*Review Article*

# Hepatorenal Syndrome: Update on pathogenesis and management

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## Summary

*Hepatorenal syndrome (HRS) in cirrhotic patients with ascites is a functional form of kidney failure with a very poor prognosis. It is one of the numerous potential causes of acute kidney injury (AKI) in patients with decompensated cirrhosis. The pathophysiology of this syndrome is complex with several mechanisms interacting simultaneously, including liver cirrhosis with ascites, portal hypertension, arterial vasodilation, systemic inflammation and bacterial translocation. Although different medical modalities of treatment of HRS are available, the liver transplantation remains the treatment of choice. The aims of medical treatment are to stabilize the patients until liver transplantation and to optimize their pre-transplant clinical conditions. Most of these therapies have targeted the haemodynamic perturbations that are thought to underlie the pathophysiology of HRS, including systemic and splanchnic vasodilation. Other management options, such as transjugular intrahepatic portosystemic shunt, renal replacement therapy and molecular absorbent recirculating system, may provide short-term benefit for patients not responding to medical therapy whilst awaiting transplantation. This review demonstrate the diagnostic approach to HRS, the underlie pathophysiology events and the therapeutic measures currently adopted in clinical practice.*

**Keywords:** *Hepatorenal syndrome, Acute kidney injury, Liver cirrhosis, Terlipressin.*

## Introduction

Hepatorenal syndrome (HRS) is a distinctive form of kidney injury occurs in patients with end-stage cirrhosis regardless of the underlying cause. It results from renal vasoconstriction in the setting of systemic and splanchnic arterial vasodilatation. Two types of HRS; type-1 characterized by a rapid and progressive deterioration in the kidney function. It commonly occurs in severe alcoholic hepatitis or in patients with end-stage cirrhosis following a septic insult such as spontaneous bacterial peritonitis and type-2 characterized by a steady but moderate degree of functional renal failure. HRS still a diagnosis of exclusion and is associated with a very poor prognosis. The best possible treatment for HRS is the liver transplant. Other managing options including, transjugular intrahepatic portosystemic shunt, renal replacement therapy and molecular absorbent recirculating system, may offer short-term benefit for patients not responding to medical therapy (vasoconstrictor drugs and albumin infusion) whilst awaiting transplantation.

## Definition

Hepatorenal syndrome (HRS) is a functional renal failure in patients with advanced chronic liver disease characterized by renal vasoconstriction[1]. In 2007, the International Ascites Club defined HRS as a potentially reversible syndrome that occurs in patients with cirrhosis, ascites and liver failure. HRS is characterized by impaired renal function, marked abnormalities in cardiovascular function and intense over activity of the endogenous vasoactive systems. Marked vasoconstriction occurs in the kidney, resulting in a low glomerular filtration rate, whereas decreased vascular

resistance occurs in the systemic circulation as a result of splanchnic and peripheral arterial vasodilatation[2].

## Classification of HRS

The classification of hepatorenal syndrome into two types has continued unchanged even in the updated diagnostic criteria, tab. (1).

***Type 1 HRS***; defined as acute onset and rapidly progressing kidney failure with a doubling of serum creatinine to more than 2.5 mg/dl in duration of less than 2 weeks. It is more acute. Type1 of HRS can develop spontaneously but more often tends to follow a precipitating event mainly infection such as spontaneous bacterial peritonitis[3].

***Type 2 HRS***; defined as a slowly progressive rise in serum creatinine to more than 1.5 mg/dl. It is usually associated with diuretic resistant refractory ascites. The differential diagnosis between the two types is based on the rate of progression and extent of renal impairment, whereas the pathophysiological differences have not yet been fully clarified[4].

According to the IAC criteria, tab. (2), acute renal failure is defined as an increase in serum creatinine of ≥ 50% from baseline to a final value > 1.5 mg/dL (133 mol/L). However, the threshold value of 1.5 mg/dL has been challenged. Meanwhile, new definition of acute renal failure, now termed acute kidney injury (AKI), has been developed and validated in patients without cirrhosis. Combining the emerging evidence and consensus of the experts, the IAC revised the criteria of AKI in patients with cirrhosis (type-1 HRS) in 2015[5]. In the new definition, AKI is defined as a sCr increase of ≥ 0.3 mg/dL (26.5 umol/L) within 48 h or of ≥ 50% from baseline within 7 days, tab. (1). Three stages of AKI and responses to treatment were also defined. The implementation of the new criteria is to allow earlier treatment of patients with type-1 HRS, which may lead to a better outcome instead of having to wait until the serum creatinine reaches ≥ 2.5 mg/dL[6].

