Hepatorenal syndrome: pathophysiology and evidence-based management update

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Hepatorenal syndrome (HRS) is a functional renal failure that develops in patients with advanced hepatic cirrhosis with ascites and in those with fulminant hepatic failure. The prevalence of HRS varies among studies but in general it is the third most common cause of acute kidney injury (AKI) in cirrhotic patients after pre-renal azotemia and acute tubular necrosis. HRS carries a grim prognosis with a mortality rate approaching 90% three months after disease diagnosis. Fortunately, different strategies have been proven to be successful in preventing HRS. Although treatment options are available, they are not universally effective in restoring renal function but they might prolong survival long enough for liver transplantation, which is the ultimate treatment. Much has been learned in the last two decades regarding the pathophysiology and management of this disease which lead to notable evolution in the HRS definition and better understanding on how best to manage HRS patients. In the current review, we will summarize the recent advancement in epidemiology, pathophysiology, and management of HRS.

Key words: hepatorenal syndrome, epidemiology, pathophysiology, management.

INTRODUCTION

Cirrhosis is a late stage liver disease caused by irreversible scarring of liver tissue and characterized by abnormal structure and function of the liver, portal HTN, hyperdynamic state, systemic vasodilation and systemic inflammatory response. Acute Kidney Injury (AKI) is one of the myriads of highly morbid complications in the susceptibility spectrum of liver cirrhosis. Hepatorenal syndrome (HRS) is one of the potential causes of AKI in cirrhotic patients and those with fulminant hepatic failure and triggered by various precipitants including bacterial infection, antibiotic therapy, GI bleeding as well as diuretics therapy [1]. A study by Velez *et al.* found a 40% probability for development of HRS-1 in patients with cirrhosis and ascites with higher probability for ATN (60%) and prerenal azotemia (45%) [2]. HRS can be defined as reversible, functional impairment of renal function in a patient with advanced liver cirrhosis or fulminant hepatic failure in absence of other potential causes of renal failure and

characterized by hallmark signs of renal vasoconstriction with peripheral arterial vasodilation [3]. In this paper we reviewed the recent advancement in the definition, pathophysiological mechanisms and management (both currently available as well as investigational therapies) of HRS.

Definition and prevalence of AKI and HRS

The prevalence of AKI in hospitalized cirrhotic patients is found to be approximately 20–50%[4]. AKI is a significant prognostic marker and predictor of short-term mortality[4, 5]. Historically, AKI in cirrhosis was defined as a serum creatinine (Cr) of 1.5 mg/dl or higher. Recent reports however demonstrated higher mortality of cirrhotic patients with AKI even if the Cr did not exceed the 1.5 mg/dl cut-off. Currently, a dynamic definition of AKI with prognostic significance in cirrhosis has been put forth by a panel of experts combining Acute Kidney Injury Network (AKIN) and Risk Injury Failure Loss of Renal function and ESRD (RIFLE) criteria forming the International Club of Ascites–AKI criteria [6].

AKI is defined as an increase in serum creatinine of ≥ 0.3 mg/dL within 48 hours in hospitalized patients or $\geq 50\%$ increase over baseline within last 3 months among non-hospitalized patients [7, 8].

HRS definition has also evolved over time. Historically, HRS was defined according to the different Cr cut-offs. HRS was classified as type 1 HRS (currently HRS-AKI) in 75% of cases and type 2 HRS (currently HRS-CKD) in 25% of cases [9]. Type 1 HRS is more rapidly progressive and is defined as a two-fold increase in serum creatinine to a level greater than 2.5 mg/dL over a period of less than two weeks [10, 11]. Type 2 HRS is less severe and characterized by an indolent decrease of renal function associated with diuretics resistant ascites [6, 12]. Notable risk factors for development of HRS in patients with liver cirrhosis includes lower mean arterial pressure (MAP) (<80 mmHg), dilutional hyponatremia and severe urinary sodium retention (urine $\text{Na} < 5$ mEq/L) [13]. The global incidence of HRS in hospitalized patients with cirrhosis and ascites is found to be around 10–19% as compared to 35–40% of patients with end stage liver disease and ascites [14–16]. Majority of HRS patients present during sixth or seventh decade with a mean age of 54 years. The mean age of HRS type 1 is 62 ± 1.2 years and that of HRS type II is 68 ± 1.6 years [17, 18]. Most of the studies found no gender or racial predilection with a few studies indicating a male preponderance [13, 17]. A study by Montoliu *et al.* reported 1-year survival for cirrhotic patients without renal failure to be 91% which is reduced to 46.9% in patients with any functional renal failure [19]. The median survival of untreated type 1 HRS is less than 2 weeks with majority of patients dying within 10 weeks of onset of renal failure whereas the median survival for type 2 HRS is around 3–6 months [20]. Jamil *et al* found the mortality rate for HRS to be 36.9% with 8.9% being discharged to hospice [21]. HRS also imposes a significant health care burden with an annual total direct medical cost burden of approximately \$3.0 to \$3.8 billion [22]. A retrospective cohort found the mean length of hospital stay to be around 30.5 days with a 30-day readmission rate of 33.1% [23]. High incidence and prevalence of HRS in cirrhotic patients coupled with high rate of disease morbidity and mortality as well as significant health care cost ranks HRS as one of the health care priorities with unmet need for additional comprehensive

treatment strategies to improve the outcome in this population.

