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## Review Article

# Hepatorenal Syndrome, Are we making any Progress? - @

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**ABSTRACT**

Hepatorenal Syndrome (HRS) poses a unique challenge to liver failure patients. The key pathophysiologic feature of HRS includes a marked reduction in renal blood flow that is caused by intense vasoconstriction of the renal circulation counteracting the pathologic systemic and splanchnic arterial vasodilation. The diagnosis of HRS requires a reduction in the glomerular filtration rate and exclusion of other causes of renal failure. Novel biomarkers including cystatin C, neutrophil gelatinase associated lipocalin (NGAL), IL-8 and liver-type fatty acid binding protein (L-FABP) have been proven to be useful for predicting HRS. All existing treatments can only be considered supportive. Other potential therapeutic options such as selectively targeting renal vasodilation are promising. Currently, liver transplant is the only treatment that improves long-term survival.

**Keywords:** Hepatorenal syndrome; Acute kidney injury; Cirrhosis

**INTRODUCTION**

Hepatorenal Syndrome (HRS) is a rapidly progressive functional form of acute renal failure. HRS typically occurs as a severe complication of advanced liver disease and is usually associated with an accelerated course of death [1]. Hepatorenal syndrome is a diagnosis of exclusion, and other potential causes of kidney injury should be excluded. Most patients with cirrhosis die from the consequences of portal hypertension and the pathophysiological changes induced by progressive liver dysfunction. In the current review, we focus on the pathophysiology, diagnosis, and treatment of HRS.

**Definition and diagnosis**

The first pathophysiologic interpretation of HRS was proposed by Frerichs and Flint in the 19<sup>th</sup> century. They described the association between advanced liver disease and renal impairment characterized by oliguria, absence of proteinuria, and normal renal pathology [2]. The definition of HRS has evolved over time and in 1996 the International Ascites Club (IAC) published the diagnostic criteria for HRS (Table 1) [3]. However, the IAC criteria had several limitations including the use of creatinine clearance which has a poor correlation with kidney function in patient with cirrhosis, and less specific and sensitive criteria such as sodium excretion fraction (FENa) and urinary output [4-6]. Moreover, not all patients with HRS have oliguria and a progressive rise in creatinine is more common. Existing data has also found that the urine volume may exceed 400 ml per day with a marked contraction of diuresis only a few days before death [4].

Acute Kidney Injury (AKI) is a common complication in patients with decompensated cirrhosis. In recent years, two consensus definitions of AKI have been developed including the Acute Dialysis Quality Initiative group for the Risk, Injury, Failure, Loss of Renal Function and End-Stage Renal disease (RIFLE) criteria and the Acute Kidney Injury Network (AKIN) group (Table 2). A recent prospective study by Wong, et al. [7] evaluated the ability of the AKIN to predict mortality within 30 days of hospitalization among patients with cirrhosis and infection. The study showed that the consensus definition of AKI accurately predicted 30-day mortality, length of hospital stay and organ failure. Most studies have demonstrated that the AKIN criteria predict mortality, infection, and the potential risk of progression to HRS [8].

A panel of experts has combined the AKIN criteria with the RIFLE criteria leading to the proposal of the Kidney Disease Improving Global Outcome (KDIGO) criteria. KDIGO diagnostic criteria includes an increase in serum creatinine by  $\geq 0.3$  mg/dl within 48 hours or an increase in SCr to  $\geq 1.5$  times the baseline within the prior 7 days; or a urine volume  $< 0.5$  ml/kg/h for 6 hours [9]. This new classification aims to identify kidney failure earlier and implement prompt and aggressive treatment (Table 3) [10].

The IAC further classifies HRS into type 1 and type 2. Type 1 HRS is characterized by a rapid and progressive impairment of renal function defined by a doubling of the serum creatinine level  $> 2.5$  milligram per deciliter (mg/dL) or  $> 226$  micromoles per liter ( $\mu\text{mol/L}$ ) in less than two weeks [11,12]. Prognosis is poor with a ten percent survival rate at 90 days. Type 2 HRS is a less severe, gradual increase in serum creatinine level (above 1.5 mg/dL) that evolves in months (Table 4) [12,13]. The differential diagnosis between the two types of HRS are based on the rate of the progression since no pathophysiological differences have been identified.

**Novel biomarkers**

The diagnostic criteria for diagnosis of HRS continues to rely on serum creatinine levels that should be interpreted with caution in patients with cirrhosis. Patients with cirrhosis have lower baseline serum creatinine than normal due to reduced production of endogenous creatinine, muscle wasting and decreased muscle mass from decreased protein and meat intake; thus, the severity of kidney failure may be underestimated [5,6]. Factors that may overestimate renal function include: medications, fluctuations in serum creatinine in patients with cirrhosis, increased volume of distribution and elevated bilirubin [14,15].