Table (1) Characteristics of type 1 and type 2 hepatorenal syndrome

| HRS types | Characteristics of type 1 and type 2 hepatorenal syndrome | | | |
|---|---|---|---|---|
| **HRS1** | Doubling of serum creatinine in < 2 wk | A precipitating factors is present in the most of case | No history of diuretic resistant ascite | The median survival of patients is only 10% at 90 days without treatment |
| **HRS2** | Renal impairment gradually Progressive | No precipitating factors | Always ascites Diuretic resistance | The median survival of patients is 6 months without treatment |

Table (2) The International Ascites Club diagnostic criteria of HRS-1(2015 criteria)

| |
|---|
| Presence of cirrhosis with ascites |
| Diagnosis of acute kidney injury (increase in sCr ≥ 0.3 mg/dL or 1.5 times over baseline) |
| No improvement of sCr after at least 2 days of diuretics withdrawal and volume expansion with albumin (1 g/kg of body weight per day up to a maximum of 100 g/day) |
| Absence of shock |
| No current or recent treatment with nephrotoxic drugs |
| No macroscopic signs of structural kidney injury as indicated by: normal findings on renal ultrasonography, absence of proteinuria > 500 mg/day and absence of microhematuria ((50 red blood cells per high power field)) |

***HRS**: hepatorenal syndrome; **sCr**: serum creatinine; **HPF**: high power field*

## Epidemiology

According to Fede et al[7], Approximately 20% of cirrhotic patients with diuretic-resistant ascites potentially develops HRS, while Ginès et al[3] found an probability of developing HRS at 1 and 5 years in patients with ascites being 18 and 39% respectively after initial diagnosis. The prevalence of HRS increases with liver disease progression, Wong et al reporting a rate of 48% in patients on the waiting list for liver transplant[8]. Despite discrepancies in literature data, the prevalence of HRS has dropped in recent years, probably as a result of a better understanding of its pathophysiology and improved clinical management[9].

## Pathophysiology

Hepatorenal syndrome can be considered the final stage of a pathophysiological condition characterized by decreased renal blood flow resulting from deteriorating liver function in patients with cirrhosis and ascites[9,10]. Many interrelated pathophysiological processes underlying the pathophysiology of HRS, including the diseased liver, portal hypertension and development of ascites arterial vasodilator effects, systemic inflammation, bacterial translocation and hepatorenal reflex[11].

## Splanchnic and Systemic Arterial Vasodilatation.

Arterial vasodilation appears to be the most important explanation for circulatory dysfunction that occurs in patients with cirrhosis and ascites[12]. This involves two major mechanisms; the first is systemic circulatory disturbances and the second one is the activation of neurohumoral systems. At first portal hypertension secondary to cirrhosis producing splanchnic vasodilatation that decreasing systemic vascular resistance and subsequent reduction in effective blood volume, which is clinically mediated by an increased production of nitric oxide (NO), carbon monoxide and/or endogenous cannabinoids[12]. The development of portal hypertension also leads to the opening of portal-systemic shunts. This opening diverts some of the splanchnic blood, together with the excess vasodilators, to the systemic circulation, which either has a direct vasodilator effect on the systemic circulation, or increases the release of nitric oxide or both. The presence of excess vasodilators in the splanchnic vasculature also causes the circulatory bed to be hyporesponsive to vasoconstrictors. Some evidence also exists that a postreceptor defect at the level of smooth muscle cells also contributes to splanchnic vasodilatation[13]. In the early stages, the effective arterial blood volume and arterial pressure are maintained by increased cardiac output resulting in a hyperdynamic circulation. In later stages, the progressive splanchnic vasodilatation results in a decrease in effective arterial blood volume that can no longer be compensated by cardiac output[3]. In order to maintain arterial pressure, systemic vasoconstrictor systems, such as the renin-angiotensin-aldosterone system (RAAS), the sympathetic nervous system (SNS) and the non-osmotic hypersecretion of arginine vasopressin (AVP), are activated leading to increased plasma renin activity and increased plasma norepinephrine levels. However, the activation of neurohumoral systems has harmful impacts on the kidneys. Development of renal sodium and solute-free water retention leads to ascites and oedema, and hypervolemic hyponatremia, respectively. This results in significant renal vasoconstriction, and so renal cortical blood flow decreases with a consequent reduction in glomerular filtration rate and subsequently HRS[14]. Structural vascular changes in the form of increased angiogenesis, which is related to increased plasma levels of vascular endothelial growth factors[15,16]. These changes, maintain splanchnic hyperemia, increased portal blood flow and portosystemic collateralization[17]. These factors are important in the pathogenesis of the hemodynamic abnormalities, which have a pivotal role in the development of renal failure in cirrhosis.

