risk patients. In patients with SBP, administering intravenous albumin (1.5 g/kg upon diagnosis, and then 1 g/kg after 48 h) in addition to antibiotics has been shown to decrease the incidence of HRS and to decrease hospital mortality as compared with treatment with antibiotics alone[26]. The authors of that study postulated that the administration of albumin prevented circulatory dysfunction by maintaining effective arterial blood volume and therefore prevented vasoconstrictor activation. However, albumin is expensive, and more studies are needed to determine if lower doses of albumin or less expensive artificial plasma expanders are as effective. In one study, administration of pentoxifylline (400 mg orally three times a day) to patients with severe acute alcoholic hepatitis decreased the incidence of HRS as well as the short-term mortality rate compared to placebo[31]. This benefit may be related to the inhibition of tumor necrosis factor production. Although both of the above studies support the idea of preventing renal failure in the setting of liver failure, there are no data evaluating the long-term survival benefit in this population. Moreover, there have been no further confirmatory studies.

General management measures

In patients with type 1 HRS, diagnostic paracentesis is generally recommended to evaluate for SBP. In addition, diuretics should be discontinued as they may potentially worsen renal function. In the absence of contraindications, patients with type 1 HRS should also be evaluated for expedited liver transplantation.

Table 2 Diagnostic criteria of hepatorenal syndrome[1]

Major criteria (all must be present for the diagnosis of HRS)
(1) Advanced hepatic failure (acute or chronic liver disease) and portal hypertension
(2) Low GFR defined as serum creatinine > 1.5 mg/dL or creatinine clearance < 40 mL/min
(3) Absence of shock, significant volume losses, ongoing infection, or treatment with nephrotoxic medications
(4) Absence of a sustained improvement in renal function after cessation of diuretics and expansion of plasma volume with 1.5 L of isotonic fluids
(5) Urine protein excretion < 500 mg/dL with no ultrasonographic evidence of obstruction or parenchymal renal disease
Additional criteria (not necessary for the diagnosis, but provide supportive evidence)
(1) Urine volume < 500 mL/d
(2) Urine sodium < 10 mEq/L
(3) Urine osmolality greater than plasma osmolality
(4) Urine red blood cells < 50 per high-power field
(5) Serum sodium concentration < 130 mEq/L

[1]Adapted from Arroyo *et al*[2].

Pharmacological therapy

Several systemic vasoconstrictors have been utilized in the treatment of type 1 HRS as summarized in Table 3. Renal vasodilators such as dopamine and prostaglandin analogues are no longer recommended due to their side effect profile and the lack of clinical evidence to support their use. Other potential forms of therapy that have not been extensively tested include endothelin blockers[32] and N-acetylcysteine[33].

The rationale behind the use of vasoconstrictors along with plasma expansion is that they will counteract the splanchnic arterial vasodilation, which is hypothesized to be the initial event in the pathogenesis of HRS. Unopposed splanchnic arterial vasodilation may cause a decrease in effective arterial volume which in turn triggers the activation of vasoconstrictors[23,34]. Vasoconstrictors that have been widely used for type 1 HRS include vasopressin analogues (ornipressin and terlipressin), a somatostatin analogue (octreotide), and alpha-adrenergic analogues (midodrine and noradrenalin). In most studies, albumin was administered concurrently.

The vasopressin analogues are effective in causing marked splanchnic vasoconstriction. Ornipressin, although effective in treating HRS, may cause significant ischemic side effects and is not currently recommended for the management of HRS[35]. Studies using terlipressin, the long-acting analogue of vasopressin, have shown significant improvement in renal function in approximately 60%-75% of patients, with a lower than 5% incidence of ischemic side effects[36-43]. In these studies, patients with Child-Pugh scores less than or equal to 13 and/or those who received albumin infusions had a more favorable outcome. However, it is important to note that GFR was not normalized in most patients who responded[37,39]. Approximately 15% of patients had recurrence of HRS once treatment was discontinued. Small, short-term, non-randomized studies suggest that treatment with terlipressin may also improve renal function in patients with type 2 HRS[34]. Terlipressin is not currently licensed

