**Therapeutics, Pharmacology and Clinical Toxicology**
Vol XIV, Number 2, June 2010
Pages 96-99


**REVIEW**

# PROPHYLAXIS AND TREATMENT OF HEPATORENAL SYNDROME

**A. Niculae, I. Al. Checherită, Ileana Peride, Cristiana David, Al. Ciocâlteu**

*Nephrology Department, "Sfântul Ioan" Emergency Clinical Hospital, Bucharest, Romania*

**Abstract. T**he hepatorenal syndrome is a syndrome of functional renal failure due to end stage liver disease. The ideal cure currently available for treating HRS is liver transplantation. Other therapeutic options appear to be those that reverse portal hypertension, splanchnic vasodilation, and/or renal vasoconstriction and renal replacement therapy. All the above mentioned represent a bridge towards liver transplantation.
**Keywords:** hepatorenal syndrome, liver transplant, vasoconstrictor therapy, TIPS, RRT

According to the diagnostic criteria of the International Ascites Club, hepatorenal syndrome (HSR) is described as an exclusion diagnosis in patients with advanced liver disease and kidney failure, in absence of other causes of renal impairment. It represents a reversible and functional renal failure that occurs in patients with advanced hepatic failure, acute and chronic liver disease, and portal hypertension [1]. The criteria of hepatorenal syndrome are fulfilled only by few patients with cirrhosis and elevated serum creatinine [2].

HRS is diagnosed by the following criteria, according to the International Ascites Club in 1996 and updates in 2007.

1. Low glomerular filtration rate (GFR), indicated by a serum creatinine level higher than 1.5 mg/dL or 24-hour creatinine clearance lower than 40mL/min

2. Absence of shock, ongoing bacterial infection and fluid loss, and current treatment with nephrotoxic medications

3. No sustained improvement in renal function (decrease in serum creatinine to <1.5mg/dL or increase in creatinine clearance to >40mL/min) after diuretic withdrawal and expansion of plasma volume with 1.5 L of plasma expander

4. Proteinuria less than 500mg/d and no ultrasonographic evidence of obstructive uropathy or intrinsic parenchymal disease

5. Chronic or acute liver disease with advanced hepatic failure and portal hypertension.

Additional criteria are not necessary for the diagnosis but provide supportive evidence: urine sodium level less than 10mEq/L, urine osmolality greater than plasma osmolality, urine volume less than 500mL/day, urine red blood cell count of less than 50 per high-power field, serum sodium concentration greater than 130mEq/L [1].

Depending on the progression of the disease, two forms of HRS can be identified: acute (type 1), characterized by a rapid deterioration in renal function; chronic (type 2), marked by an insidious onset and a slowly progressive course. HRS type 1 is defined by an increase of serum creatinine up to at least 2.5mg/dL within two weeks, frequently following a precipitating event such as infection, whereas HRS type 2, is characterized by a serum creatinine of at least 1.5 mg/dL and refractory ascites.

Gastrointestinal bleeding, injudicious use of lactulose resulting in abundant diarrhea and excessive diuretic therapy or paracentesis, are the main

**Andrei Niculae**
Nephrology Department, "Sfântul Ioan" Emergency Clinical Hospital,
Vitan Bârzeşti, No. 13, Sector 4, Bucharest
email: niculaeandrei@yahoo.com

events that lead to volume contraction in patients with decompensated liver disease [3]. To avoid the last, a stepwise approach for the treatment of ascites is recommended. Bed rest and a low-sodium diet (60–90mmol/day, equivalent to about 1,5-2g of salt per day) is advised in all patients.

An important step is to identify the lowest effective dose of a diuretic in each individual patient, as diuretic induced renal impairment occurs in 20% of patients with ascites. Renal impairment, due to diuretic drugs is usually moderate and rapidly reversible.

Spironolactone is prescribed at increasing doses (100mg/day as initial dosages; if there is no response within 4 days, 200mg/day; if no further response, 400mg/day). Furosemide is added at increasing dosages every two days (40-160mg/day), in case there is no response to the highest dose of spironolactone. Therapeutic paracentesis, combined with plasma volume expansion using albumin (8g/L of ascites removed) is helpful in diuretic resistance cases, being associated with a low incidence of circulatory disfunction after treatment.

Spontaneous bacterial peritonitis (SBP) is the main precipitating factor of type 1 HRS. When this develops in patients with type 2 HRS, the probability of developing type 1 HRS is very high. Patients with cirrhosis and spontaneous bacterial peritonitis present a high risk to develop HRS; this can be markedly reduced with the intravenous administration of albumin (1.5g per kilogram of body weight at diagnosis and 1.0g per kilogram 48 hours later) [4].