## Bacterial Translocation and Systemic Inflammation

Translocation of the bacteria from the intestinal lumen to mesenteric lymph nodes and then into the systemic circulation lead to an inflammatory state and vasodilation[14]. In the clinical setting, increased levels of pro-inflammatory cytokines, such as tumor necrosis factor α (TNF α), interleukin-6 (IL-6) and NO, in the splanchnic area lead to reduced systemic vascular resistance and increased cardiac output[18].

## Diagnosis

Two forms of HRS, types I and II, have been described. The differential diagnosis between the two types is based on the rate of progresion and extent of renal impairment[19]. According to the IAC criteria, acute renal failure is defined as an increase in serum creatinine ≥ 50% from baseline to a final value > 1.5 mg/dL (133 mol/L). However, the threshold value of 1.5 mg/dL has been challenged. A new definition of acute renal failure, now termed acute kidney injury (AKI), has been developed and validated in patients without cirrhosis. Combining the emerging evidence and consensus of the experts, the IAC revised the criteria of AKI in patients with cirrhosis (type-1 HRS) in 2015[20]. In the new definition, AKI is defined as a serum creatinine increase of ≥ 0.3 mg/dL (26.5 umol/L) within 48 h or of ≥ 50% from baseline within 7 days, tab. (2). Three stages of AKI and responses to treatment were also defined. The significance of this new criteria is an early identification of kidney failure and thereby implementing prompt, aggressive and earlier treatment of patients with type-1 HRS, which may lead to a better outcome instead of having to wait until the serum creatinine reaches ≥ 2.5 mg/dL[21]. Diagnostic criteria of HRS type of AKI in patients with cirrhosis HRS – AKI.

* Diagnosis of cirrhosis and ascites.
* Serum creatinine>133µmol/l (1.5 mg/dl).
* No improvement of serum creatinine (decrease to a level of ≤133µmol/l) after at least 2 days with diuretic withdrawal and volume expansion with albumin. The recom-mended dose of albumin is 1 g/kg of body weight per day up to a maximum of 100 g/day.
* Absence of shock.
* No current or recent use of nephrotoxic drugs (NSAIDs, aminoglycosides, iodinated contrast media, etc.).
* No macroscopic signs of structural kidney injury, defined as:
  - Absence of proteinuria (>500 mg/day).
  - Absence of microhaematuria (>50 RBCs per high power field)
  - Normal findings on renal ultrasonography.

## Prevention

As the majority of cases of type 1 HRS are precipitated by some event, the prevention of these precipitating events should considerably reduce the incidence of type 1 HRS. Strategies to prevent these precipitating events include avoidance of excess diuresis, use of albumin with large volume paracentesis of >5 l, prevention of bacterial infections (including SBP), and antibiotic prophylaxis with gastrointestinal bleed. Indeed, the use of norfloxacin as a primary prophylaxis in patients who have cirrhosis with ascites who are at high risk of developing renal failure with an episode of SBP was able to reduce the incidence of SBP and renal failure and improved survival[14,22].

## Treatment

The aims of medical treatment are to stabilize the patients until liver transplantation and to optimize their pre-transplant clinical conditions. Most of these therapies have targeted the haemodynamic perturbations that are thought to underlie the pathophysiology of HRS, including systemic and splanchnic vasodilation**.**

## Vasoconstrictor Therapy and Albumin

The most effective method currently available is the administration of vasoconstrictor drugs and albumin infusion, with the aims of improving splanchnic arterial circulation and plasma volume expansion, respectively. Several vasopressor therapies have been trialed in HRS, including terlipressin, norepinephrine and midodrine plus octreotide. Twenty one studies showed an increase in mean arterial pressure of at least 5 mmHg correlated with improvement in renal function regardless of which vasopressor was used[23].

## Terlipressin

Is the most widely used agent as a treatment for type 1HRS. Apart from improving the systemic blood pressure, terlipressin also causes vasoconstriction in the splanchnic circulation, decreasing portal inflow and thereby reducing portal pressure[24]. It should be started at 0.5-1 mg every 4-6 h. If there is no early response (>25% decrease in creatinine levels after 2 days), the dose can be doubled every 2 days up to a maximum of 12 mg/day. Treatment can be stopped if serum creatinine does not decrease by at least 50% after 7 days of the highest dose, or if there is no reduction after the first 3 days. In patients with early response, treatment should be extended until a reversal of HRS or for a maximum of 14 days[25].