Table 3 Non-invasive therapies

Author and Year	*n* (# Type 1, # Type 2)	Study design	Intervention	Outcome measures	Mean baseline SCr	Mean follow-up SCr	Other results	Comments
Moreau *et al* 2002[38]	99 (99/0)	Multicenter, retrospective	Terlipressin (75% received albumin)	Reduction of SCr to < 130 μmol/L or a decrease of at least 20% at end of treatment)	272 ± 114 μmol/L	Responders: 138 ± 59 μmol/L Nonresponders: 382 ± 210 μmol/L	Renal function improved in 58% of patients.	Twenty-three patients had adverse events that may have been terlipressin-related. Three patients required RRT 40% survival at 1 mo.
Kiser *et al* 2005[44]	43 (32/11)	Observational (retrospective cohort)	Vasopressin (AVP) *vs* octreotide *vs* combination	Clinical response; SCr 1.5 mg/dL or less	3.9 ± 3.3 mg/dL	Responders: SCr decreased by 62% ± 9% Nonresponders: SCr increased by 46% ± 119%	42% complete response with AVP *vs* 38% with AVP and octreotide *vs* 0% with octreotide alone.	No adverse effects related to AVP. RRT rates: 50% in AVP group, 58% in combination group, and 31% in octreotide alone group.
Solanki *et al* 2003[43]	24 (24/0)	Randomized placebo-controlled single-blind	Terlipressin *vs* placebo (all patients received albumin) for 4-15 d	Reversal of HRS and survival at 15 d	Terlipressin: 2.9 ± 0.1 mg/dL Placebo: 2.2 ± 0.2 mg/dL	Terlipressin: 1.2 ± 0.2 mg/dL at d 15 Placebo: no survival at d 15 (SCr 3.9 ± 0.2 mg/dL on d 8)	In terlipressin group, 5 of 12 patients survived. None survived by d 15 in placebo group.	
Ortega *et al* 2002[39]	21 (16/5)	Prospective, nonrandomized	Terlipressin with albumin *vs* without albumin for 4-14 d	SCr 1.5 mg/dL or lower	Terlipressin with albumin: 3.6 ± 1.5 mg/dL Terlipressin without albumin: 3.4 ± 0.3 mg/dL	Terlipressin with albumin: 1.5 ± 0.2 mg/dL Terlipressin without albumin: 3.4 ± 0.7 mg/dL	10 of 13 patients who received terlipressin and albumin responded. Of 8 patients who received terlipressin alone, 2 responded.	One patient had ischemic side effects (finger ischemia). At 1 mo, there was a 5% recurrence of HRS after complete response.
Pomier-Layrargues *et al* 2003[61]	19 (NS)	Randomized, double-blind, placebo-controlled, crossover	Placebo, then octreotide (Group 1) *vs* octreotide, then placebo (Group 2) (all patients received albumin)	20% decrease in SCr after 4 d	Group 1: 215 ± 32 μmol/ Group 2: 208 ± 16 μmol/L	Group 1: 222 ± 41 μmol/L after placebo; 270 ± 54 μmol/L after octreotide Group 2: 194 ± 34 μmol/L after octreotide; 204 ± 47 μmol/L after placebo	Treatment with octreotide was not effective.	The study included types 1 and 2 HRS patients (numbers in each group not specified). No side effects reported.
Colle *et al* 2002[42]	18 (18/0)	Chart review (retrospective analysis)	Terlipressin (some patients received albumin)	Decrease in SCr to < 130 μmol/L or decrease of at least 20% leading to a stable value; evaluation of predictive factors	Patients with improved SCr: 276 ± 47 μmol/L[1] Patients without improved SCr: 295 ± 89[1] μmol/L	Patients with improved SCr: 130 ± 13 μmol/L Patients with improved SCr: 411 ± 89 μmol/L	11 patients had improved renal function	Some of these patients were included in the Moreau study. Patients with improved renal function had less severe cirrhosis than patients without. Patients without a precipitating factor for HRS or who responded to terlipressin were more likely to survive.
Halimi *et al* 2002[41]	18 (16/2)	Multicenter pilot (retrospective)	Terlipressin for 2-16 d	> 30% decrease in baseline SCr	298 ± 124 μmol/L	145 ± 85 μmol/L	13 of 18 had improved renal function; 8 had a normal SCr at d 5	Three patients had ischemic side effects. One had severe bronchospasms after terlipressin administration, and subsequently died.

