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Review Article

Hepatorenal Syndrome- An Update

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Abbreviations: HRS-Hepatorenal Syndrome; AKI-Acute Kidney Injury; CKD-Chronic Kidney Disease; GFR- Glomerular Filtration Rate; EABV-Effective Arterial Blood Volume; RAI-Relative Adrenal Insufficiency; DAMP-Damage Associated Molecular Pattern; PAMP-Pathogen Associated Molecular Pattern; TLR-Toll-Like Receptor; AKIN-Acute Kidney Injury Network; RIFLE-Risk, Injury, Failure, Loss, and End stage kidney disease; KDIGO-Kidney Disease Improving Global Outcome; ICA-International Club of Ascites; NAKI-Non-Acute Kidney Injury; ATN-Acute Tubular Necrosis; NGAL-Neutrophil Gelatinase Associated Lipocalin; FeNa-Fractional Excretion of Sodium; MAP-Mean Arterial Pressure; RRT-Renal Replacement Therapy; SBP-Spontaneous Bacterial Peritonitis; TIPS-Transjugular Intrahepatic Portosystemic Shunt; sCr- Serum Creatinine; SLK- Simultaneous Liver-kidney Transplant

Introduction

Advanced liver disease is characterized by portal hypertension, increased splanchnic blood flow, hyperdynamic circulation with increased cardiac output, deranged coagulation profile, and decreased central blood volume. Renal dysfunction is a common, life-threatening complication arising from the complex pathophysiological changes occurring in advanced liver disease [1,2], which could be prerenal, intrarenal, or post renal. Patients with cirrhosis develop a specific phenotype of renal dysfunction that has been termed Hepatorenal syndrome (HRS). HRS has been defined as renal dysfunction that occurs because of reduced renal perfusion, due to hemodynamic alterations in arterial circulation, as well as overactivity of the endogenous vasoactive systems [3]. Definition, terminology, and classification of HRS have evolved considerably over time due to various changes in staging and diagnosis of Acute Kidney Injury (AKI).

Pathophysiology

Pathophysiology of HRS is based upon observational studies in humans. Inducing liver injury in animal models with carbon tetrachloride and thioacetamide leads to kidney injury as well, hence similar reproducible studies in animal models are lacking. HRS has been termed as a functional dysfunction based on [4]:

1) Absence of significant renal histological changes in post-mortem examinations.
2) Reversibility of renal dysfunction by liver transplant.
3) Classical images of HRS showing extreme but reversible renal vasoconstriction.
4) Ability to use kidneys from patients with HRS as grafts for renal transplantation.

All clinical and histopathological observations point to uncompensated circulatory dysfunction as the hallmark of HRS. Other major factors include systemic inflammation, cirrhotic cardiomyopathy, and adrenal insufficiency.

Circulatory Dysfunction

Splanchnic vasodilatation occurs due to increased production of vasodilators like nitric oxide, carbon monoxide, prostacyclins, and endocannabinoids [5]. This leads to hemodynamic changes triggered by elevated intrahepatic vascular resistance causing the kidney functions to decline in cirrhosis.

Initial stages of the disease are characterized by moderate splanchnic vasodilation and slightly reduced Systemic Vascular Resistance (SVR), which is balanced by an increase in cardiac output. With advanced disease, vasodilation further worsens, and cannot be balanced by the increase in cardiac output, leading to decrease in Effective Arterial Blood Volume (EABV) and systemic arterial pressure [6].

Decrease in EABV and systemic arterial pressure results in activation of Systemic vasoconstrictor pathways, such as the Renin-Angiotensin-Aldosterone System (RAAS), sympathetic nervous system, and arginine vasopressin leading to sodium retention, impaired solute-free water excretion, and renal vasoconstriction, and, consequently, reduced renal blood flow [7].

As liver disease proceeds there is a degree of reduction of cardiac output due to development of cirrhotic cardiomyopathy, thus suggesting a role of cirrhotic cardiomyopathy in the pathogenesis of HRS [8].