Recent research showed that in patients with ascitic fluid that contains less than 15g of protein per liter and who present liver function impairment, renal function or both (a bilirubin level above 3 mg per deciliter (51μmol per liter), a Child–Pugh score greater than 10, a serum sodium level below 130mmol per liter, or a serum creatinine concentration above 1.2mg per deciliter (106μmol per liter), the long-term administration of oral norfloxacin (400mg per day) reduces the risk of the HRS and improves survival [5]. Beneficial effects of norfloxacin seem to be related to its ability to prevent bacterial translocation, suppress proinflammatory cytokines and improve circulatory function [6,7,8].

50% of patients with variceal haemorrhage develop bacterial infections, antibiotic prophylaxis improving survival by 10%. Prophylaxis with antibiotics is recommended in two clinical settings, variceal bleeding and a history of previous SBP.

Other important causes of renal failure are the use of NSAIDs, angiotensin-converting enzyme (ACE), radiologic contrast media and aminoglycosides. The drugs used for the treatment of bleeding esophageal and gastric varices (β-blockers and somatostatin) reduce GFR; their administration must be monitored carefully.

Pentoxifylline treatment (400mg orally three times daily) improves short-term survival in patients with severe alcoholic hepatitis, appearing to be related to a decreased risk of developing HRS, most probably by inhibiting the synthesis of tumor necrosis factor alpha. Treatment is given for 28 days. [9]

Liver transplantation is the ideal treatment of HRS; however, death occurs in most patients before transplantation, due to the long waiting lists in the majority of transplant centers. Alternative therapies are required to increase survival chances for patients with HRS until transplantation can be performed. Pharmacotherapy, mechanical shunt, extracorporeal liver support therapy, are included among the alternatives therapies, and in patients with advanced uremia, renal replacement therapy (RRT) is needed.

Due to side effects and lack of adequate data confirming the benefits, the use of dopamine and prostaglandin analogues (renal vasodilators) was abandoned [10]. Nowadays systemic vasoconstrictors associated to plasma expansion are considered to be the best therapy, since several uncontrolled studies have confirmed a beneficial role in HRS. Their actions consist in suppressing the arterial splanchnic vasodilation and endogenous vasoconstrictor system activation with improvement of renal function [11].

Vasopressin has a preferential vasoconstrictor action on the splanchnic versus the renal vascular bed. The use of ornipressin (a synthetic polypeptide analogue of arginine-vasopressin) was abandoned due to the ischemic side effects (intestinal ischemia, tongue necrosis and ventricular arrhythmia).

Recent studies show that terlipressin (triglycyllysine-vasopressin) is the most successful vasoconstrictor. Administration of terlipressin (0.5-2mg/4–6h intravenously) appears to bring an improvement in renal function in about 60% of the patients and the incidence of ischemic side-effects is about 10%. Some studies consider that concomitant albumin infusion (20-40g/day) may have a favorable response [12].

An improvement in renal function, but without survival advantage at 3 months, was observed in a

European multicenter, randomized, controlled trial of terlipressin and albumin versus albumin alone in 46 patients with type I or type II HRS [13].

Somatostatin analogues (octreotide), and alpha-adrenergic agonists (midodrine and noradrenaline) have also been used. Oral monotherapy with midodrine slightly improved systemic hemodynamics but failed to improve renal function in patients with type 2 HRS, whereas octreotide with albumin infusion proved to be ineffective [14,15]. However, when both agents were given in combination with albumin infusion, a significant improvement in renal function and survival was observed in patients with type 1 HRS [16].

Kiser *et al.* compared vasopressin and octreotide therapy in 43 patients with type 1 HRS. Patients who were treated with vasopressin had a significantly higher HRS recovery rate and improved survival and were more likely to receive a liver transplant [17]. The administration of norepinephrine associated with albumin and furosemide resulted in reversal of HRS in 10 (83%) of 12 patients with type 1 HRS, and side effects such as ischemic episodes, were observed in only two. It is interesting to observe that two of the responders to norepinephrine had previously failed terlipressin therapy.

The main player in the pathogenesis of the homeostatic abnormalities in cirrhosis, hepatic failure and HRS, is portal hypertension. Transjugular intrahepatic portosystemic stent-shunting (TIPS) uses a metallic stent to reinforce a parenchymal track created by balloon dilatation between a branch of the hepatic vein and a branch of the portal vein.