Guevara *et al* 1998[49]	16 (Type NS)	Open pilot study	Ornipressin and albumin for 3 *vs* 15 d	Efficacy	3-d arm: 2.9 ± 0.5 mg/dL 15-d arm: 3.0 ± 0.5 mg/dL	3-d arm: 2.2 ± 0.4 mg/dL 15-d arm: 0.7 ± 0.1 mg/dL	75% of patients had improved renal function.	Treatment was stopped in 4 patients on the 15-d protocol because of ischemic complications.
Angeli *et al* 1999[62]	13 (13/0)	Nonrandomized	Dopamine and albumin (Group A) *vs* midodrine, octreotride, and Ⅳ albumin (Group B)	Efficacy	Group A: 3.6 ± 0.6 mg/dL Group B: 5.0 ± 0.9 mg/dL	Group A: 5.1 ± 1.5 mg/dL at 15 d (only 1 patient survived to d 20) Group B: 3.3 ± 0.7 mg/dL at 20 d	All Group B patients had improved GFR. 7 of 8 patients in Group A had worsening renal function and died.	No significant side effects.
Holt *et al* 1999[33]	12 (NS)	Open label	N-acetylcysteine for 5 d	Efficacy	222 ± 27 μmol/L	169 ± 7 μmol/L		67% survival at 1 mo, and 58% at 3 mo (2 patients received liver transplants).
Mulkay *et al* 2001[40]	12 (12/0)	Pilot	Terlipressin for 1 wk to 2 mo	Safety and efficacy	3.4 mg/dL	1.8 mg/dL		Three patients received liver transplants, and had near-normal renal function. The other 9 died during follow-up. No ischemic complications.
Duvoux *et al* 2002[48]	12 (12/0)	Pilot	Noradrenalin (NA), albumin, and furosemide for at least 5 d	Safety and efficacy	2.6 ± 1.1 mg/dL pre-furosemide/albumin; 3.9 ± 1.8 mg/dL after infusion (pre-NA)	1.6 ± 0.8 mg/dL	Reversal of HRS in 10 of 12 patients	Two patients had previously received terlipressin (underwent 48-h washout before starting NA). Transient myocardial ischemia was observed in 1 patient.
Hadengue *et al* 1998[63]	9 (9/0)	Double-blind, short-term, controlled crossover study	Terlipressin and placebo for 2 d in randomized order	Efficacy	Baseline CrCl: 15 ± 2 mL/min	CrCl after terlipressin (includes both groups): 27 ± 4 mL/min CrCl after placebo (includes both groups): 16 ± 3 mL/min		No side effects reported.
Uriz *et al* 2000[37]	9 (6/3)	Pilot	Terlipressin with albumin for 5-15 d	Reduction of serum creatinine to < 1.5 mg/dL	3.9 ± 0.7 mg/dL	1.5 ± 0.2 mg/dL	Reversal of HRS in 7 of 9 patients.	One patient did not complete the study due to pancreatitis. No ischemic complications.
Angeli *et al* 1998[45]	8 (0/8) + 17 cirrhotic patients without HRS	Open label	Midodrine (one dose)	Renal function and renal hemodynamics (acute effects)	GFR: 39.0 ± 6.4 mL/min	GFR: 45.1 ± 7.6 mL/min	No significant acute effect on renal hemodynamics or renal function.	This study looked at the acute effect of one dose of midodrine. The results include cirrhotic patients without HRS.
Gulberg *et al* 1999[64]	7 (7/0)	Nonrandomized	Orinpressin, dopamine, and albumin for 5-27 d	2× increase in Crcl (to > 40 mL/min)	Treatment success group: 4.6 ± 0.9 mg/dL, and improved to 1.3 ± 0.2 mg/dL	Treatment success group: 1.3 ± 0.2 mg/dL	HRS was reversed in 4 of 7 patients	Two responders had a relapse. One of them responded to retreatment, but treatment was stopped in the other because of a ventricular tachyarrhythmia. Treatment was stopped in another patient because of intestinal ischemia.

