Current Treatment Strategies for Hepatorenal Syndrome

Elsa Solà, M.D., Mónica Guevara, M.D., Ph.D., Pere Ginès, M.D., Ph.D.

Hepatorenal syndrome (HRS) is a unique form of severe functional kidney failure due to intense renal vasoconstriction that develops in patients with cirrhosis in the absence of significant histological abnormalities of the kidneys.^{1,2} Detailed discussions of the pathophysiology of HRS and the diagnostic approach to HRS are presented in two other articles in this issue of *Clinical Liver Disease* and can also be found elsewhere.^{1,2}

The diagnosis of HRS is essentially a process of excluding other causes of kidney failure. Therefore, the identification of objective parameters that can be used in the differential diagnosis between HRS and other causes of kidney failure in patients with cirrhosis is of the utmost importance. Recent studies suggest that the measurement of the neutrophil gelatinase-associated lipocalin concentration in urine, a biomarker of tubular damage, may be of value in the differential diagnosis between HRS and other causes of acute kidney failure in patients with cirrhosis, but information is still limited.^{3,4} The current diagnostic criteria for HRS have been reported elsewhere.⁵ There are two types of HRS corresponding to the severity and progression of kidney failure (Table 1). Type 1 HRS is associated with rapidly progressive kidney failure and a very low survival expectancy, the median survival time being only 2 weeks if it is not treated; type 2 HRS is associated with stable or slowly progressive kidney failure and has a better prognosis than type 1 HRS.^{1,2}

Management of HRS

The main objective in the management of patients with HRS, particularly those awaiting liver transplantation (LT), is

the reversal of kidney failure in order to provide a successful bridge to transplantation. The best available therapy for HRS (other than LT) is the use of vasoconstrictors plus albumin.¹

General Management

The general management of patients with HRS depends on the severity of kidney failure and associated complications. Patients with type 1 HRS (especially those awaiting LT) should be treated in an intensive care setting. Decisions about the management of patients who are not candidates for transplantation should be individualized. Once type 1 HRS has been diagnosed, treatment should be started as early as possible to prevent further progression of kidney failure. There should be frequent clinical assessments for the possibility of associated complications of cirrhosis (particularly bacterial infections), and if these occur, they should be treated as quickly as possible. Intravenous fluids should be administered carefully in order to prevent pulmonary edema and the development or progression of hypervolemic hyponatremia. Patients with type 2 HRS can be managed as outpatients if there are no associated complications of cirrhosis that require hospitalization.

Treatment of Type 1 HRS

Vasoconstrictor Drugs

Terlipressin. The administration of vasoconstrictors associated with intravenous albumin is currently considered the treatment of choice for the management of type 1 HRS.^{1,6} The rationale behind this therapy is the improvement of circulatory function through vasoconstriction of the extremely

Abbreviations: GFR, glomerular filtration rate; HRS, hepatorenal syndrome; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; RRT, renal replacement therapy; TIPS, transjugular intrahepatic portosystemic shunt.

From the Liver Unit, Hospital Clinic, University of Barcelona School of Medicine; Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd); and Instituto Reina Sofía de Investigación Nefrológica (IRSIN), Barcelona, Spain.

Elsa Solà was the recipient of a grant from the Carlos III Institute of Health (FI10/00438). Some of the studies reported in this review were performed with the support of grants from the Health Research Fund (FIS PI080126 and EC/90077) and the Network Center for Biomedical Research in Hepatic and Digestive Diseases. The Network Center for Biomedical Research in Hepatic and Digestive Diseases is funded by the Carlos III Institute of Health (Spanish Ministry of Health). This study was partly funded by the FIS EC07/90077 - Instituto De Salud Carlos III.

Potential conflict of interest: Nothing to report.