**Table 1: Initial diagnostic criteria for hepatorenal syndrome – 1996**

Diagnostic criteria for Hepatorenal syndrome	
<b>Major criteria</b>	Chronic or acute liver disease with advanced hepatic failure and portal hypertension
	Low GFR as indicated by serum creatinine $> 1.5$ mg/dL or 24-hour creatinine clearance $< 40$ mL/min
	Absence of shock, on-going bacterial infection, and current or recent treatment with nephrotoxic drugs and absence of gastrointestinal fluid losses or renal fluid losses.
	No sustained improvement in renal function (decrease in serum creatinine $\leq 1.5$ mg/dL or increase in creatinine clearance to $\geq 40$ mL/min) following diuretic withdrawal and expansion of plasma volume with 1.5 L of isotonic saline.
	Proteinuria $< 500$ mg/dL and no sonographic evidence of obstructive uropathy or parenchymal renal disease.
<b>Minor criteria</b>	Urine volume $< 500$ mL/day
	Urinary sodium $< 10$ mEq/L
	Urinary osmolality greater than plasma osmolality
	Urine RBCs $< 50$ /HPF
	Serum sodium $< 130$ mEq/L

\*RBCs = red blood cells, HPF = high power field

**Table 2:** Current diagnostic criteria for definition and classification of AKI

	RIFLE criteria (2002)	AKIN (2007)	KDIGO (2012)	ICA-AKI (2015)
<b>Diagnostic criteria</b>	↑ in SCr to ≥1.5 times baseline, within 7 days; or GFR ↓ >25%; or UO <0.5 ml/kg/h for 6 h.	↑ in SCr by ≥0.3 mg/dL within 48 hrs; or ↑ in SCr ≥1.5 times baseline within 48 hrs; or UO <0.5ml/kg/h for 6 h.	↑ in SCr by ≥0.3 mg/dL within 48 hrs; or ↑ in SCr ≥1.5 times which is known or to have occurred within the prior 7 days; or UO <0.5 ml/kg/h for 6h.	↑ in SCr by ≥0.3 mg/dL within 48 hrs; or ↑ in SCr by ≥50% from baseline that is known or presumed to have occurred within the prior 7 d
<b>Stage 1</b>	<i>Risk:</i> SCr ↑ 1.5-1.9 x baseline; or GFR ↓ 25-50%; or UO<0.5ml/kg/h for 6h	↑ by ≥0.3 mg/dL within 48 hrs or to ≥1.5-2 x baseline	↑ by ≥0.3 mg/dL within 48 hrs or to ≥1.5-2 x baseline	↑ by ≥0.3 mg/dL within 48 hrs or to ≥1.5-2 x baseline
<b>Stage 2</b>	<i>Injury:</i> SCr ↑ 2.0-2.9 x baseline; or GFR ↓ 50-75%; or UO<0.5ml/kg/h for 12h	↑ to 2-3 x baseline	↑ to 2-3 x baseline	↑ to 2-3 x baseline
<b>Stage 3</b>	<i>Failure:</i> SCr ↑ ≥3.0 x baseline; or GFR ↓ 50-75%; or SCr ↑ ≥4.0 mg/dl with an acute ↑ of at least 0.5 mg/dL; or UO < 0.3ml/kg/h for ≥ 24 h; or anuria for ≥12 h.	↑ to 3 x baseline; or to >4mg/dL with an acute increase >0.5 mg/dL; or on RRT	↑ to 3 x baseline; or to >4mg/dL with an acute increase >0.5 mg/dL; or on RRT	↑ to 3 x baseline; or to >4mg/dL with an acute increase >0.5 mg/dL; or on RRT

RIFLE = Risk, Injury, Failure, Loss of Renal Function and End-stage Renal disease, AKIN = Acute Kidney Injury Network, KDIGO = Kidney Disease: Improving Global Outcomes, ICA = International Club of Ascites, AKI = Acute Kidney Injury, GFR = Glomerular Filtration Rate, SCr = serum creatinine, UO = Urine Output, RRT = Renal Replacement therapy.

**Table 3:** Diagnostic criteria of hepatorenal syndrome type of acute kidney injury in patients with cirrhosis

Revised diagnostic criteria for Hepatorenal syndrome
<ul style="list-style-type: none"> <li>• Cirrhosis with ascites</li> <li>• Diagnosis of AKI per the ICA-AKI criteria</li> <li>• No response after at least 2 consecutive days with diuretic withdrawal and volume expansion with albumin</li> <li>• Absence of shock</li> <li>• No current or recent treatment with nephrotoxic drugs</li> <li>• Absence of parenchymal kidney disease, as indicated by proteinuria &gt; 500 mg/day, microhematuria (&gt; 50 RBCs/HPF), and a normal renal ultrasonography.</li> </ul>
*New ICA diagnostic criteria are based either on an increase in serum creatinine ≥0.3 mg/dl within 48 hours or ≥ 50% during the week before admission.