Pathophysiology of HRS

The pathophysiologic mechanisms of HRS are complex interplay between different hemodynamic and inflammatory events. Hemodynamic events include vascular events (splanchnic vasodilatation, systemic vasoconstriction, imbalance between vasodilator and vasoconstrictor substances etc.), cardiac dysfunction, failure of renal auto-regulation, hepatorenal reflex, adrenal insufficiency, intra-abdominal hypertension and inflammatory events including systemic inflammatory response, as shown in **Figure 1** [3].

Role of vascular events

Arterial vasodilatation is the central player in the pathophysiologic pathway underlying HRS. Architectural derangement in liver cirrhosis leads to increased resistance of blood flow through the liver with resultant portal hypertension, opening of porto-systemic shunts, and preferential pooling of the blood into the splanchnic circulation [3, 12]. Hepatic dysfunction coupled with porto-systemic shunting leads to hepatic escape and increased production of various vasodilator mediators (e.g. nitrous oxide [NO]). NO is particularly important and the key regulator vascular hemodynamic and has been found to be increased in patients with cirrhosis. Studies have found that NO production blockade may blunt cirrhosis induced hemodynamic and renal impairments [2]. Vasodilators are the key component in the progression of circulatory failure in HRS with resultant arterial vasodilatation especially in the splanchnic circulation, decrease in systemic vascular resistance, decrease in effective arterial blood volume, and hypotension [24]. Hypotension in turn stimulates the baroreceptors in the carotid body and aortic arch with subsequent increase in sympathetic nervous system (SNS) activity, increased level of circulating norepinephrine, increased cardiac output and tachycardia leading to hyperdynamic circulation [25]. Hypotension also activates the renin-angiotensin-aldosterone system (RAAS), with subsequent increase in angiotensin formation and aldosterone secretion. Increased activity of the SNS and the RAAS leads to renal vasoconstriction primarily affecting renal cortex, and salt and water retention [3]. Although

experimental evidence indicates a role for other vasoconstrictors including endothelin 1, thromboxane A₂ and adenosine in renal vasoconstriction, human data is lacking [2]. The derangement of renal circulation coupled with cirrhosis-induced hypertrophy of thick ascending limb of the loop of Henle might further augment renal salt retention as seen in animal studies [26]. Hypotension also stimulates the non-osmotic release of vasopressin from the posterior pituitary gland which acts on the vascular smooth muscles to increase the vascular tone and on the distal tubules to increase free water retention which leads to subsequent hyponatremia. Despite the systemic vasodilation, which is mainly accounted for by the splanchnic vasodilatation, the activation of the different neuro-humoral pathways mentioned above leads to vasoconstriction in localized vascular beds including the femoral

artery, brain and the kidney. This localized vasoconstriction progresses in parallel to the progression of the hepatic disease and the activation of the SNS, RAAS and vasopressin. In early cirrhosis (patients in the pre-ascitic and diuretic-responsive ascites), neuro-humoral factors along with the increase in cardiac output help to maintain the effective circulating volume with no apparent change in kidney function. With progression of cirrhosis (diuretic-resistant ascites and beyond), a vicious cycle of failure of compensatory mechanisms to maintain an effective circulating volume coupled with worsening of renal vasoconstriction, renal microvascular damage, vascular rarefaction and irreversible defect in renal cortex leading to increase in Cr and development of HRS [3]. This in turn leads to irreversible renal damage and progressive treatment resistance.

Figure 1. Pathophysiological pathways underlying development of HRS.

Role of cardiac dysfunction

Hyperdynamic circulation is common in patients with liver disease and is characterized by a progressive increase in cardiac output (CO) aiming at maintaining the systemic circulation [27]. The coupling of arterial vasodilation, decrease in the effective circulatory volume, decreased systemic vascular resistance and hypotension are the leading causes of hyperdynamic circulation observed in cirrhotic patients and the leading cause myocardial dysfunction in them [28]. There are myriad of myocardial abnormalities observed in cirrhotic patients including systolic dysfunction, diastolic dysfunction, conduction abnormalities, chronotropic incompetence, cardiac myopathy etc. In addition to hyperdynamic circulation, various other factors stimulating myocardial dysfunction in patients with HRS include abnormal activation of various neuro-humoral pathways namely

SNS and RAAS, autonomic dysfunction, reduced baroreflex sensitivity as well as inhibitory effect of circulating cytokines namely NO and TNF- α leading to myocardial fibrosis and myocardial contractile dysfunction [3, 27]. Studies have demonstrated that patients who later developed HRS had relatively lower CO at baseline compared to cirrhotic patients who did not subsequently develop HRS. Decreased cardiac response to stress have equally been implicated in the development of HRS [3]. Another study found that use of non-selective beta-blocker predisposed patients with decompensated liver cirrhosis to HRS-I (24% vs 11%) [29]. These studies indicate that relative reduction in the CO predisposes patients to HRS development probably through worsening renal perfusion and subsequent renal vasoconstriction. Growing evidence indicates the vital role and interaction of cardiorenal pathways (CRS) in the development of renal dysfunction in patients with advanced liver cirrhosis and summarized as hepatocardiorenal syndrome [30]. Studies have indicated that HRS and CRS shares various cardinal pathophysiologic pathways including endothelial dysfunction, neurohumoral activation, vascular hyperresponsiveness, baroreflex with implication for modification of therapeutic and prognostic factors related to management renal dysfunction in patients with HRS [30].