Terlipressin should be adminstrated with albumin (at a dose of 1 g/kg per day on the first day, without exceeding 100 g/d, followed by 20-40 g/d). Albumin serves to expand the circulating plasma volume by raising the oncotic pressure[26]. Terlipressin has an acceptable side-effects profile. Side effects include abdominal pain with cramps and diarrhea until intestinal ischemia; cardiac tachiarrhythmias and chest pain can be observed, in general ECG monitoring is recommended. Vasoconstriction induced by terlipressin may cause also cyanosis, livedo reticularis, necrosis of the skin and extremities[27].

## Midodrine

Is an α agonist commonly used in the United States as an alternative to terlipressin and is used in combination with octreotide and albumin (at a dose of 0.5-3 mg/h). The aim is to raise mean arterial pressure by 10 mmHg and urinary output > 200 mL every four hours. The maximum period of treatment must not exceed 2 weeks[28]. The administration of albumin may improve the effect of vasoconstrictors. The dose of albumin recommended is 1 g/kg of body weight on the first day, up to a maximum of 100 g, followed by 20-40 g/day.

## Types of Response to Treatment with Vasoconstrictors and Albumin

* Complete response (reversal of HRS); decrease of serum creatinine to be below 133 µmol/l (1.5 mg/dl).
* Relapse of HRS: recurrence of renal failure (creatinine >133 µmol/l (1.5 mg/ dl) after discontinuation of therapy.
* Partial response: decrease in serum creatinine to ≥50% of its pre-treatment value, without reaching a level below 133µmol/l (1.5 mg/dl).
* No response: no decrease of serum creatinine or decrease to <50% of its pretreatment value, with a final level above 133 µmol/l (1.5 mg/dl). A randomized controlled trial of 49 patients comparing terlipressin with octreotide/midodrine illustrated a significantly higher rate of improvement in renal function with terlipressin (≥ 50% serum creatinine decrease, 70.4% vs. 28.6%, P = 0.01), although there was no significant difference in survival between the two groups[29]. Terlipressin is a bridging option, despite its high cost, to liver transplantation in patients who are transplant candidates as it may improve both renal function and short-term survival for patients awaiting a liver transplant.

## Transjugular Intrahepatic Portosystemic Shunt

TIPS aims to reduce portal pressure by inserting an intrahepatic stent, which shunts portal blood into the systemic circulation, and in theory may benefit some patients with HRS. However, many patients with HRS are ineligible for TIPS due to contraindications including severe hyperbilirubinaemia or Child-Pugh class C (e.g., Bilirubin >5 mg/dL, Child-Pugh score >11). Moreover, the risks associated with TIPS, namely hepatic encephalopathy, liver failure, cardiac failure and renal injury due to contrast, also need to consider[30]. EASL guidelines recommend that though the insertion of TIPS may improve renal function in some patients, there are insufficient data to support the use of TIPS as a treatment of patients with type 1 HRS[31].

## Renal Replacement Therapy.

The indications for renal replacement therapy (RRT) in patients with HRS are the same as those for AKI patients without cirrhosis. RRT is among the so-called bridging therapies designed to support patients awaiting liver transplant[32]. There is a preference for continuous renal replacement therapy over intermittent haemodialysis in haemodynamically unstable patients[33]. EASL recommends that renal replacement therapy may be useful in patients who do not respond to vasoconstrictor therapy, and who fulfill the criteria for renal support[31].

## Molecular Absorbent Recirculating System (MARS)

The introduction of the extracorporeal albumin dialysis system as a means of filtering out various substances that might be detrimental in advanced cirrhosis was initially met with enthusiasm. It is used to reduce serum levels of bilirubin and creatinine[34,35]. It improves short-term survival in patients with AKI and may provide a bridge to liver transplantation for patients with HRS who are unresponsive to vasopressors and ineligible for TIPS[36]. (MARS) removes albumin-bound and water-soluble substances, including NO and TNF, which are involved in pathogenesis of HRS. The redu-

ction of serum levels of creatinine during albumin dialysis is related to the creat-enine being filtered out during the dialysis process rather than improvement of renal function.

## Liver transplantation

This is the treatment of choice for both type-1 and type-2 HRS[37], as this will reverse both portal hypertension and liver failure, the two main factors leading to systemic circulatory disturbances in HRS. Renal function also improves after liver transplantation, which is associated with a reduction in vasoconstrictive activities[38]. Simultaneous liver –kidney transplantation is not necessary for patients with isolated HRS and should only be considered in selected patients at high risk for non-recovery of renal function, such as patients with heavy proteinuria and other evidence of advanced primary renal disease.

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