**Table 4:** Differences between hepatorenal syndrome type 1 and type 2

Hepatorenal syndrome	Onset	Precipitant events	Diuretic resistant refractory ascites	Survival
<b>Type 1</b>	Rapid	Yes, including SBP, gastrointestinal bleeding, and large volume paracentesis	No	10% survival in 90 days without treatment.
<b>Type 2</b>	Gradual	No precipitant events	Always	Median survival 6 months.

The diagnosis of HRS is based solely upon clinical criteria. To date, accurate laboratory and imaging biomarkers of renal function are lacking. Cystatin C and Neutrophil Gelatinase-Associated Lipocalin (NGAL) have been advocated as renal biomarkers. Cystatin C is a low molecular weight protein produced by all nucleated cells and eliminated exclusively by glomerular filtration [16]. In contrast to serum creatinine, cystatin C is independent of gender, age, muscle mass, inflammation and malignancy and is not affected by serum bilirubin level [17,18]. In patients with cirrhosis, studies have shown that equations combining serum creatinine and cystatin may be superior to predict Glomerular Filtration Rate (GFR) compared with serum creatinine equations alone, mainly if the GFR is below 60 ml/min/1.73 m<sup>2</sup> [19]. In a study by Slack, et al. [20] cystatin C GFR was found to be predictive of Acute Kidney Injury (AKI) 48 hours before its occurrence, hence an early marker of AKI. In patients with liver cirrhosis and normal creatinine levels, cystatin C has proven to be a useful marker for predicting hepatorenal syndrome and survival [21].

Neutrophil Gelatinase-Associated Lipocalin (NGAL) is a small

protein produced by several organs such as the kidney, lung, stomach and colon [22]. In the kidney, NGAL is synthesized in the renal tubular epithelial cells and its expression has been shown to become markedly elevated following ischemic or nephrotoxic insults [23]. In animal models, NGAL has been detected within two hours following the onset of ischemia [23]. In clinical studies, NGAL has been shown to predict AKI at an early stage, determine the severity of AKI, and differentiate acute tubular necrosis (ATN) from HRS [24-26]. In a study by Fagundes, et al. [27] patients with ATN had urinary NGAL levels that were markedly higher when compared to patients with pre-renal azotemia due to volume depletion, Chronic Kidney Disease (CKD) and HRS. Among HRS patients the highest values were found in those with HRS associated with infections, followed by classical type 1 and type 2 HRS [27]. Other markers such as interleukin-18 (IL-18), kidney injury molecule -1 and liver fatty acid-binding protein are elevated in liver disease patients with kidney injury due to ATN [28-30]. However, due to insufficient evidence, systematic use of circulating NGAL, circulating cystatin C, urinary NGAL, and cystatin C-based clearance are not recommended for early diagnosis of AKI in cirrhosis.

Recent studies have shown that plasma protein profiles including osteopontin and Tissue Inhibitor of Metalloproteinase (TIMP-1) may improve prediction of pre-liver transplant kidney injury recovery after liver transplant [31,32]. Further validation with prospective studies are warranted to evaluate the value in perioperative management and decision making.

### Epidemiology

Cirrhosis is a global burden and is associated with high morbidity and mortality [33]. According to the Centers for Disease Control (CDC), chronic liver disease and cirrhosis were responsible for 38,000 deaths in 2014, ranking it as the twelfth most common cause of death in the United States (US) [34]. Approximately 60 percent of individuals will develop ascites within a period of 10 years following the diagnosis of cirrhosis [35]. HRS occurs frequently in cirrhotic patients with ascites, generally males in their sixth or seventh decade [36,37].

Over the past 20 years, the incidence and prevalence of HRS has decreased due to medical advancements in cirrhosis management. Gines et al. estimated the incidence of HRS to be 18 percent at one year and 39 percent in five years in patients with cirrhosis and ascites [38]. A most recent study by Montoliu et al. [39] determined that 49

percent of cirrhotic patients with ascites developed functional renal impairment with 7.6 percent of cirrhotic patients developing HRS. The prevalence of HRS in patients with cirrhosis and ascites ranges from 13 to 45.8 percent [36]. However, the current definition excludes the coexistence of other forms of acute and chronic kidney disease, failing to identify hepatorenal pathology in a larger subset of patients.