Role of renal prostaglandins and renal autoregulation

As mentioned earlier, due to the decreased effective circulating volume and reduction in mean blood pressure, there is a compensatory increase in

the SNS and RAAS which induces renal vasoconstriction. In the kidney, renal vasoconstriction is usually balanced by increased intrarenal production of vasodilating prostaglandin (I₂ and E₂), NO and Kallikrein [31]. However, in advanced cirrhosis and in those with precipitating factors like infection, sepsis, variceal bleeding, ischemia, and those taking non-steroidal anti-inflammatory agents, there is a decrease in renal vasodilators coupled with increased release of renal vasoconstrictor namely Endothelin-1. This disturbance in the renal vasoconstrictor-vasodilator counterbalance system results in intensification of renal vasoconstriction and subsequent decline in renal function and forms the basis for development of HRS. Despite these known abnormalities, neither prostaglandin infusion nor ET-1 receptor blockers have proven beneficial in HRS treatment [3].

Loss of renal autoregulation may also play a vital role in renal dysfunction. Under steady state, two mechanisms including tubuloglomerular feedback and renal myogenic response play an essential role in renal autoregulation through maintain renal blood flow and GFR [32]. However, this autoregulation is lost in liver cirrhosis with rightward shift of the renal perfusion pressure/renal blood flow curve, indicating lower renal blood flow for any given renal perfusion pressure [3]. This rightward shift directly correlates with the circulating (endogenous) norepinephrine level, indicating that increased SNS activity plays a role in the abnormal autoregulation seen in HRS [3].

Role of hepatorenal reflex

Various studies indicate the presence of intrahepatic vascular sensors which are involved in the extracellular fluid volume regulation [33]. Adenosine is a central player in this reflex in addition to serotonin. Distorted hepatic architecture in liver cirrhosis results in changes in sinusoidal pressure which stimulates the release of adenosine, activating the hepatic afferent SNS with resultant activation efferent renal SNS and subsequent renal vasoconstriction [34, 35]. In presence of effective hemodynamic status, an increase in portal pressure resulted in reduction of renal blood flow and vice versa [2]. Another study found that lumbar sympathetic block resulted in improvement of renal function in patients with liver cirrhosis [36].

Role of adrenal insufficiency

Adrenal insufficiency or hepatorenal syndrome in cirrhotic patients results from a combination of factors including low cholesterol, arterial

vasoconstriction affecting the adrenal gland, damage to adrenal gland due to coagulopathy and overstimulation and exhaustion of hypothalamic-pituitary axis due to increased PAMPs and pro-inflammatory cytokine production [37]. Hepato-adrenal syndrome has been found to affect 25–65% of patients with decompensated cirrhosis [2]. Relative adrenal insufficiency (as evidenced by inadequate cortisol production) has been observed in 80% of cirrhosis patients with HRS as compared to 30% with normal kidney function suggesting a role for adrenal insufficiency in HRS development [3]. However, further characterization of HRS associated with hepatoadrenal syndrome as well as the role of vasoconstrictor therapy and glucocorticoids in such patients need to be elucidated for potential therapeutic benefit.

Role of intra-abdominal hypertension

Recently it has been increasingly recognized that increased intra-abdominal pressure (IAP) and intra-abdominal hypertension (IAH) may play a vital role and a potential independent risk factor in the development of HRS [38]. IAP associated with tense ascites in patients with cirrhosis has been found to lead to IAH as well as abdominal compartment syndrome (ACS) which can both predict development of acute kidney injury [39]. According to the world society for abdominal compartment syndrome, IAH was defined as sustained or repeated pathologic elevation of IAP ≥ 12 mmHg and a sustained elevation > 20 mmHg was found to be associated with organ dysfunction [38]. Renal dysfunction has been found to be one of the earliest consequences of IAH with multifactorial mechanistic pathways. Pathways including diminished renal blood flow with persistently increased IAP and renal parenchymal compression and compartment syndrome as well as significantly elevated renal vascular resistance coupled with other factors including reduced cardiac output, elevated levels of RAAS, catecholamines and inflammatory cytokines results in shunting of blood from renal cortex with resultant impairment of glomerular and tubular function and eventual renal impairment [40–42]. An animal found that there was a 555% increase in renal vascular resistance when IAP was elevated from 0 to 20 mmHg which was 15 times that of increase in systemic vascular resistance [40]. Another study found that a decrease in IAP following paracentesis was associated with a transient increase in GFR and urine output in

patients with cirrhosis [43, 44]. However, large volume paracentesis without plasma expansion was found to cause rebound precipitation of HRS [45]. Thus, there is a need for careful monitoring of systemic hemodynamics coupled with guided plasma exchange with intravenous albumin to prevent post paracentesis circulatory dysfunction and renal impairment.