Kaffy *et al* 1999[65]	5 (NS)	Pilot	Octreotide for 5 d	Efficacy	194 μmol/L in 4 patients	96 μmol/L in 4 patients	Improvement of SCr in 4 of 5 patients,	but 4 of 5 patients eventually died. HRS rapidly recurred when octreotide was stopped, and did not respond to further octreotide infusion.

SCr: Serum Creatinine; RRT: Renal replacement therapy; NS: Not Specified; CrCl: Creatinine Clearance. Cr conversion from μmol/L to mg/dL: divide by 88.4.

Table 4 Invasive therapies

Author and Year	N (# Type 1, # Type 2)	Study design	Intervention	Outcome measures	Mean baseline SCr	Mean follow-up SCr	Other results	Comments
Brensing *et al* 2000[50]	31 (14/17); an additional 10 were too sick to receive TIPS	Phase Ⅱ	TIPS	Safety and survival	(Of the 31 patients who received TIPS) 2.3 ± 1.7 mg/dL	Wk 4: 1.5 ± 1.2 mg/dL	Renal function improved within 2 wk after TIPS and subsequently stabilized.	Three-month survival rate was 81% (10% of non-shunted patients survived, but they were felt to be too sick to receive TIPS). There was 1 TIPS-related death.
Wong *et al* 2004[46]	14 (14/0)	Prospective	Midodrine, octreotide, albumin, and TIPS	Efficacy (serum creatinine < 135 μmol/L for at least 3 d)	Responders: 233 ± 29 μmol/L Nonresponders: 345 ± 83 μmol/L	Responders: 112 ± 8 μmol/L after medical therapy Nonresponders: 476 ± 139 μmol/L after medical therapy.	Renal function improved in 10 of 14 patients (71%) with medical therapy. Five responders received TIPS; their renal function continued to improve. Mean GFR was 96 ± 20 mL/min by 12 mo post-TIPS.	TIPS was performed in responders who were stable. Two of the five responders who did not receive TIPS underwent liver transplantation, and their SCr remained normal at the time of liver transplantation.
Alessandria *et al* 2002[36]	16 (0/11, and an additional 5 with "organic renal disease")	Prospective, nonrandomized	Terlipressin for 7 d (and TIPS in stable patients)	Efficacy	2.4 ± 0.9 mg/dL	After terlipressin therapy: 1.8 ± 0.8 mg/dL After TIPS: 1.4 ± 0.3 mg/dL	Terlipressin: 8 of 11 HRS patients had improved renal function (and 7 of the 8 responders had reversal of HRS (SCr < 1.5 mg/dL) Subsequent TIPS: 8 of 9 patients (89%) who underwent TIPS had improved renal function by 1 mo.	Renal function improved significantly after TIPS in all patients who responded to terlipressin. One HRS patient who did not respond to terlipressin underwent TIPS and responded. In the non-HRS group (with "organic renal disease", only one patient had an improved SCr (from 3.7 to 1.8 mg/dL) with terlipressin treatment.
Guevara *et al* 1998[49]	7 (7/0)	Prospective	TIPS	Efficacy	4.9 ± 0.8 mg/dL	1 wk after TIPS: 3.7 ± 1.0 mg/dL 1 mo after TIPS: 1.8 ± 0.4 mg/dL	Renal function improved in 6 of 7 patients.	Mean survival was 4.7 ± 2 mo.
Witzke *et al* 2004[53]	30 (NS)	Prospective	CVVHD (if mechanically ventilated) *vs* intermittent HD if not ventilated	Survival	N/A	N/A	8 of 15 patients who received HD survived. None of the ventilated patients (received CVVHD) survived.	Note that the sickest patients (on a ventilator) all received CVVHD.