View this article online at wileyonlinelibrary.com

© 2013 by the American Association for the Study of Liver Diseases

doi: 10.1002/cld.209

TABLE 1: Clinical Types of HRS

Type 1. Rapidly progressive decrease in kidney function [defined as a 100% increase in the serum creatinine level to a final value > 2.5 mg/dL (> 221 mmol/L) in 2 weeks]. The clinical presentation is usually that of acute kidney failure. The median survival is only 2 weeks if it is not treated.
Type 2. Stable or slowly progressive decrease in kidney function that does not meet the criteria for type 1 HRS. The typical clinical presentation is that of refractory ascites. The median survival is approximately 6 months.

dilated splanchnic arterial bed, which subsequently improves arterial underfilling, reduces the activity of the endogenous vasoconstrictor systems, and increases kidney perfusion.^{1,2} The available vasoconstrictors used for HRS include vasopressin analogues such as terlipressin and alpha-adrenergic agonists such as noradrenaline and midodrine (Table 2). Most published data concern the use of intravenous terlipressin. Results from recent randomized controlled studies and systematic reviews indicate that treatment with terlipressin together with albumin is associated with marked improvements of kidney function in approximately 40% to 50% of patients.^{7,8} Moreover, a systematic review of randomized controlled studies has shown that vasoconstrictor therapy for HRS improves survival.⁹ Although there are no dose-finding efficacy studies, the treatment is typically started intravenously with 1 mg/4-6 hours, and the dose is increased up to a maximum of 2 mg/4-6 hours after 3 days if there is no response to therapy (defined as a reduction of the serum creatinine level > 25% of the pretreatment values). In responders, the goal is to achieve the lowest levels of serum creatinine possible. Treatment is stopped when there is no further reduction of creatinine. In nonresponders, the duration of treatment is based on the effect on serum creatinine. If there is no decrease in creatinine or if its level increases, treatment should be stopped after 3 to 4 days of the maximum dose of terlipressin. If the reduction in serum creatinine is very slow, treatment can be maintained as long as the serum creatinine level decreases and there are no side effects of therapy. Recent studies suggest that the administration of terlipressin as a continuous intravenous infusion may improve its efficacy and decrease adverse events.^{10,11} However, data are limited, and more studies are needed to confirm these results. A response to therapy is considered when there is a marked reduction in high serum creatinine levels, at least below 1.5 mg/dL. The incidence of ischemic side effects secondary to treatment with vasoconstrictors that require the discontinuation of treatment is approximately 10%. The recurrence of HRS after the withdrawal of therapy occurs in less than 15% of patients, and retreatment with terlipressin is generally effective.

Other vasoconstrictors. Vasoconstrictors other than terlipressin that have been used in the management of HRS include noradrenaline and midodrine plus octreotide, both in combination with albumin.⁶ They represent alternative treatments to

terlipressin because of their low cost and wide availability. Administered as a continuous intravenous infusion, noradrenaline appears to be effective for the treatment of type 1 HRS, although studies are still limited, and the number of treated patients is relatively small. A recent randomized trial compared the safety and efficacy of treatment with terlipressin versus noradrenaline for patients with HRS.¹² Approximately 40% of the patients responded to treatment in both groups, and the adverse event profiles were similar in all patients. Therefore, noradrenaline seems to be as effective and safe as terlipressin for the treatment of HRS.

The combination of oral midodrine and octreotide in association with albumin has been shown to improve kidney function in patients with HRS, although the number of treated patients is relatively small, and no randomized comparative studies with other vasoconstrictors have been performed. A small study of 14 patients with type 1 HRS analyzed the efficacy of a transjugular intrahepatic portosystemic shunt (TIPS) for patients with type 1 HRS after the improvement of systemic hemodynamics and kidney function with a combination of midodrine, octreotide, and albumin. Medical therapy improved kidney function and renal sodium excretion in 10 of the 14 patients before TIPS insertion. TIPS insertion in five of the responders further improved kidney function and renal sodium excretion.¹³ A relatively large retrospective study evaluated the effects of treatment with octreotide plus midodrine on kidney function and 1-month survival in 87 patients with type 1 HRS versus a control group (21 subjects).¹⁴ A significantly higher proportion of patients treated with octreotide plus albumin showed a sustained reduction in serum creatinine in comparison with the control group (40% versus 10%, $P < 0.05$), and the 1-month mortality rate was significantly lower (43% versus 71%, $P < 0.05$). Another recent study also analyzed the effects of the combination of octreotide and midodrine plus albumin on kidney function and survival in 75 patients with