Role of systemic inflammation

Systemic inflammation is a well-recognized hallmark of cirrhosis and is associated with increased pro-inflammatory cytokines such as C-reactive protein (CRP), TNF, interleukins and endotoxins, level of which increases in parallel with the progression of the liver disease [46]. These inflammatory markers may be elevated even without any evidence of active infection, and are probably related to the bacterial translocation from the intestinal lumen into mesenteric lymph nodes which causes both stimulation and upregulation of the inflammatory markers which are further upregulated in presence of active infection [3, 47, 48]. Pathogen associated molecular patterns (PAMPs) and damage associated molecular patterns (DAMPs) are the two groups of molecules which drive inflammation in patients with cirrhosis in absence of overt bacterial infection through activation of pattern recognition receptors namely toll-like receptors (TLRs), release of proinflammatory cytokines and arterial production of vasodilators [45]. PAMPs include bacterial components namely lipopolysaccharide which results in translocation of gut bacteria and DAMPs include intracellular components namely ATP, high motility group protein B1, heat shock protein released from injured hepatocytes resulting in proinflammatory response [45]. Circulating cytokines are also increased in spontaneous bacterial peritonitis (SBP) and acute-on-chronic liver failure (ACLF) both of which are common triggers for HRS [2]. In SBP for example, the release of inflammatory mediators leads to further deterioration of the circulatory dysfunction, decrease in cardiac output (CO) through direct myocardial toxicity, and worsening renal vasoconstriction with subsequent HRS. The role of inflammation in the pathogenesis of HRS is further supported by studies that showed that the majority (78%) of HRS-AKI patients had evidence of either documented infection or systemic inflammatory response (SIRS) as

compared to only 14% of patients who had AKI from hypovolemia [49]. Studies have also shown that there is a distinct cytokine profile for hepatorenal AKI including higher IL-6, TNF- α , IL-8, VCAM-1 and lower level of MIP-1 α as compared to other causes of AKI in cirrhosis [50]. Probably the most compelling evidence that bacterial translocation and systemic inflammation play an important role in the pathogenesis of HRS stems from studies that showed that gut decontamination with rifaximin leads to improvement in systemic hemodynamics and kidney function in cirrhotic patients with ascites [51] and studies that showed that antibiotic prophylaxis after variceal bleeding and for SBP prophylaxis reduced the risk of HRS in cirrhotic patients [52]. In addition to causing systemic inflammation, DAMPs and PAMPs may play a direct role on the kidneys by upregulating the expression of components of innate immunity including TLR4 and caspase-3 in renal tubular cells with resultant renal ischemia and damage [53].

Various other probable pathological mechanisms for development of HRS are being increasingly researched. Acute upper gastrointestinal bleeding in patients with advanced liver cirrhosis has been linked to the development of HRS through various pathways including reduction of renal perfusion secondary to blood loss as well as systemic vasodilation [54]. Severity of blood loss as well as baseline liver function determine the rate of development of renal failure which is a strong predictor of mortality in these patients [55]. Although no precise contribution of cholemic nephropathy has been found in progressive renal impairment in HRS patients but studies suggest that treatment responsiveness to vasoconstrictors reduced with increasing serum bilirubin indicating a probable mechanistic pathway [56]. Porto-pulmonary hypertension has been found to cause circulatory derangement in patients with HRS but its specific role on renal impairment is yet to be identified [57].

Diagnosis of HRS

HRS poses a diagnostic challenge as there is no specific test or radiological study that confirms the diagnosis. HRS is usually suspected in a patient with well-established liver cirrhosis and ascites who presents with progressive rise in serum creatinine, oliguria, associated with normal

urine sediment, minimal or no proteinuria and very low urine sodium excretion [12]. All potential other causes of AKI including ATN, glomerulonephritis, vasculitis, interstitial nephritis, obstructive nephropathy, ischemic and toxin induced nephropathy needs to be excluded based on clinical features and laboratory findings prior to diagnosing HRS [3, 18]. Having said that, there is still little to no role of renal biopsy to diagnose HRS due to the presence of concomitant coagulopathy and due to the fact that HRS patients mostly have normal urinary sediments with minimal hematuria and proteinuria [58]. Currently, no single urinary biomarker is available for diagnosis of HRS. Although classic teaching suggested that HRS patients have a FeNa<1, recent clinic-pathological correlation studies demonstrated that FeNa<1 is common in cirrhotic patients with AKI and it did not differentiate between HRS and other causes of AKI [59, 60]. The diagnostic potential of other novel urinary biomarkers to diagnose HRS has been tested. Among studied biomarker, the investigational urinary biomarker neutrophil gelatinase-associated lipocalin (NGAL), which is derived from damaged tubular cells, seems to be promising. Recent studies correlated higher urinary NGAL level with mortality in cirrhotic patients with AKI and demonstrated higher urinary NGAL level in those with ATN compared to HRS patients [60, 61]. Nevertheless, in these studies there was an overlap in urinary NGAL levels between ATN and HRS patients partially due to the effect of prolonged renal vasoconstriction on the tubular integrity which eventually leads to tubular necrosis [2]. Urinary NGAL is also not currently available outside of investigational studies and has not been tested in the clinic [61]. A study by Ring-Larsen *et al.* identified that renal blood flow could be an early indicator of renal impairment in cirrhotic patients even before clinically evident salt and water retention or laboratory diagnosis of renal impairment [62]. A significant reduction in renal blood flow (1.13 ml/g-min) was observed in patient with cirrhosis and oliguria as compared to normal individual (3.72 ml/g-min) or cirrhotic patients without ascites (2.34 ml/g-min) or decompensated patients (1.82 ml/g-min) or cirrhotic patients with azotemia (1.47 ml/g-min)[62]. Current ICA criteria provide a useful framework for the HRS diagnosis and are summarized in Table 1.