In early stages of liver disease, the kidneys can maintain adequate glomerular filtration rate (GFR) by causing vasodilation of afferent arteriole by vasodilatory renal prostaglandins E2 and

I2 despite reduced renal blood flow. As the disease progresses there is a disruption of balance leading to reduced vasodilatory prostaglandins and intense kidney vasoconstriction leading to compromised kidney perfusion thus decreasing the GFR, ultimately leading to the development of HRS **(Figure 1)**.

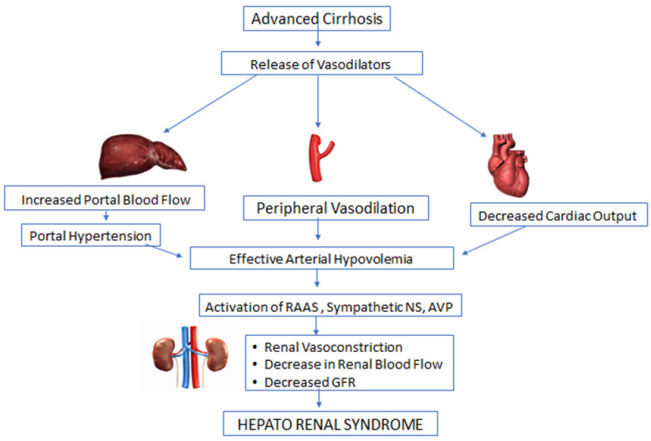

Figure 1: Pathophysiology of HRS.

Systemic Inflammation

Recently, the concept of systemic inflammatory disease in cirrhosis has emerged, with growing evidence that inflammation plays a role in HRS [9].

Two diverse groups of molecules are responsible for the inflammatory response in cirrhotic patients: Pathogen-Associated Molecular Patterns (PAMPs) and damage-associated molecular patterns (DAMPs) [10]. PAMPs are bacterial products, such as lipopolysaccharide, flagellin, and nigericin, arising from translocation of gut bacteria, whereas DAMPs are released from injured hepatocytes, including high mobility group protein B1, heat shock protein, adenosine triphosphate, and double stranded genomic DNA. Without any apparent active bacterial infection, PAMPs and DAMPs drive inflammation [11] through release of pro-inflammatory cytokines by activating toll-like receptors (TLRs), leading to an increased arterial production of vasodilators (such as nitric oxide) and, consequently, further reducing the SVR and EABV **(Figure 2)**.

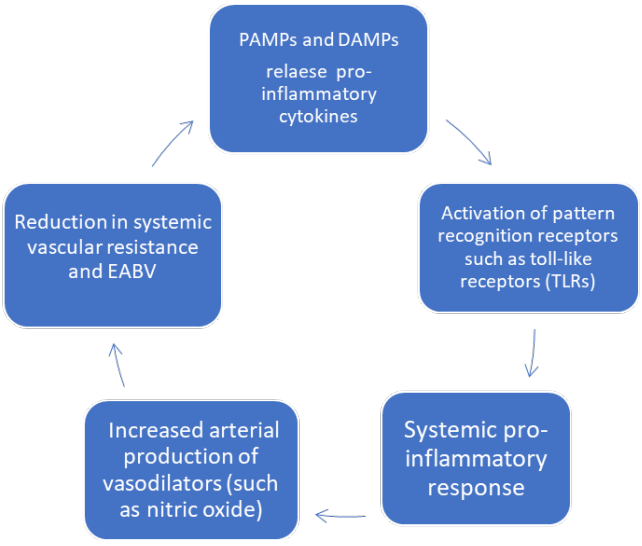

Figure 2: PAMP and DAMP's driving systemic inflammation and peripheral vasodilatation.

Hepato-Adrenal Syndrome

Relative Adrenal Insufficiency (RAI) or hepatoadrenal syndrome is present in a subset of patients with decompensated cirrhosis [12]. RAI decreases arterial pressure, increases serum concentrations of renin and noradrenaline and increases risk of HRS [13].

Pathophysiology of RAI is not fully understood but may be due to exhaustion of substrates for synthesis of cortisol and impairment of the hypothalamus-pituitary axis by circulating PAMPs and pro-inflammatory cytokines [14].

Glucocorticoid replacement therapy has been shown to improve patients with RAI and septic shock but a similar effect for effective prevention and treatment of HRS with RAI has still not been proven [15].