TABLE 2: Pharmacological Treatment for HRS

Vasoconstrictors
Terlipressin: 1 mg/4–6 hours intravenously. The dose is increased up to a maximum of 2 mg/4–6 hours after 3 days if there is no response to therapy (defined as a 25% or greater reduction in serum creatinine compared to pretreatment levels). A response to therapy is defined as a decrease in serum creatinine levels below 1.5 mg/dL (133 μmol/L). The treatment is usually applied for 5 to 15 days.
Midodrine and octreotide: 7.5 mg of midodrine orally 3 times daily (increased to 12.5 mg 3 times daily if needed) and 100 μg of octreotide subcutaneously 3 times daily (increased to 200 μg 3 times daily if needed). The duration of treatment depends on the effects on serum creatinine.
Norepinephrine: 0.5–3 mg/hour as a continuous intravenous infusion aimed at increasing the mean arterial pressure by 10 mm Hg. The treatment is continued until the serum creatinine level decreases below 1.5 mg/dL.
Albumin Administration
Concomitant administration of albumin and vasoconstrictor drugs (1 g/kg of body weight on day 1 followed by 20–40 g/day).

FIGURE 1. Proposed treatment algorithm for patients with type 1 HRS. *A complete response is defined as a decrease in the serum creatinine level to a value less than 1.5 mg/dL (see the text for the duration of treatment). **See Angeli and Ginès.²¹ Adapted with permission from *American Journal of Kidney Diseases*.¹ Copyright 2012, Elsevier, Inc.

type 1 or 2 HRS versus a cohort of 87 controls.¹⁵ The results were similar to those of the previous study. Transplant-free survival was higher for the treatment group (median = 101 days) versus the control group (median = 18 days, $P < 0.0001$). Kidney function had significantly improved at 1 month in the treatment group [glomerular filtration rate (GFR) = 48 mL/minute] versus the controls (GFR = 34 mL/minute, $P = 0.03$), and the 1-month survival rate was significantly higher for the treatment group versus the control group.¹⁵ Therefore, both studies suggest that treatment with oral midodrine plus octreotide may represent an effective alternative to terlipressin for patients with HRS because it improves kidney function and is associated with increased short-term survival. Finally, a recent retrospective analysis evaluated post-LT outcomes of patients treated with octreotide, midodrine, and albumin.¹⁶ In that study, patients treated before LT were compared with a control cohort that underwent LT in the era before this therapy was used. Forty-three patients with HRS underwent LT (27 cases and 16 controls). There were no differences between the groups in the proportion of patients requiring hemodialysis before LT (48% of cases versus 50% of controls, $P = 1.00$). After LT, the mean GFRs were similar for the cases and controls at 1 month (57 versus 53 mL/minute/1.73 m², $P = 0.61$) and at 1 year ($P = 0.13$). Eleven of the 27 cases responded to octreotide, midodrine, and albumin before LT. In comparison with the nonresponders, there was no difference in GFR 1 month after LT. There were no differences between the

groups for patients requiring long-term hemodialysis after LT (7.7% of cases versus 12.5% of controls, $P = 0.61$). The results of this analysis suggest that a pre-LT treatment with a combination of midodrine and octreotide in association with albumin is not associated with an additional benefit in improving kidney function after LT.¹⁶

Thus, although some studies suggest that treatment with oral midodrine plus octreotide in combination with albumin is effective for patients with HRS, the number of treated patients is still limited, and the studies are retrospective. Therefore, large randomized comparative trials with other vasoconstrictors are needed.