**Pathophysiology**

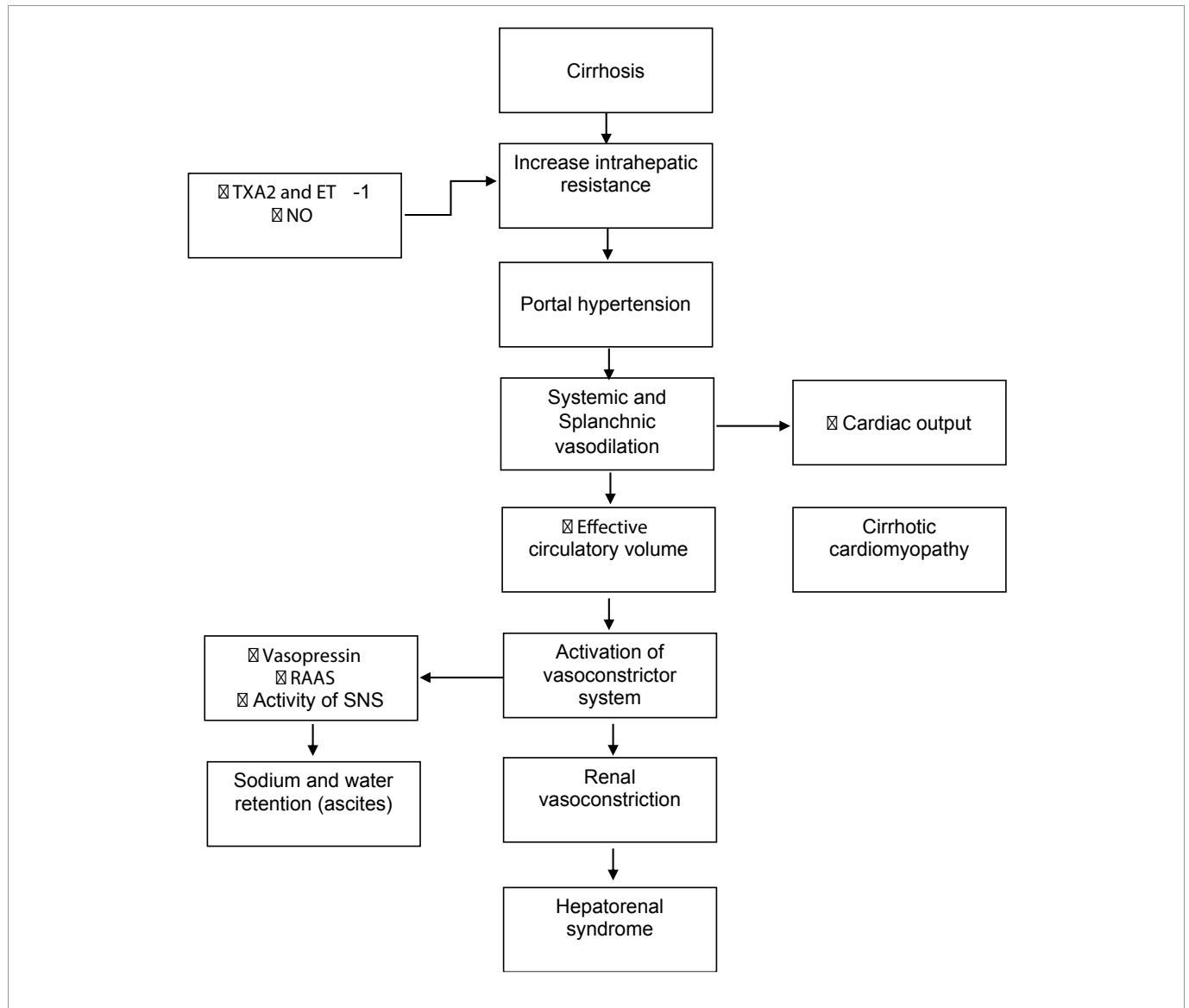
The pathogenesis of HRS is complex and not completely understood. Several proposed mechanisms contribute to the development of HRS, but the arterial vasodilation theory is the most widely accepted (Figure 1).

Cirrhosis is the irreversible fibrosis of the liver caused by hepatitis B virus and hepatitis C infection, alcoholism, and nonalcoholic steatohepatitis. Injury from toxins result in inflammation and destruction of the liver parenchyma leading to structural and dynamic changes including fibrosis, nodules, angiogenesis and

vascular occlusion [4,40]. Formation of nodules, granulomas and inflammation lead to centrilobular venule compression and a reversible increase in intrahepatic resistance. Nitric Oxide (NO) is one of the major vasodilator molecules that contributes to the increase of intrahepatic vascular resistance. In cirrhotic livers, NO production and bioavailability is significantly diminished by two mechanisms. First the NO synthesizing enzyme endothelial NO synthase (eNOS) is inhibited by negative regulators(caveolin-1); which are up-regulated in cirrhosis; hence decreasing NO production. During cirrhosis, increased superoxide radicals spontaneously react with NO, thereby decreasing NO bioavailability as a vasodilator [41].

In cirrhosis, not only are vasodilators decreased, but vasoconstrictors such as thromboxane A2 and endothelin-1 (ET-1) are increased. Increased ET-1 production activates hepatic stellate cells which facilitates the development of portal hypertension [42].