Keller *et al* 1995[54]	26 (NS); an additional 81 patients had liver disease and renal failure, but were not diagnosed with HRS	Retrospective	HD	Risk factor evaluation and outcomes	N/A	N/A	7 of 16 patients with HRS who received HD survived, while only 1 out of 16 patients with HRS who did not receive HD survived.	
Mitzner *et al* 2000[55]	13 (Type 1)	Prospective, randomized, controlled	MARS and HDF and standard medical therapy *vs* HDF and medical therapy	Survival	MARS + HDF: 3.8 ± 1.5 mg/dL HDF alone: 4.4 ± 1.3 mg/dL	MARS + HDF: 2.3 ± 1.5 mg/dL HDF alone: 3.8 ± 0.5 mg/dL	At one week: 62.5% mortality in the treatment group, and 100% mortality in the group who did not receive MARS.	None of these patients underwent liver transplantation or received TIPS or vasopressin analogues during the observation period.
Jalan *et al* 2003[66]	8 (5/2, and one patient without HRS)	Prospective, nonrandomized	MARS	Safety and efficacy	162 (51–312) μmol/L	108 (34–231) μmol/L	50% survival at 3 mo follow-up	All of the patients had alcoholic hepatitis and were encephalopathic. Renal function improved in all patients. Of the 5 patients with type 1 HRS, 3 remained anuric, but there was normalization of SCr in the other 2 patients. SCr was normalized in both patients with type 2 HRS by the end of treatment.
Mitzner *et al* 2001[55]	8 (NS)	Uncontrolled	MARS	Multiple organ function changes	380 ± 182 μmol/L	163 ± 119 μmol/L	Improvement in multiple organ functions	

SCr: Serum creatinine; CrCl: Creatinine clearance; TIPS: Transjugular intrahepatic portosystemic shunt; NS: Not Specified; CVVHD: Continuous veno-venous hemodialysis; HD: Hemodialysis; MARS: Molecular adsorbents recirculating system; HDF: Hemodiafiltration. Cr conversion from μmol/L to mg/dL: divide by 88.4.

for use in North America, but a double-blind, randomized, placebo-controlled trial is now being conducted in the USA and Germany in patients with type 1 HRS. Alpha-1 adrenoreceptor agonists and a somatostatin analogue are readily available in North America and have been studied in type 1 HRS. An observational study compared vasopressin infusion with octeotride infusion in patients with HRS, and found a complete response rate of 41% in the patients treated with vasopressin compared with 0% in the patients treated with octreotide[44]. In type 1 HRS, alpha-1 agonists have only been used in combination with other agents. Few nonrandomized, prospective studies have evaluated treatment with both midodrine and octreotide[45-47]. The study by Angeli[45] included only five patients and showed that after 20 d of treatment, all patients had serum creatinine levels below 2 mg/dL. In the study by Wong *et al*[46], 10 of 14 patients with HRS treated with midodrine, octreotide, and albumin had their serum creatinine stable at less than 1.5 mg/dL for three days. The use of noradrenalin in combination with intravenous albumin and furosemide was studied in 12 patients[48]. HRS was reversed in 83% of patients, with an adverse event rate of 17%. These small studies suggest a short-term benefit in improving renal function in HRS patients, although larger, randomized studies are required before recommending the routine use of these agents in clinical practice. Other drugs, such as N-acetylcysteine and misoprostol, have been proposed as therapy for HRS, but have not been well-studied.

Non-pharmacologic therapy

Transjugular intrahepatic portosystemic shunts (TIPS), by reducing portal hypertension, may be useful in treating HRS (Table 4), although no trials have shown a survival advantage[49-51].