Definition and Classification

Impairment of renal function has been determined by an increase in serum creatinine (sCr). However, it is not the best marker for determining renal injury in patients with cirrhosis due to [16]:

1) Impaired hepatic production of creatine (precursor of creatinine)
2) Reduced muscle mass
3) Tubular secretion of creatinine
4) Inaccurate measurement of creatinine by calorimetric methods in the presence of elevated bilirubin

Despite the caveats, serum creatinine remains the most widely available and used assay for GFR estimation in patients with cirrhosis. Also, in dynamic conditions like acute renal failure, serial changes in serum creatinine and urine output are a better reflection of renal function.

The definition of acute renal failure has evolved over the past two decades with a better understanding of its pathophysiology and treatment outcomes. The RIFLE (risk, injury, failure, loss, and end stage kidney disease) classification was the earliest definition coined at the Consensus Conference of the Acute Dialysis Quality Initiative Group in 2002. It defined renal injury in term of percentage changes in serum creatinine or GFR, a decrease in urine output, or both [17]. In 2005 the term acute kidney injury (AKI) was proposed by the second multidisciplinary collaborative forum (AKIN) to include the entire spectrum of acute renal failure. Absolute increase in serum creatinine of 0.3 mg/dL within 48 hours of baseline was added as part of the definition of AKI [18].

Kidney Disease Improving Global Outcome (KDIGO) organization in 2012 defined AKI as [19]

1) Increase in serum creatinine(sCr) by at least 0.3 mg/dL (26.5 μmol/L) within 48 hours.
2) Increase in serum creatinine(sCr) to at least 1.5 times baseline within the previous week.
3) Urine and or volume below 0.5 mL/kg/h for six hours.

The definition of HRS has similarly evolved over the past two decades aligning with changes made according to RIFLE, AKIN, and KIDIGO criteria.

Hepatorenal syndrome is a diagnosis of exclusion and other potential etiologies of acute or subacute kidney injury in patients with liver disease should be ruled out before a diagnosis of HRS is made.

In 1990 HRS was defined by the international ascites club as an increase in sCr of at least 50% from baseline to a final concentration of at least 1.5 mg/dL in cirrhotic patients. They further classified HRS into two clinical: Type 1 and Type 2 [20].

Studies demonstrated that diagnosis of AKI in patients with cirrhosis, based on an absolute increase in sCr by at least 0.3 mg/dl or 50% from baseline, led to earlier identification of patients at increased risk of more severe disease, prolonged hospital stays, and ICU admissions [21,22]. This led the ICA to issue a revised set of consensus recommendations, without the cut-off value of sCr ≥1.5 mg/dl, thus ensuring early diagnosis and faster treatment. The lowest value of sCr in the past three months can be taken as baseline to avoid diagnostic delays. The ICA consensus updated the term hepatorenal syndrome (HRS) type 1 and renamed it HRS-AKI. HRS-AKI can be diagnosed even when the sCr is below 2.5 mg/dL. The terminology HRS type 2 was removed and replaced by HRS-NAKI **(Table 1)** [23].

Differential Diagnosis

Patients with liver disease are also predisposed for development of Acute Tubular Necrosis (ATN) and as the diagnostic criteria of HRS does not rule out the presence of tubular damage, ATN cannot be confidently excluded with the above criteria and may coexist along with HRS in patients with liver disease.

Urinary sodium (>40 mEq/L), fractional excretion of sodium (FeNa >2%), and low urine osmolality (<400 mOsm/L) are features suggestive of ATN. However, these parameters are not good predictors of ATN in patients with cirrhosis and ascites as [24]:

- Urinary sodium can be elevated secondary to diuretics, in patients with large-volume ascites.
- Low FeNa has also been observed in patients with biopsy-proven ATN.

Hence urinary sodium and FeNa have been excluded from diagnostic criteria of HRS.