In early stages of the disease, the heart attempts to compensate by increasing its rate and cardiac output, which temporarily



**Figure 1:** Pathogenesis of hepatorenal syndrome  
 TXA2: Thromboxane 2, ET-1: Endothelin-1, NO: Nitric Oxide, RAAS: Renin Angiotensin-Aldosterone System, SNS: Sympathetic Nervous System

maintains the effective arterial blood volume. As cirrhosis progresses, the heart's ability to compensate declines resulting in cirrhotic cardiomyopathy [43]. This condition is characterized by impaired myocardial contractility with systolic and diastolic dysfunction and electromechanical abnormalities. Electrophysiological changes occur (prolonged QT interval) and the ability of the heart to respond to inotropic and chronotropic stimuli is reduced; thus contributing to a reduction in kidney perfusion [44]. Cardiac output  $<1.5$  L/min/m<sup>2</sup> has been associated with an increased risk for HRS and poor survival [45].

As the effective arterial blood volume declines, compensatory neurohormonal vasoconstrictor systems such as the Renin-Angiotensin-Aldosterone System (RAAS), the sympathetic nervous system (SNS) and arginine vasopressin are stimulated [46]. These combined mechanisms lead to renal vasoconstriction and sodium and water retention that causes ascites, hyponatremia and edema [2]. Renal vasoconstriction and a reduced Mean Arterial Pressure (MAP) lead to hypoperfusion of the kidneys and further renal impairment. As the cirrhosis advances and circulatory dysfunction progresses the baroreflex sensitivity (BRS) in cirrhotic patients is affected, the renal perfusion cannot be maintained and HRS occurs [47].

Cortisol also plays an important role in the hemodynamic hemostasis and in the pathogenesis of HRS. Patients with cirrhosis may develop relative adrenal insufficiency and have a higher risk of developing type 1 HRS versus patients with cirrhosis and normal adrenal function [48]. The potential role of cortisol is likely related to inadequate circulatory response to stress.

Current evidence has demonstrated that cirrhosis is characterized by a systemic inflammatory state that could be the triggering factor of HRS. The presence of Systemic Inflammatory Response Syndrome (SIRS) with or without infection has shown to be an independent prognostic factor in patients with cirrhosis and acute functional renal failure [40]. Bacterial translocation in individuals with advanced cirrhosis may also prompt an inflammatory response that leads to the release of proinflammatory cytokines such as tumor necrosis factor alpha (TNF- $\alpha$ ) and nitric oxide resulting in further splanchnic dilation [49].

Shah, et al. [50] using an animal model of cirrhosis demonstrated increased Toll-like Receptor 4 (TLR4) expression in the proximal renal tubules. The upregulation of TLR4 receptor is most likely related to increased gut bacterial translocation. Treatment with norfloxacin resulted in an attenuation of renal TLR4 expression and improvement of renal function tests, in addition to a significant reduction of HRS [51]. These findings suggest that cirrhosis is more than just a vasomotor disorder.

### Precipitating factors

The onset of renal failure in HRS is typically insidious. HRS can be precipitated by an acute insult, such as a bacterial infection (spontaneous bacterial peritonitis), volume depletion, and gastrointestinal bleeding [52]. Spontaneous Bacterial Peritonitis (SBP) can trigger HRS primarily in those with underlying renal impairment. SBP is an infection of the ascitic fluid that occurs in the absence of an intra-abdominal source. Interestingly, antibiotics alone do not lead to improvement in renal function in two thirds of patients with HRS type 1 associated with infections [53]. On the other hand, diuretics do not cause HRS, but diuretics can cause azotemia, especially if fluid is removed too aggressively in those without peripheral edema. Diuretic-

induced azotemia improves with the discontinuation of therapy and fluid repletion while HRS frequently worsens, even after diuretics are discontinued [10]. Certain medications such as Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) can also precipitate HRS in those with borderline renal function [54].