A recent long-term study showed improvement of renal function in 31 nontransplantable cirrhotic patients with HRS but without severe liver failure (bilirubin 15mg/dL, Child-Pugh score 12, and absence of spontaneous severe encephalopathy) in whom limited portal decompression was achieved using 8 to 10 mm stents. The survival rates were 81%, 71%, 48% and 35% at 3, 6, 12 and 18 months, and for 14 patients with type I HRS, they were 64%, 50% and 20% at 3, 6 and 12 months [18]. The degree of liver failure contraindicates the placement of a portosystemic shunt, due to the perfusion reduction of the liver parenchyma, resulting in further deterioration of liver function. Therefore, TIPS is only indicated in highly selected patients with HRS and has only played a marginal role in the treatment of HRS. Vasoconstrictor therapy associated with TIPS insertion improve but do not normalize renal function, neurohumoral, and hemodynamic changes in HRS.

RRT is an option for patients who did not respond to vasoconstrictors or TIPS, developed volume overload, severe metabolic acidosis, or hyperkalemia, until liver transplantation. Continuous RRT (CRRT) is demonstrated to be better tolerated than intermittent hemodialysis (HD), in patients with liver failure, as evidenced by better cardiovascular stability, gradual correction of hyponatremia, and less fluctuation in intracranial pressure.

Continuous venovenous hemofiltration (CVVH) is recommended as treatment of advancing uremia in HRS [19]. CVVH allows the administration of nutritional support, often vital to the survival of these patients and considered to optimize their condition before orthotopic liver transplantation. Moreover, CVVH seems to decrease the intracranial pressure in patients with HRS, which is an important aspect, especially in patients suffering from hepatic encephalopathy; whereas hemofiltration or hemodialysis stimulates an increase. In these patients with HRS, anticoagulation should be avoided or excluded totally, especially in those manifesting pre-existing coagulopathy, by giving the replacement fluid in the predilutional mode. Conventional or low-molecular-weight heparin is usually recommended, when anticoagulation is needed. Because the liver plays a significant role in citrate metabolism, dose adaptation and close metabolic monitoring would be required for regional citrate anticoagulation, especially after prolonged usage [20]. Bicarbonate is suggested to be used instead of lactate as the buffer for the replacement solution in minimizing metabolic acidosis.

The molecular adsorbent recirculating system (MARS) is a cell-free, modified dialysis technique that is able to remove both albumin-bound and water-soluble substances by using a combination of albumin-enriched dialysate and CRRT [21]. Using MARS in HRS is assumed to have the advantage of removing albumin-bound toxins (*e.g.*, bile acids), which have a detrimental effect on hepatocytes and other organs, including the kidney. This will stabilize liver function and improve other end-organ damage [22]. MARS also has the ability to remove both water-soluble cytokines (TNF-α and IL-6) and albumin-bound vasoactive agents (*e.g.*, NO), which have been implicated in the pathogenesis of HRS.

In a prospective randomized controlled trial, MARS effectively removed strongly albumin-bound toxic metabolites, improved renal function, and prolonged survival in 8 patients (mean survival

25+/-5 days) with type 1 HRS and severe liver failure (bilirubin >15mg/dL, Child Pugh score 12.5+/-1.2) compared with 5 untreated control patients (mean survival 4.6+/-1.8 days). MARS results require further evaluation to be considered as a bridge to transplantation. Until then, MARS should not be used in the treatment of HRS outside of clinical trials [23].

Liver transplantation continues to be the best treatment for suitable candidates with HRS, as it cures both the diseased liver, and the renal dysfunction. After liver transplantation, renal sodium excretion and hemodynamic abnormalities normalize within 1 month and renal resistive indices decrease to normal values during the first posttransplantation year. Even if renal function improved after transplantation in HRS patients, it never reached a level of function demonstrable in non HRS patients. The HRS group required a longer stay in an intensive care unit, longer hospitalization and more dialysis treatment after transplantation. The incidence of end stage renal disease in the HRS group was 7% compared with 2% in the non HRS group [24].

HRS is a life threatening complication of liver cirrhosis. With increased knowledge regarding liver cirrhosis, portal hypertension, ascites as well as HRS, new pharmacological treatments have proven useful in improving the short-term outcome of HRS.