Urine biomarkers of tubular injury have long been studied to differentiate between ATN and AKI-HRS in patients with cirrhosis. Biomarkers include [25,26]:

- Tubular proteins released during cell damage→ N-acetyl-β-D-glucosaminidase, α-glutathione S transferase)
- Tubular proteins up-regulated by injury →kidney injury molecule-1, neutrophil gelatinase associated lipocalin (NGAL), liver-type fatty acid binding protein
- Plasma proteins with diminished tubular reabsorption → α-1-microglobulin, β-2-microglobulin, retinol binding protein
- Inflammatory markers → Interleukin-18

NGAL has shown the greatest diagnostic accuracy in differentiating ATN from AKI-HRS.

Urinary NGAL performs better than plasma NGAL when measured after a two-day volume challenge recommended in the management of AKI. The urinary NGAL cut-off value of 220 µg/g of creatinine obtained after the fluid challenge has the highest diagnostic accuracy for ATN [27].

Table 1: Comparison of old (1990) vs new definition (2015) of HRS.

OLD DEFINITION	**NEW DEFINITION**
HRS TYPE 1	**HRS AKI**
• Cirrhosis with ascites • Doubling of initial serum creatinine to a concentration of at least 2.5 mg/dL or a 50% reduction in less than two weeks	• Cirrhosis, acute liver failure, acute on chronic liver failure with ascites • Absolute increase in sCr ≥0.3 mg/dl within 48 h and/or • Urinary output ≤ 0.5 ml/kg B.W. ≥6 h or • Percent increase in sCr ≥50% using the last available value of outpatient sCr within 3 months as the baseline value
• No response to withdrawal of diuretics in kidney function after volume expansion with intravenous albumin 20-25%(1 g/kg/day maximum 100gm) for two days • Absence of shock, • No current or recent treatment with nephrotoxic drugs, • No sign of kidney injury. o Absence of proteinuria >500 mg/day o Normal renal ultrasonography o Urine red cell excretion of fewer than 50 cells per high power field	
HRS TYPE 2	**HRS- NAKI**
Renal failure progression that does not meet the criteria for type I	**HRS – AKD** • eGFR <60 ml/min per 1.73 m2 for <3 months in the absence of other (structural) causes Percent increase in sCr <50% using the last available value of outpatient sCr within 3 months as the baseline value
	HRS – CKD • eGFR <60 ml/min per 1.73 m2 for ≥3 months in the absence of other (structural) causes

Table 2: Staging of AKI according to international ascites club [23].

STAGING OF AKI	
STAGE I	Increase in sCr ≥0.3 mg/dL. or increase in sCr ≥1.5-fold to twofold from baseline **STAGE 1A →** sCr <1.5 mg/dL **STAGE 1B →** sCr ≥1.5 mg/dL
STAGE II	Increase in sCr at least twofold to threefold from baseline
STAGE III	Increase in sCr at least threefold from baseline or sCr ≥4.0 mg/dL with an acute increase ≥0.3 mg/dL or initiation of renal replacement therapy

Prevention

Acute impairment of renal function is a common, life threatening complication in patients with cirrhosis,1,2 so it is imperative to take appropriate steps to prevent development of Hepatorenal Syndrome (HRS) once a patient is diagnosed with cirrhosis.

Preventive strategies:

1. Minimize hemodynamic and circulatory dysfunction,
2. Avoid agents that precipitate AKI,
3. Reverse acute decompensation,
4. Delay progression of disease in compensated patients.

Hyponatremia, liver size, increased plasma renin activity, severity of ascites, as well as acute hemodynamic changes associated with large volume paracentesis, are important precipitant factors for development of HRS [28,29]. 30% of patients with spontaneous bacterial peritonitis (SBP) develop HRS emphasizing the need for antibiotic prophylaxis in such cases. Antibiotic prophylaxis in patients at risk of SBP not only prevents the development of HRS but also reduces overall mortality [30].

Albumin plays an important role in delaying the development and improving the overall survival in patients with HRS (1.5gm/kg on day 1 followed by 1gm/kg on day 3). Albumin along with antibiotics in patients with SBP improves the circulatory functions [31]. Along with its role as a volume expander albumin also has antioxidant and anti-inflammatory properties that help stabilize endothelial functions. It binds to endotoxins and inactivates them which improve circulation and kidney function [32]. Albumin administration following large volume paracentesis prevents hypotension and hyponatremia, both of which can precipitate HRS [33]. Long-term use of weekly Albumin has been shown to improve overall survival and reduce incidence of HRS [34]. However, it is expensive and may cause volume overload.