### Differential diagnosis

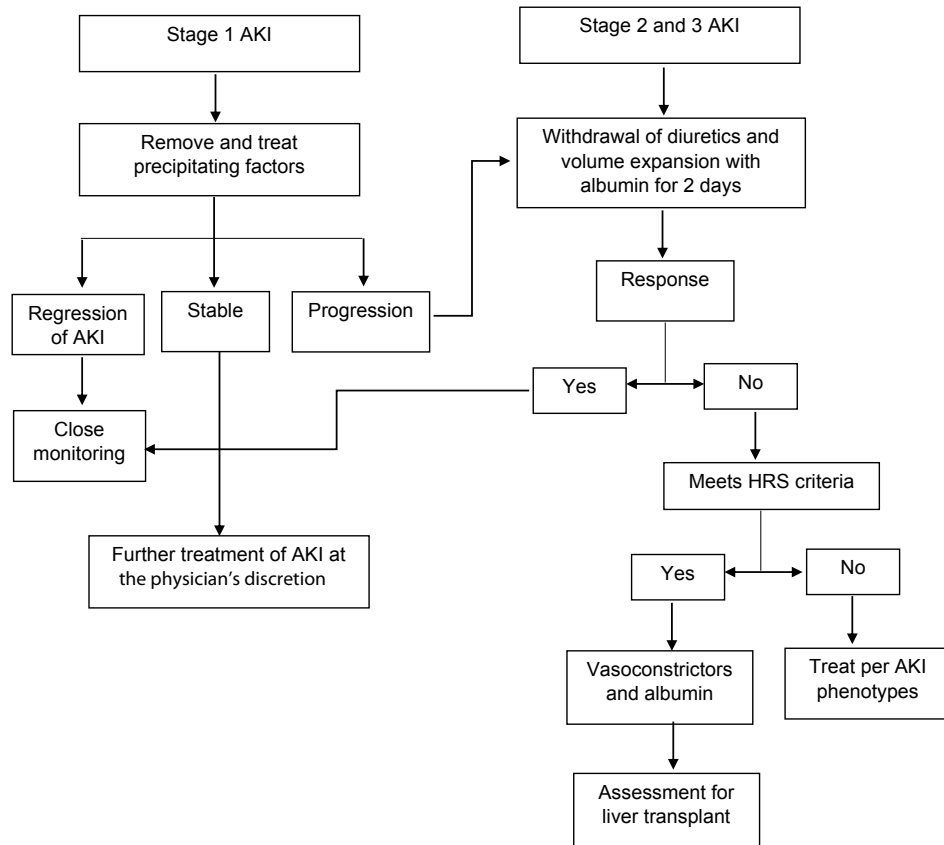
HRS is a diagnosis of exclusion and other potential etiologies of acute or subacute kidney injury such as ATN and prerenal disease need to be ruled out. Differentiating HRS from these conditions is clinically relevant given the marked difference in prognosis. ATN and most etiologies of prerenal disease are typically reversible. Prognosis in HRS (particularly type 1) is poor with the majority of patients dying within weeks of the onset of renal injury [38].

Acute tubular necrosis is a rapid rise in serum creatinine as opposed to a gradual increase of serum creatinine in HRS. Patients with cirrhosis may develop ATN post aminoglycoside therapy, radiocontrast administration, or low effective circulating plasma volume as seen in sepsis or bleeding. It remains unclear if prolonged renal ischemia in HRS can lead to ATN [1]. Some of the conventional laboratory methods used to differentiate prerenal disease from ATN may not be helpful in those with hepatic disease. ATN usually correlates with a FENa above two percent and granular and epithelial cell casts in the urine sediment. However, the FENa may remain below one percent in cirrhotic patients who develop ATN due to the persistent renal ischemia induced by the hepatic disease [55]. The urinalysis may also be misleading since epithelial and granular cell casts may be observed with marked hyperbilirubinemia alone; hence not diagnostic of ATN. HRS is diagnosed following the cessation of potential nephrotoxins and a fluid challenge.

### TREATMENT

The ideal therapy for HRS is improvement of liver function from either recovery of alcoholic hepatitis, treatment of decompensated hepatitis B with effective antiviral therapy, recovery from acute hepatic failure, or liver transplantation. The ability of liver function to improve from alcohol abstinence and effective antiviral therapy of hepatitis B is significant [56]. However, when improvement of liver function is not possible in the short term, medical therapy should be initiated to reverse the AKI associated with HRS. Angeli, et al. proposed a new algorithm for the management of AKI in patients with cirrhosis based on the new ICA-AKI diagnostic criteria (Figure 2). Recommendations concerning medical therapy also rely on several factors, including: Intensive Care Unit (ICU) admission, availability of medications (national and regional variability), and liver transplant candidate suitability.

In patients with HRS who are admitted to the ICU, several studies support initial management with norepinephrine in conjunction with albumin rather than other medical treatments. Norepinephrine is given intravenously as a continuous infusion with the goal of raising the MAP by 10 mm Hg and albumin is given for at least two days as an intravenous bolus [57]. Intravenous vasopressin may also be effective. Vasopressin and its analogs (ornipressin and terlipressin) should reduce splanchnic vasodilation [58]. Although the efficacy of terlipressin and norepinephrine appear similar, adverse effects (mainly abdominal pain, chest pain, or arrhythmia) are more commonly seen with terlipressin. Additionally, the cost of terlipressin therapy is more than three times the cost of norepinephrine therapy [59].