Table 1

Diagnostic criteria for HRS [3, 89]

- Acute or chronic liver disease with presence of advanced hepatic failure, portal hypertension and ascites
- Acute Kidney Injury defined as per new guideline as an increase in serum Creatinine of 0.3 mg/dL or more within 48 hours or more than 50% increase within 7 days
- No improvement in serum creatinine after at least 48 hours of diuretics withdrawal and volume expansion with albumin (1g/kg body weight to up to 100g/day)
- Absence of other apparent causes of acute kidney injury including shock, bacterial infection, fluid loss, current or recent treatment with nephrotoxic drugs, absence of ultrasonographic evidence of obstruction or parenchymal kidney disease
- Other criteria
 - Urine volume < 500 ml/day
 - Urine Na < 10 mEq/L
 - Proteinuria > 500 mg/day
 - Microhematuria (> 50 RBC/HPF)

Prognosis of HRS

Prognosis in cirrhotic patients with HRS is grim. Mortality is specifically high in patients with HRS-AKI (formerly known as HRS type 1) with some studies documenting as high as 80% mortality rate within 2 weeks of detection and majority of patients (90%) not surviving beyond 3 months [3]. Mortality for HRS-CKD (formerly known as HRS type 2) is relatively better with a median survival of about 6 months [63]. Factors predictive of 30-day mortality included etiology and severity of liver disease, age, low serum Na, high bilirubin and high model of end stage liver disease (MELD) score etc [64, 65]. MELD score was an independent predictor of HRS mortality with survival of 1 month for a score of 20 or more compared to 8 months in those with a score <20 [3].

Prevention of HRS

Due to its poor prognosis, HRS is better prevented than treated. Inadvertent use of non-steroidal anti-inflammatory drugs (NSAIDs) and medications that induce renal vasoconstriction such as angiotensin enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB) should be avoided in patients with ascites especially in those with refractory ascites as they might induce HRS [66]. All nephrotoxic medications including aminoglycosides and iodinated contrast agents should be used cautiously in cirrhotic patients due to increased risk of AKI. Antibiotic prophylaxis for secondary prevention of subacute bacterial peritonitis (SBP) is with history of previous

SBP and in those with low ascetic protein concentration (<1.5 g/dl) and evidence of advanced liver disease (Child-Pugh score ≥ 9 and serum bilirubin ≥ 3 mg/dL, serum creatinine >1.2 mg/dl, blood urea nitrogen ≥ 25 mg/dl or serum sodium ≤ 130 mEq/L) [67]. A 7-day course of antibiotic prophylaxis specially with ceftriaxone or quinolone is recommended for patients with concurrent variceal bleeding [67]. In patients who developed SBP, the concomitant administration of albumin and antibiotics reduces the frequency of HRS compared to treatment with antibiotics alone [68].

In patients with refractory ascites, diuretic treatment should be discontinued and ascites should be managed with paracentesis as the first line of therapy [68]. Concomitant albumin infusion (8 g/L of ascites removed) is recommended to prevent post-paracentesis syndrome. Consideration for transjugular intrahepatic portosystemic shunt (TIPS) should be made on a case by case basis to manage refractory ascites although the ability of TIPS to prevent HRS has not been studied [68].

Management of HRS

Appropriate management of HRS is a complex interplay of supportive, pharmacological, interventional as well as definitive management coupled with treatment directed towards potential triggers of liver failure. This paper will review the evidence related to management of HRS published in the last 15 years as shown in Table 2.

Table 2 – Evidence table for different modalities of treatment for Hepatorenal syndrome (HRS) published between 2005 and 2020

Author (Year of publication; Type of study; sample size)	Study Objective	Type of HRS	Intervention groups (n) Duration of Follow up	Drugs used- Name, dose, duration	Effect on survival or mortality rate	Reversal of HRS	Effect on renal function	Adverse events	Conclusion
Piano <i>et al.</i> [80] (2020; Prospective cohort; n=364)	To evaluate impact of response to treatment with Terlipressin and albumin on post-transplant outcome	HRS-1	Terlipressin plus albumin in two groups: With HRS (n=82) vs Without HRS (n=259) F/U- 1 year	Terlipressin plus albumin	Transplant free survival 60% for responder's vs 33% for non-responders	NS	Improved Non-responders need RRT more (20%) than responders (0%)	NS	Terlipressin plus albumin independent predictor of CKD at 1 year and decrease the need for RRT.
Krishna <i>et al.</i> [81] (2020; prospective cohort; n=50)	To evaluate the effect of Terlipressin and albumin on HRS outcome	HRS-1	Terlipressin plus albumin F/U- 90 days	Terlipressin plus albumin	No HRS recurrence in 74%	79%	Decrease in S. Cr by (1.22± 0.96) by Day 10.	Loose stool; Hyponatremia	Terlipressin plus albumin was safe and effective and bridge eligible patients to liver transplant.
Israelsen <i>et al.</i> [79] (2020; RCT; n=30)	To evaluate whether reversing cardio suppressive effect of Terlipressin with dobutamine would increase GFR	HRS-1	Terlipressin Plus Dobutamine (T vs D vs T+D) F/U- 14 days	Terlipressin Plus Dobutamine	NS		GFR was improved by Terlipressin monotherapy as compared to Dobutamine monotherapy. Combination therapy improved cardiac output, increased renin system but no effect on GFR.	NS	Dobutamine reversed cardio suppressant effect of Terlipressin in cirrhosis
Hiruy <i>et al.</i> [154] (Retrospective study; 2020; n=88)	To evaluate the effect of standardizing albumin, Midodrine and Octreotide on treatment response	HRS-1 and HRS-2	Gr A: Standardized approach with Midodrine plus Octreotide plus albumin (n=28)		No significant difference in mortality between the groups)		10% response in prestandardization vs 25% in poststandardization group RRT more in prestandardization		Improved response rate after standardizing therapy