Other Treatments. The use of TIPS has been suggested as an alternative therapy to vasoconstrictor drugs for HRS, but its applicability in patients with type 1 HRS and such advanced liver disease is very limited.¹⁷ Two small studies indicate that TIPS improves GFR and reduces the activity of the renin-angiotensin-aldosterone system and the sympathetic nervous system in approximately 60% of patients. However, these studies excluded patients with previous hepatic encephalopathy, Child-Pugh scores ≥ 12 , and serum bilirubin levels > 5 mg/dL.^{17,18} Therefore, the applicability of TIPS to patients with type 1 HRS is very low because TIPS is considered to be contraindicated in patients with features of severe liver failure, which are common findings in the setting of type 1 HRS.

Renal replacement therapy (RRT)---mainly hemodialysis---has been used in the management of patients with type 1 HRS and especially candidates for LT in an attempt to keep patients alive until LT is performed. Unfortunately, the potential beneficial effect of this approach has not been evaluated in randomized studies. Most patients with type 1 HRS develop side effects during RRT, which can include severe arterial hypotension, bleeding, and infections that may contribute to death during treatment. Additionally, indications for RRT (severe fluid overload, acidosis, and hyperkalemia) are uncommon in patients with type 1 HRS, at least in the early stages.

Other methods, including the molecular adsorbent recirculating system and fractionated plasma separation and adsorption (Prometheus), are alternatives to dialysis that clear substances from the circulation, including endogenous vasodilators. They appear to be promising, but more data are needed to consider them useful therapeutic alternatives for HRS.¹⁹

Liver transplantation. LT is the treatment of choice for both type 1 HRS and type 2 HRS.¹ An important problem is that patients with type 1 HRS have a high mortality rate on the waiting list for LT. Therefore, these patients should be assigned a high priority for transplantation. Because kidney failure is reversible after LT, patients with HRS should not be treated with combined liver-kidney transplantation. Combined liver-kidney

transplantation is appropriate only for patients who have been on RRT for more than 6 to 8 weeks and have a low probability of recovery of kidney function.^{6,20}

An important issue is whether to treat patients with type 1 HRS with vasoconstrictors before transplantation with the aim of performing LT in patients with normal or improved kidney function. Although some data are in conflict, the treatment of type 1 HRS before transplantation may improve outcomes after transplantation.^{16,18,21} Recent guidelines support such a treatment strategy.⁶

The management of type 1 HRS is summarized in Fig. 1.

Treatment of Type 2 HRS

Data on the use of vasoconstrictors in combination with albumin for patients with type 2 HRS are scarce. Uncontrolled trials support the efficacy of this therapy in improving kidney function, but recurrence after treatment withdrawal is very frequent. More studies are required to understand the role of vasoconstrictors plus albumin in these patients. TIPS may improve kidney function and reduce the risk of progression to type 1 HRS, but randomized controlled studies are lacking.

CORRESPONDENCE

P. Ginès, M.D., Liver Unit, Hospital Clinic, University of Barcelona School of Medicine, Villarroel 170, 08036 Barcelona, Catalonia, Spain. E-mail: pginès@clinic.ub.es