## References


**1. Arroyo V, Gines P, Gerbes AL, et al.** Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. *Hepatology* **(1996) 23:164–176.**

**2. Gines P, Guevara M, Arroyo V, Rodes J.** Hepatorenal syndrome. *Lancet* **(2003) 362:1819–1827.**

**3. Ciocâlteu A,** Tratat de Nefrologie, Editura Național, București, **2006**, cap. Insuficiență renală acută, **pag 568-569.**

**4. 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: 403-409.**

**5. Fernández J, Navasa M, Planas R, et al.** Primary prophylaxis of spontaneous bacterial peritonitis delays hepatorenal syndrome and improves survival in cirrhosis. *Gastroenterology* **2007;133:818-824.**

**6. Wiest R, Garcia-Tsao G.** Bacterial translocation (BT) in cirrhosis. *Hepatology* **2005;41:422-433.**

**7. Albillos A, de la Hera A, González M, et al.** Increased lipopolysaccharide binding protein in cirrhotic patients with marked immune and hemodynamic derangement. *Hepatology* **2003;37:208-217.**

**8. Francés R, Zapater P, González Navajas JM, et al.** Bacterial DNA in patients with cirrhosis and noninfected ascites mimics the soluble immune response established in patients with spontaneous bacterial peritonitis. *Hepatology* **2008;47:978-985.**

**9. Wong F, Blendis L.** New challenge of hepatorenal syndrome: prevention and treatment. *Hepatology* **2001;34:1242-1251.**

**10. Arroyo V, Bataller R, Guevara M.** Treatment of hepatorenal syndrome in cirrhosis. **In: Arroyo V, Gines P, Rodes J, Schrier RW, editors.** Ascites and renal dysfunction in liver disease. Pathogenesis, diagnosis, and treatment. *Malden (MA):* **Blackwell Science, 1999. p. 492–510.**

**11. Guevara M, Gines P, Fernandez-Esparrach G, et al.** Reversibility of hepatorenal syndrome by prolonged administration of ornipressin and plasma volume expansion. *Hepatology* **1998;27:35–41.**

**12. 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.**

**13. Fabrizi F, Dixit V, Martin P.** Meta –analysis: terlipressin therapy for hepatorenal syndrome, *Aliment Pharmacol Ther* **2006, 24: 935-944.**

**14. Pomier-Layrargues G, Paquin SC, Hassoun Z, Lafortune M, Tran A.** Octreotide in hepatorenal syndrome: A randomized, double-blind, placebo-controlled, crossover study. *Hepatology* **38:238–243,2003.**

**15. Angeli P, Volpin R, Piovan D, et al.** Acute effects of the oral administration of midodrine, an alpha-adrenergic agonist, on renal hemodynamics and renal function in cirrhotic patients with ascites. *Hepatology* **28:937–943,1998.**

**16. Angeli P, Volpin R, Gerunda G, et al.** Reversal of type 1 hepatorenal syndrome with the administration of midodrine and octreotide. *Hepatology* **29:1690 –1697,1999.**

**17. Kiser TH, Fish DN, Obritsch MD, et al.** Vasopressin, not octreotide, may be beneficial in the treatment of hepatorenal syndrome: A retrospective study. *Nephrol Dial Transplant* **20:1813 –1820, 2005.**

**18. Brensing KA, Textor J, Perez J, et al.** Long term outcome after transjugular intrahepatic portosystemic stent-shunt in non-transplant cirrhotics with hepatorenal syndrome; a phase 2 study. *Gut* **2000;47:288-295.**

**19. Epstein M, Perez GO.** Continuous arterio-venous ultrafiltration in the management of the renal complications of liver disease. *Int J Artif Organs* **1986;9:217-218.**

**20. Kramer L, Bauer E, Joukhadar C, et al.** Citrate pharmacokinetics and metabolism in cirrhotic and noncirrhotic critically ill patients. *Crit Care Med* **2003;31:2450-245.**

**21. Mitzner SR, Stange J, Klammt S, et al.** Improvement of hepatorenal syndrome with extracorporeal albumin dialysis MARS: Results of a prospective, randomized, controlled clinical trial. *Liver Transpl* **6:277–286,2000.**

**22. Faubion WA, Guicciardi ME, Miyoshi H,et al.** Toxic bile salts induce rodent hepatocyte apoptosis via direct activation of Fas. *J Clin Invest* **103:137–145,1999.**

**23. Mitzner SR, Klammt S, Peszynski P, et al.** Improvement of multiple organ functions in hepatorenal syndrome during albumin dialysis with the molecular adsorbent recirculating system.

**24. Jeyarajah DR, Gonwa TA, Mc Bride M, et al.** Hepatorenal syndrome: Combined liver kidney transplants versus isolated liver transplant. *Transplantation* **1997;64:1760-1765.**