Management

Treatment of HRS should begin as soon as the diagnosis is confirmed as early treatment leads to higher reversal and better outcomes. Reversal of HRS is defined by at least 50% reduction in sCr to a value below 1.5gm/dl. The updated diagnostic criteria with removal of minimum serum creatinine criteria aids in earlier diagnosis and treatment, rather than waiting for sCr to reach 2.5 g/dl. Treatment of HRS depends on the stage of AKI **(Table 2)**. Initial management of HRS starts with a fluid

Table 3: Dosing regimens, side effects, goals of treatment of vasoconstrictors for HRS.

DRUG	DOSING	SIDE EFFCETS
Terlipressin	I.V boluses → 0.5- 1 mg every 4-6 hours to a to maximum dose of 2 mg every 4 hours in cases of nonresponse. Expected response → Decrease of sCr by 25%. Duration of Treatment → Till complete response or 14 days in non-responders. Continuous infusion → 2 mg – 12 mg / day depending on response	Diarrhea, abdominal pain, peripheral ischemia, myocardial infarction, mesenteric ischemia, pulmonary edema Lesser side effects with continuous infusion (Patients should be monitored at least twice daily for signs of ischemia in skin, tongue, and fingers)
Noradrenaline	I.V infusion → 0.5- 3 mg/h Expected response – 10mm hg increase in MAP Duration of Treatment - Till HRS is resolved or maximum 14 days	Nausea, vomiting, anxiety, cardiac dysrhythmias Requires to be administered through a central line and monitoring in ICU.
Midodrine	7.5-15 mg orally T.I.D Expected response – 10mm hg increase in MAP	Bradyarrhythmias, paresthesia, abdominal pain,
Octreotide	100-200 µg S.C T.I.D	Diarrhea, cholelithiasis, hyperglycemia

challenge of 20-25% albumin 1m/kg/day for 2 days regardless of the stage of AKI and withdrawal of diuretics, beta-blockers and other drugs causing AKI.

Mainstay of treatment includes vasoconstrictors, Albumin, and reversal of precipitating factors, and antibiotics for SBP. Stage 1A AKI is mostly secondary to hypovolemia and resolves in more than 90% of patients with fluid challenge and diuretic withdrawal as compared to 40% patients with stage 1B disease. Hence use of vasoconstrictors is recommended for patients with AKI-HRS stage 1B or greater [35].

Vasoconstrictors: These drugs act by causing splanchnic vasoconstriction which results in reduction in the portal pressure and increases the EABV. These effects are more pronounced when combined with Albumin. Ascites decreases the mean arterial pressure (MAP) which further decreases renal blood flow. Vasoconstrictors also increase the MAP which results in increased likelihood of reversal of HRS [36]. Terlipressin, Noradrenaline, and combination of Octreotide and Midodrine are the available options **(Table 3)**.

Terlipressin

Terlipressin is a Synthetic vasopressin analog with predominant vasopressin 1A action causing splanchnic vasoconstriction [37]. It also acts on vasopressin 1B receptor causing release of adrenocorticotropic and cortisol hormones, which helps in counteracting the relative adrenal insufficiency seen in patients with decompensated cirrhosis. It also has indirect vasopressin mediated anti-inflammatory effects [38]. Terlipressin also acts on vasopressin 2 receptors, worsening hyponatremia and may cause volume overload [39]. Studies have demonstrated that combination of Terlipressin and Albumin is more effective than Albumin alone in treating AKI [40].

Other agents

Noradrenaline (intravenous) and Midodrine (oral) act via activation of alpha1 adrenergic receptors on vascular smooth muscle cells. Another somatostatin analog, Octreotide acts via inhibiting secretion of glucagon, a splanchnic vasodilator, and is a direct mesenteric vasoconstrictor [41].

Efficacy of vasoconstrictors

Studies evaluating Terlipressin, Norepinephrine, and/or Octreotide/ Midodrine have found Terlipressin, in combination with intravenous Albumin, to be the most effective drug treatment for AKI-HRS [42]. Combination of Terlipressin plus Albumin have an efficacy ranging from 19% to 56% compared to 3-14% of Albumin alone in reversal of HRS. Terlipressin alone was found markedly inferior to a combination of Terlipressin and Albumin [43-46].