Table 2 (continued)

						Gr B: Nonstandard zed approach (n=60)		group (45%) vs post standardization group (21%)		
Kade <i>et al.</i> [155] (Observational study; 2020; n=10)	To evaluate the efficacy of MARS in patients with alcohol related acute-on-chronic liver failure	HRS-I						Liver transplantation more in prestandardization (23%) vs poststandardization (3.6%) group		MARS hemodynamically safe to support function of liver and kidneys
								27% reduction in S Cr, 19% decrease in bilirubin, 37% reduction in ammonia and 14% reduction in Urea. MARS resulted in improvement of hepatic encephalopathy and reduction of MELD-Na score		
								50 % survival rate. 14-day survival starting from first MARS treatment was 90%		
Park <i>et al.</i> [156] (Observational study; 2020; n=157)	To assess outcome in pre and post liver transplant RRT	HRS-I				Pre-transplant RRT (n=16) Post-treatment RRT (n=69)		No in hospital mortality in pretransplant RRT compared to 16% in post- transplant RRT. In patients who did not undergo pretransplant RRT, the mortality rate increased to 20.8%		Pretransplant RRT improve posttransplant survival outcome. Thus, if indicated it is better to perform RRT while waiting for Liver transplant.

Table 2 (continued)

Nand <i>et al.</i> [138] (RCT; 2019; n=30)	To evaluate the role of two different modes of CRRT- CVVHD and CAVHD in reducing fluid overload, hyperbilirubinemia and uremia	HRS-1 and HRS-2	GR A: CVVHD (n=15) Gr B: CAVHD (n=15)		Survival rate 30 % for both groups. Both modes of CRRT well tolerated without new episode of hypotension or requirement of inotropes.		No significant difference between the groups	Complication rate low	CRRT best modality to treat hemodynamically unstable and critically ill patients
Nguyen-Tat <i>et al.</i>[150] (2019; Observational study; n=106)	To evaluate the efficacy of Terlipressin plus albumin in patients with HRS-2	HRS-2	Terlipressin plus albumin F/U- NS		HRS recurrence rate of 50%. Overall survival and survival free of Liver TX is similar between HRS I and II of TX	46%			Terlipressin plus albumin can be used in patients with HRS II
Gupta <i>et al.</i>[110] (2018; Prospective cohort; n=30)	To evaluate the effectiveness of Norepinephrine for treatment of HRS	HRS-1	Norepinephrine plus albumin F/U- 14 days	Norepinephrine (1–4 mg/hour by continuous infusion for 14 days to achieve MAP of 12 mmHg) Albumin 20% daily IV infusion (20–40 g/day)	NS	73%	Significant decrease in S. Cr (3.26±0.48 to 1.28±0.14) and significant increase in Cr. Clearance (21±4.1 to 67.7±12.1mL/min), improvement of urine output in responders.	Acceptable safety	Norepinephrine plus albumin induced HRS reversal with acceptable safety
Saif <i>et al.</i>[95] (2018; RCT; n=60)	Comparison of Norepinephrine and Terlipressin in the management of HRS	HRS-1	Gr A: Norepinephrine plus albumin (n=30) vs. Gr B: Terlipressin plus albumin (n=30)	Norepinephrine (0.5 to 5mg/h) to achieve MAP of 10mmHg.	Similar survival between two groups (All responders survived and non-responders did not)	Gr A: 53% vs. 57 % for Gr B	Insignificant difference between the groups for decreasing S. Cr and increasing urine output	No significant side effects. Well tolerated	No benefit of increasing the dose and duration for non-responders.

Table 2 (continued)

			F/U-30 days	Albumin (20–40g/day— stopped if CVP>18cm of saline) Terlipressin (IV bolus of 0.5 mg/6h and increased in stepwise manner every 3 days to maximum of 2 mg/6 h)						No difference in outcome between the groups. Norepinephrine is cheaper and can be used instead of Terlipressin
Arora <i>et al.</i> [111] (2018; RCT; n=120)	To compare efficacy of Terlipressin with Norepinephrine in ACLF patients with HRS	HRS-1	Terlipressin plus albumin (n=60) vs. Norepinephrine plus albumin (n=60) F/U- 28 days	Terlipressin (2–12 mg/day) Norepinephrine (0.5–3.0 mg/h)	Improved 28-day survival for Terlipressin group (48% vs 20%)	40% for Terlipressin vs. 17% for Norepinephrine	Greater 4 and 7 days response for Terlipressin group. Significant reduction in requirement for RRT for Terlipressin group (57% vs 80%)	Adverse events higher in Terlipressin group (23% vs 8.3%)	Infusion of Terlipressin gives earlier and higher response than Norepinephrine with improved survival	
Stine <i>et al.</i> [147] (RCT; 2018; n=12)	To evaluate the safety and efficacy of addition of Pentoxifylline to treatment with Midodrine, Octreotide and albumin	HRS-1	Gr A: Midodrine plus Octreotide plus albumin plus Pentoxifylline (n=6) Gr B: Midodrine plus Octreotide plus albumin plus placebo (n=6) F/U- 14 days	Pentoxifylline- 400 mg three times daily or renal dose adjustment as needed	Overall cohort 30- and 180-day survival is 58% vs 33% Similar survival between the groups	HRS reversal similar between the groups	Liver transplantation, change in creatinine similar between the groups.	No serious adverse event	Addition of Pentoxifylline to Midodrine, octreotide and albumin is safe compared to standard of care	