**Figure 2:** Proposed algorithm for the management of Acute Kidney Injury (AKI) per the International Club of Ascites (ICA) classification that combines Kidney Disease: Improving Global Outcomes KDIGO) criteria and conventional criteria in patient with cirrhosis and ascites. Modified from original algorithm by Angeli P, et al. Gut April 2015. HRS: Hepatorenal syndrome

In patients with HRS who are not admitted to the ICU, management varies on accessibility to certain drugs such as terlipressin. Initial treatment with terlipressin in combination with albumin is superior as oppose to midodrine, octreotide, and albumin [60]. However, terlipressin has not been approved by the Federal Drug Association (FDA) for the use in the United States. A recent randomized controlled trial showed that terlipressin plus albumin were significantly more effective than midodrine and octreotide plus albumin in the treatment of HRS. Terlipressin significantly increased the rate of complete response (defined as a serum creatinine  $\leq 1.5$  mg/dL at 14 days) compared with midodrine and octreotide. In addition, survival and treatment related adverse events did not differ between the two groups [60]. In a recent meta-analysis, terlipressin therapy significantly reduced mortality compared with albumin alone or no therapy (RR 0.76, 95% CI 0.61 to 0.95) and increased the proportion of patients who achieved reversal of HRS, however terlipressin also increased the risk of cardiovascular adverse events (RR 7.26, 95% CI 1.70 to 31.05) [61].

In patient with cirrhosis and HRS, terlipressin has been used either as a continuous intravenous infusion or as intravenous boluses. In a recent randomized controlled trial involving 78 subjects with decompensated cirrhosis and type 1 HRS, terlipressin (via a continuous intravenous infusion) demonstrated a significantly lower rate of adverse events (35.29% versus 62.16%,  $p < 0.025$ ) and was shown to be

more effective at lower doses as compared to intravenous boluses [62]. In the US, terlipressin therapy is not available and an initial treatment with a combination of midodrine, octreotide, and albumin is recommended. Midodrine is a systemic vasoconstrictor, and octreotide is an inhibitor of endogenous vasodilator release and theoretically combined therapy improves renal and systemic hemodynamics [63]. In a retrospective study that included sixty patients with HRS, therapy with midodrine and octreotide was associated with significantly lower mortality (43 versus 71 percent) and a significantly higher proportion of patients who had resolution of HRS (40 versus 10 percent) [64].

In highly selected patients who fail to respond to medical therapy with the above regimens, who are awaiting liver transplantation, and who have no contraindications, Transjugular Intrahepatic Portosystemic Shunt (TIPS) can be successful.

However, the procedure is associated with numerous complications including: increase in the rate of hepatic encephalopathy, worsening liver function, bleeding and contrast induced renal damage. There may also be a delayed improvement in renal function. Large-scale studies on the effects of TIPS with HRS are lacking [65]. The goal of medical therapy or TIPS in patients with HRS is reversal of the AKI. However, an increase in MAP with alpha adrenergic agonists and somatostatin analogs is significantly associated with a decrease

in serum creatinine [66]. A two-week therapy with norepinephrine, terlipressin, or octreotide is recommended. However, if renal function failed to improve, these drugs can be considered futile [67]. If partial improvement in renal function is observed, therapy may be continued up to a month. To date, no clinical data is available to support this practice.

In patients who fail to respond to medical therapy, develop severely impaired renal function, are not suited candidates for TIPS, and are not candidates for liver transplantation or have a reversible form of liver injury and are expected to survive, Renal Replacement Therapy (RRT) can be offered as a bridge to liver transplantation or liver recovery. In one retrospective, single-center study, 30 percent of patients who required dialysis survived to liver transplantation [68]. Hemodialysis is frequently difficult to perform in patients with HRS since decompensated hepatic function is associated with hemodynamic instability.

To date, there are only a few treatment options available for HRS. For this reason, artificial liver support therapies for HRS may be crucial in the management of HRS. Extracorporeal support systems in liver disease can be further classified as cell and non-cell based systems [69]. Extracorporeal Albumin Dialysis (ECAD) is a non-cell based system that uses a cell-free, albumin containing dialysate that is re-circulated and perfused via charcoal and anion exchanger columns [11]. ECAD facilitates the removal of albumin-bound substances.

Molecular Adsorbent Recirculating System (MARS) is a type of ECAD that removes various types of hepatotoxins and is currently used in patients with hepatic failure in the ICU [70]. MARS has shown to improve hepatic encephalopathy, but it has failed to demonstrate a survival benefit in patients with acute on chronic liver disease [71]. In a randomized controlled trial assessing the impact of MARS on HRS, the length of survival in the MARS group was significantly higher when compared with the control group ( $25.2 \pm 34.7$  days versus  $4.6 \pm 1.8$  days,  $p < 0.05$ ) [72]. No difference was seen in mortality by 3 months. Further studies are needed to elucidate the use of MARS as a bridge therapy to liver transplantation.

Several other drugs have been used in the treatment of HRS, such as N-acetylcysteine, misoprostol and angiotensin-converting enzyme inhibitors. None of these approaches were shown to be beneficial, and are not recommended.

Peritoneovenous shunt is rarely used because of an appreciable rate of complications and the lack of evidence that peritoneovenous shunting prolongs patient survival [73].