Norepinephrine has been found to be an effective alternate for Terlipressin in AKI-HRS, with similar rates of HRS reversal in some randomized studies [46,47]. Norepinephrine is cost effective compared to Terlipressin, but requires central line placement, intensive care unit admission, which may offset the cost benefit. Terlipressin in comparison can be given through a peripheral line in wards.

Both Octreotide and Midodrine monotherapy and combination of Midodrine/Octreotide have limited benefits in treating HRS [48,49].

Table 4: Eligibility Criteria for Simultaneous Liver–Kidney Transplantation.

Organ Procurement and Transplantation Network (2017) [55]	
1	AKI for 6 consecutive weeks with one or a combination of both 1. Dialysis 2. GFR ≤25 ml/min
2	CKD with GFR ≤ 60 ml/min for 90 d with one of the following: End Stage Kidney Disease GFR ≤30 ml/min at the time or after registration on kidney waiting list

Albumin: Albumin's multifaceted mode of action makes it the colloid of choice in treatment of HRS. Apart from being a volume expander and consequently increasing the EABV, Albumin has several other benefits. It is an antioxidant with a positive inotropic effect [50] and immunomodulatory properties. As compared to hydroxyethyl starch, Albumin causes reduced endothelial activation as lower plasma levels of von Willebrand related antigen and factor VII are seen in patients who were administered Albumin. Its ability to bind with variety of substances like bile acids, hormones cytokines, endotoxins, and bacterial products results in significant reduction in serum creatinine. Albumin (20%, 25%) should be used at a dose of 20-40g/day till HRS reverses. Serial central venous pressure measurements can be used to assess central blood volume and avoid circulatory overload [44].

Renal replacement therapy: Renal replacement therapy is indicated in patients unresponsive to drug treatment, worsening acidosis, electrolyte disturbances, or circulatory overload. RRT is usually a bridge to transplantation and does not provide any survival benefit [51]. Patients with cirrhosis and AKI who are not candidates for transplant have a mortality of 90%, making RRT futile in these settings [52].

Transjugular intrahepatic portosystemic shunt (TIPS): TIPS aims to reduce the portal pressures by creating an intrahepatic shunt in patients who have refractory ascites, diuretic intolerant, or uncontrolled variceal bleeding. Significant reduction in plasma renin activity, aldosterone, and noradrenaline levels has been reported [53]. Role of TIPS to reverse or limit the progress of HRS is limited as patients with markedly elevated bilirubin, overt encephalopathy or active infection are not good candidates for the procedure.

Liver transplantation: Liver Transplant (LT) remains the best optional treatment for HRS. The functional nature of HRS means that renal function is expected to improve after LT. However, accurately predicting renal recovery after transplant remains a mystery. About 10% of patients with AKI or chronic kidney disease (CKD) may continue to have renal failure post LT alone [54].

Renal recovery after LT depends on factors like duration of kidney disease, presence, or absence of ATN, age, etiology of AKI. In such cases, simultaneous liver-kidney transplant (SLK) should be considered. The Organ procurement and transplantation network policy has developed listing criteria for SLK

transplant and includes elements like duration of AKI, need for dialysis, and evidence of CKD. It includes patients with sustained AKI, defined as those who need dialysis or calculated creatinine clearance or GFR of 25ml/min **(Table 4)** [55].

Newer Modalities

The efficacy of albumin and vasoconstrictors is limited to less than half of the patients with HRS, which leads to search for newer novel agents. One such agent Serelaxin (recombinant human relaxin 2) acts on renal vasculature and results in increased renal blood flow, decreased renal vascular resistance, and reversal of endothelial dysfunction. It has also shown to reduce intrahepatic vascular resistance in animal models [56,57]. Treatments targeting systemic inflammation like DAMPs and PAMPs need further research. Assessment of arterial kidney resistive indexes by doppler ultrasonography, contrast enhanced ultrasonography and magnetic resonance elastography need to be further explored for better diagnosis and management of HRS [58].

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