Table 2 (continued)

Wong <i>et al.</i> [83] (Controlled clinical trial; 2017; n=58)	To evaluate the effect of SIRS on the effect of Terlipressin on	HRS-I	Gr A: Terlipressin plus albumin vs. Gr B: Placebo plus albumin F/U- NS	NS	Larger proportion of patients who received Terlipressin (46%) survived for 90 days without a transplant than patients who received placebo (23%)	43% in patients who received Terlipressin vs 6.7% for patients who received placebo			
Goyal <i>et al.</i> [96] (2016; RCT; n=41)	To compare the efficacy of Norepinephrine with Terlipressin in the treatment of HRS-1	HRS-I	Gr A: Norepinephrine plus albumin (n=21) vs. Gr B: Terlipressin plus albumin (n=20) F/U= 14 days	Norepinephrine (IV infusion 0.5–3 mg/h) Terlipressin (IV 0.5–2 mg/6h) Albumin (IV 20 g/day)	NS	47.6% in Gr A vs 45% in Gr B	Significant decrease in serum Cr and increase in MAP for both groups	Fewer adverse events in Gr A.	Norepinephrine as effective and safe as Terlipressin for treatment of HRS. Lower baseline MELD score was found to be a predictor of response of treatment.
Sarwar <i>et al.</i> [97] (Quasi experimental; 2016; n=24)	To determine the efficacy of Terlipressin and albumin in improving renal function	HRS-I	Terlipressin plus albumin F/U- NS	Terlipressin (Incremental dosage up to a maximum dose of 12 mg/day)			Complete response defined as a decline of creatinine <1.5 mg/dL. Complete response in 58% of patients, partial response in 29% and 12.5% with no response		Terlipressin plus albumin effective treatment of HRS-1. Baseline Cr, hyperkalemia and portal vein thrombosis associated with response.
Boyer TD <i>et al.</i> [84] (Clinical trial; 2016; n=196)	Phase 3 study to evaluate the efficacy and safety of Terlipressin plus albumin vs. placebo plus albumin	HRS-I	Gr A: Terlipressin plus albumin (n=97) vs. Gr B: Placebo plus albumin (n=99) F/U- 14 days	Terlipressin (1mg/6h)	Transplant free survival and overall survival similar in both groups.	Complete reversal (2 serum Cr ≤ 1.5 mg/dL 40 hours apart).	S. Cr decrease in Terlipressin group by 1.1 mg/dL vs 0.6 mg/dL in placebo	Similar adverse event in both groups. More ischemic events	Similar HRS reversal in both groups. Greater improvement of renal function in Terlipressin group.

Table 2 (continued)

				Significantly greater portion of patients in complete reversal with Terlipressin survived until day 90.	Complete reversal in 20% of Terlipressin group vs 13% in placebo				in Terlipressin group	
Cavallin <i>et al.</i> [92] (RCT; 2016; n=78)	Compare administration of Terlipressin as continuous infusion vs. IV bolus	HRS-1	Gr A: Terli-Inf plus albumin vs. Gr B: Terli-bol plus albumin	Terli-Inf- Continuous IV infusion at dose of 2 mg/day Terli-bol- IV bolus at initial dose of 0.5 mg/4h to a maximum dose of 12 mg/day Albumin - 1g/kg on day 1 followed by 20–40g/day				Complete response- decrease in S. Cr from baseline to 1.5mg/dl Partial response- a $\geq 50\%$ Decrease in S. Cr from baseline Rate of response to treatment similar in both groups. (76% vs. 64%)	Rate of adverse effect lower in Terli-inf (35%) vs. Terli-bol group (62%)	Terlipressin given at continuous IV infusion is better tolerated than IV bolus and at a much lower effective dose (2.23 vs. 3.51mg/day).
Rodriguez <i>et al.</i> [144] (Observational; 2015; n=56)	Effect of Terlipressin plus albumin in HRS-2 patient awaiting liver transplantation	HRS-2	Terlipressin plus albumin F/U- 12 months	No difference in mortality rate between responders and non-responders	33% in patients who underwent transplantation.	61% response to therapy and 35% relapse No significant difference in S Cr and GFR at 3,6 and 12 months for patients who went to transplantation with HRS reversal vs. those without reversal. No significant difference in development of AKI, RRT, survival, length of hospitalization				Treatment of HRS-2 with Terlipressin plus albumin did not have any beneficial effect in pretransplantation and posttransplantation outcome