References

1. Fagundes C, Ginès P. Hepatorenal syndrome: a severe, but treatable, cause of kidney failure in cirrhosis. *Am J Kidney Dis* 2012;59:874–885.
2. Arroyo V, Fernández J, Ginès P. Pathogenesis and treatment of hepatorenal syndrome. *Semin Liver Dis* 2008;28:81–95.
3. Fagundes C, Pepin MN, Guevara, Barreto R, Casals G, Solà E, et al. Urinary neutrophil gelatinase-lipocalin as biomarker in the differential diagnosis of impairment of kidney function in cirrhosis. *J Hepatol* 2012;57:267–273.
4. Verna EC, Brown RS, Farrand E, Pichardo EM, Forster CS, Sola-Del Valle DA, et al. Urinary neutrophil gelatinase-associated lipocalin predicts mortality and identifies acute kidney injury in cirrhosis. *Dig Dis Sci* 2012;57:2362–2370.
5. Salerno F, Gerbes A, Ginès P, Wong F, Arroyo V. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. *Gut* 2007;56:1310–1318.
6. Ginès P, Angeli P, Lenz K, Moller S, Moore K, Moreau R, et al. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. *J Hepatol* 2010;53:397–417.
7. Sanyal AJ, Boyer T, Garcia-Tsao G, Regenstein F, Rossaro L, Appenrodt B, et al.; for Terlipressin Study Group. A prospective, randomized, double blind, placebo-controlled trial of terlipressin for type 1 hepatorenal syndrome (HRS). *Gastroenterology* 2008;134:1360–1368.
8. Martín-Llahí M, Pépin MN, Guevara M, Díaz F, Torre A, Monescillo A, et al.; for TAHRS Investigators. Terlipressin and albumin vs albumin in patients with cirrhosis and hepatorenal syndrome: a randomized study. *Gastroenterology* 2008;134:1352–1359.
9. Glud LL, Christensen K, Christensen E, Krag A. Systematic review of randomized trials on vasoconstrictor drugs for hepatorenal syndrome. *Hepatology* 2010;51:576–584.
10. Angeli P, Fasolato S, Cavallin M, et al. Terlipressin given as continuous intravenous infusion is the more suitable schedule for the treatment of type-1 hepatorenal syndrome (HRS) in patients with cirrhosis: results of a controlled clinical trial. *Hepatology* 2008;48:378A.
11. Gerbes AL, Huber E, Gulberg V. Terlipressin for hepatorenal syndrome: continuous infusion as an alternative to i.v. bolus administration. *Gastroenterology* 2009;137:1179–1181.
12. Singh V, Ghosh S, Singh B, Kumar P, Sharma N, Bhalla A, et al. Noradrenaline vs terlipressin in the treatment of hepatorenal syndrome: a randomized study. *J Hepatol* 2012;56:1293–1298.
13. Wong F, Pantea L, Sniderman K. Midodrine, octreotide, albumin, and TIPS in selected patients with cirrhosis and type 1 hepatorenal syndrome. *Hepatology* 2004;40:55–64.
14. Esrailian E, Pantangco ER, Kyulo NL, Hu KQ, Runyon BA. Octreotide/midodrine therapy significantly improves renal function and 30-day survival in patients with type 1 hepatorenal syndrome. *Dig Dis Sci* 2007;52:742–748.
15. Skagen C, Einstein M, Lucey MR, Said A. Combination treatment with octreotide, midodrine, and albumin improves survival in patients with type 1 and type 2 hepatorenal syndrome. *J Clin Gastroenterol* 2009;43:680–685.
16. Rice JP, Skagen C, Said A. Liver transplant outcomes for patients with hepatorenal syndrome treated with pretransplant vasoconstrictors and albumin. *Transplantation* 2011;91:1141–1147.
17. Guevara M, Ginès P, Bandi JC, Gilabert R, Sort P, Jiménez W, et al. Transjugular intrahepatic portosystemic shunt in hepatorenal syndrome: effects on renal function and vasoactive systems. *Hepatology* 1998;28:416–422.
18. Brensing KA, Textor J, Perz J, et al. Long term outcome after transjugular intrahepatic portosystemic stent-shunt in nontransplant cirrhotics with hepatorenal syndrome: a phase II study. *Gut* 2000;47:288–295.
19. Kribben A, Gerken G, Haag S, Herget-Rosenthal S, Treichel U, Betz C, et al.; for HELIOS Study Group. Effects of fractionated plasma separation and adsorption on survival in patients with acute-on-chronic liver failure. *Gastroenterology* 2012;142:782–789.e3.
20. Charlton MR, Wall WJ, Ojo AO, Ginès P, Textor S, Shihab FS, et al.; for International Liver Transplantation Society Expert Panel. Report of the first international Liver Transplantation Society expert panel consensus conference on renal insufficiency in liver transplantation. *Liver Transpl* 2009;15:S1–S34.
21. Angeli P, Ginès P. Hepatorenal syndrome, MELD score and liver transplantation: an evolving issue with relevant implications for clinical practice. *J Hepatol* 2012;57:1135–1140.