Renal replacement therapy

Patients with HRS who progress to severe renal failure can be initiated on renal replacement therapy (RRT), generally given as continuous hemofiltration. Dialysis

is usually used as a bridge in patients who are awaiting liver transplantation, and is not recommended for patients who are unlikely to recover from liver failure or are unlikely to receive liver transplantation because of other contraindications. Survival on dialysis is generally dependent on the severity of liver disease[52]. There are only a few small studies evaluating the effects of dialysis in HRS[53,54]. Keller *et al*[54], in a retrospective study, found that 7 of 16 patients with HRS who received RRT survived, while only 1 out of 16 patients with HRS who did not receive RRT survived. In the prospective study by Witzke *et al*[53], 30 patients with Child-Pugh C cirrhosis and HRS were treated with continuous veno-venous hemodialysis (CVVHD) if they were on mechanical ventilation, or with intermittent hemodialysis if they were not on mechanical ventilation. No patients on mechanical ventilation survived for more than 30 d, but 8 of 15 patients who were not on mechanical ventilation survived for more than 30 d. The absence of a control group and lack of randomization make it difficult to draw any firm conclusions from this study.

Molecular absorbent recirculating system (MARS) is a form of albumin dialysis, which removes "toxins" such as tumor necrosis factor-alpha, interleukin-6, and nitric oxide *via* binding to dialysate albumin. A small, randomized trial showed a survival advantage of MARS when compared to standard therapy in HRS patients[55]. To date, there have been no other published trials comparing MARS to standard RRT.

Transplantation

Liver transplantation (LT) is the only effective and permanent treatment for HRS[10,14,56,57] that cures both the liver and renal failure. However, the 5-year survival rate in LT recipients with HRS is significantly less than in LT patients without HRS[56]. Patients who undergo LT may sometimes require postoperative hemodialysis. It is preferable to delay administration of cyclosporine or tacrolimus until renal impairment improves in these patients, as these drugs may further worsen renal function. The issue of whether to transplant a kidney in addition to a liver (LKT, combined liver kidney transplantation) is an important one as well. HRS alone is not considered an indication for a LKT[58]. A renal biopsy may be helpful in some patients to identify the etiology of the renal failure and to determine the presence and extent of glomerular scarring[59]. LKT should be reserved for patients with irreversible renal failure, including HRS patients who are on dialysis for more than 8 wk or patients with progressive primary renal disease[59]. United Network of Organ Sharing (UNOS) data indicate a 5-year survival of LKT recipients of 62% compared with 50% for patients with a serum creatinine > 2.0 mg/dL receiving isolated LT (P = 0.0001). One center's results demonstrated a 5-year patient survival of 48% for LKT patients, 67% for HRS patients receiving isolated LT, and 70% for patients with a serum creatinine > 2.0 mg/dL receiving isolated LT (P not significant comparing all groups)[58]. It is not clear if the advances in management of HRS in recent years have had an impact on post-transplant outcomes. In a case-control study by Restuccia *et al*, patients with HRS treated with vasopressors and albumin prior to LT had similar survival outcomes compared to those patients who underwent OLT without HRS[60]. However, the study had only 9 patients with HRS and as correctly stated by the authors, further confirmation in a larger series of patients is required. Clearly, further prospective studies are needed to guide transplant physicians to determine whether they should transplant the liver and the kidney or the liver alone in patients with liver failure and kidney failure.

CONCLUSION

Renal failure occurs commonly in patients with severe liver disease and its causes are multifactorial. Patients with type 1 HRS generally have a fatal outcome without expedited liver transplantation. Therapy with terlipressin and albumin looks promising, but there is a paucity of data to make firm conclusions. Use of other vasoconstrictors or TIPS remains experimental. The only proven treatment option is expedited liver transplantation. Dialysis is often used as a bridge to liver transplantation, but there are no controlled studies to support renal replacement therapy in type 1 HRS. Further research is necessary to better elucidate the mechanisms of HRS and to identify treatment strategies to reduce morbidity and mortality in patients with liver disease.

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