Serelaxin is a recombinant form of the human peptide hormone relaxin-2. In rat models of cirrhosis, it has shown to improve renal blood flow and oxygenation via reversal of endothelial dysfunction and increased activation of NO signaling in the kidney [74]. In a phase 2 randomized open-label parallel-group study in patients with alcohol related cirrhosis and portal hypertension, serelaxin infusion induced a significant increase in renal arterial blood flow by 65 percent (95% CI 40%, 95%,  $p < 0.001$ ) from baseline. Serelaxin administration was safe, well tolerated, and no adverse effects on systemic blood pressure or hepatic perfusion were reported [75]. This suggest the therapeutic potential of selective renal vasodilation as a new treatment for renal dysfunction in cirrhosis.

Liver transplant is the only treatment for HRS that improves long-term survival. Liver transplantation can correct the abnormality of renal blood flow, but it may be gradual. Patients with HRS have

a better survival compared to transplant patients without HRS. Approximately 80% of type 1 HRS patients survive for 5 years post-transplant [76]. Treatment with vasoconstrictors does not appear to affect outcomes of liver transplant. In a study evaluating the effects of terlipressin plus albumin versus placebo plus albumin on transplant outcomes, no differences were found in survival of transplant recipients [67]. Combined liver-kidney transplant has been selected for some patients with HRS, however, the procedure may represent an ethical challenge to organ allocation [77].

## PREVENTION

Hepatorenal syndrome often develops in patients with systemic bacterial infection and/or severe alcoholic hepatitis. Several therapies have shown to be effective in preventing the development of HRS.

In patients with SBP, albumin infusion has been reported to reduce renal impairment and mortality. Intravenous albumin (1.5 g/kg) should be administered at the time of diagnosis of infection with an additional dose of albumin (1 g/kg) given on day three of antibiotic treatment. A meta-analysis including four trials of two hundred and eighty-eight patients evaluated the impact of albumin infusion (in addition to antibiotics) on renal impairment and mortality in patients with SBP. The study showed that albumin infusion was associated with a significant decrease in the incidence of renal impairment (8 versus 31 percent) with a pooled odds ratio of 0.21 (95% CI, 0.11-0.42). A reduction in mortality in patients who received albumin as compared to controls was also significant (16 versus 35 percent). These recent data support the use of albumin infusion in patients with SBP [78].

The most common precipitating factor for HRS is spontaneous bacterial peritonitis. In a randomized controlled trial of patients with cirrhosis and low protein ascitic levels  $<1.5$  g/dL with advanced liver failure (Child-Pugh score  $>9$  points and serum bilirubin  $>3$  mg/dL); or impaired renal function (serum creatinine  $>1.2$  mg/dL, blood urea nitrogen (BUN)  $>20$  mg/dL, or serum sodium  $<130$  mEq/L), primary prophylaxis with norfloxacin was shown to reduce the incidence of SBP. Norfloxacin significantly decreased the one-year probability of developing SBP (7 versus 61 percent) and hepatorenal syndrome (28 versus 41 percent). Norfloxacin also proved to significantly improve the three-month (94 versus 62 percent) and one year (60 percent versus 48 percent) probability of survival compared to placebo [51]. These beneficial effects could be related to the prevention of bacterial translocation and reduction of pro-inflammatory burden. Norfloxacin has a great impact in the clinical course of patients with advanced cirrhosis delaying the development of HRS.

Rifaximin is a minimally absorbed oral antibiotic that is concentrate in the gastrointestinal tract. Long-term use of rifaximin has been associated with reduced risk of variceal bleeding, hepatic encephalopathy, SBP and HRS in patients with alcohol-related decompensated cirrhosis [79]. A lower incidence rate ratio of AKI and HRS, in addition to a decrease risk of requiring RRT has also been shown in patients with cirrhosis and rifaximin when compared to matched control cases [80]. Randomized controlled trials are required to evaluate the effects of rifaximin in the general population of cirrhotic patients.

## PROGNOSIS

Overall, the mortality of patients with liver failure is considerably worse if they develop HRS [81]. Without therapy, most patients

die within weeks of the onset of the renal impairment. In turn, the outcome of patients with HRS, as well as recovery of kidney function, is strongly dependent upon reversal of the hepatic failure [82]. The rate of recovery of kidney function following recovery of liver failure is uncertain; reported rates are affected by varying pre-transplant kidney function and differences over time in indications for dialysis and ineligibility for liver transplantation. However, a significant proportion of patients who have progressed to dialysis and survive to receive a liver transplant do recover kidney function [83].

## CONCLUSION

Hepatorenal syndrome is a complication of end-stage cirrhosis characterized by intense renal vasoconstriction and a markedly decreased glomerular filtration. HRS is not associated with structural changes and is fully reversible with liver transplantation. Reversal or improvement may be observed with vasoconstrictors such as terlipressin and the reversal of endothelial dysfunction by serelaxin. It is crucial to differentiate HRS from other AKI phenotypes since the therapeutic approach may vary. Currently available biomarkers may be able to predict the progression and mortality in patients with AKI. A combination of functional and structural biomarkers may direct prompt therapy in HRS.

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