Table 2 (continued)

Srivastava <i>et al.</i> [119] (RCT; 2015; n=40)	To compare the efficacy of Terlipressin plus albumin with concurrent low-dose dopamine, furosemide and albumin	HRS-1 and HRS-2	Gr A: Terlipressin plus albumin (n=20) vs. Gr B: Triple therapy (Dopamine, furosemide and albumin) (n=20) F/U- 5 days	Terlipressin (0.5 mg/6h infusion) Albumin (20 g/day) Dopamine (2µg/kg/min) Furosemide (0.01 mg/kg/h)			HRS-1: Similar increase in urine output and urine sodium in both groups. Similar decrease in plasma renin activity in both groups. HRS-2: Similar result.	Triple therapy improved renal function similar to Terlipressin but is less expensive
Heidenann <i>et al.</i> [64] (Retrospective cohort; 2015; n=119)	Delineate treatment patterns and clinical outcome in patients with HRS treated with Terlipressin	HRS-1 and HRS-2	Terlipressin plus albumin F/U- 30 days	Gr A: Pt responding to treatment (n=65) Gr B: Pt not responding to therapy (n=54)	One-month survival significantly longer in responders		Age, alcohol abuse, duration of treatment and MELD score independent predictor of survival	Survival post treatment depends on age, etiology of liver disease and duration of treatment.
Cavallin <i>et al.</i> [102] (RCT; 2015; n=49)	Compare effectiveness of Terlipressin plus albumin with midodrine plus octreotide plus albumin group	HRS-1 and HRS-2	Terli group: Terlipressin plus albumin (n=27) Mid/Oct group: Midodrine plus Octreotide (n=22)	Terlipressin – IV infusion of 3 mg/24h progressively increased to 12 mg/24h Midodrine - Initial oral dose of 7.5 mg TDS with maximum dose of 12.5 mg TDS Octreotide- SC 100 µg TDS to 200µg TDS			Significant higher rate of recovery of renal function in Terli group (70%) vs. Mid/Oct (29%)	Lower baseline MELD score associated with better survival

Table 2 (continued)

Table 2 (Continued)											
				Albumin (1g/kg on day 1 followed by 20-40 g/day)							
Nguyen-Tat <i>et al.</i> [157] (Clinical trial; 2015; n=57)	Effect of Terlipressin and albumin in patients with HRS	HRS-1 and HRS-2	Terlipressin plus albumin (n=57) F/U- 65 days	Median Terlipressin dosage- 20 mg for 5 days	Median survival 167 days in responders vs. 27 days for non-responders Median survival free of RRT and transplantation (81 days vs. 4 days)			Complete response in 51% vs. 5% partial response		Terlipressin plus albumin is effective in majority of patients with HRS. Non-response associated with high baseline bilirubin.	
Wong <i>et al.</i> [158] (Retrospective cohort; 2015; n=62)	To assess outcomes of HRS-1 patients after liver transplantation and factors predicting HRS reversal	HRS-1				After transplantation HRS reversal in 76% of patients at a mean time of 13 ±2 days	Patients without HRS reversal had significantly higher pretransplant serum Cr, longer duration of HRS, longer duration of pretransplant dialysis (27 days vs. 10 days) and increased posttransplant mortality compared to those with HRS reversal.			Only predictor of HRS1 nonreversal post-transplant was duration of pretransplant dialysis with a 6% increase risk of nonreversal with each additional day of dialysis	
Wan <i>et al.</i> [91] (RCT; 2014; n=56)	Comparative study between high and low dose of Terlipressin	HRS-1	Terlipressin plus albumin F/U- 14 days	Low dose Terlipressin (n=29): 1mg/12h High dose Terlipressin (n=27): 1 mg/6-8h	No significant decrease between the groups for 14-day survival		Significant increase in urine volume, decrease in BUN and S. Cr. for high dose compared to low dose.	No serious adverse effect between the groups		Both dosage lead to significant beneficial effect in as little as 3 days. Better lasting efficacy at high-dose. No difference in 2-week survival between the groups	

Table 2 (continued)

Sourianarayanan <i>et al.</i> [133] (Retrospective cohort; 2014; n=30)	To investigate the outcome of different therapies (pharmacological, RRT and Liver transplantation)	HRS-1			Decreased mortality in transplanted patients (5.3% vs. 65%) No median survival difference for non-transplanted patients or between those who received RRT vs those who did not or between those who received pharmacological therapy vs those who did not.				Liver transplantation offered better survival for HRS-1 patients. RRT did not improve survival in patients who did not receive liver transplantation
Ghosh <i>et al.</i> [99] (RCT; 2013; n=46)	Evaluate the safety and efficacy of Terlipressin and Norepinephrine in HRS-2	HRS-2	Gr A: Terlipressin plus albumin (n=23) Gr B: Norepinephrine plus albumin (n=23) F/U- 14 days	NS	8 patients in Gr A and 9 patients in Gr B died within 90 days of follow up.	74% HRS reversal for both groups	No major adverse effect.	Baseline MELD, Urine output, urine sodium, serum creatinine and MAP associated with response. Norepinephrine less expensive than Terlipressin	
Tavakkoli <i>et al.</i> [159] (RCT; 2012; n=23)	To evaluate the efficacy of Norepinephrine in comparison to Midodrine-Octreotide group.	HRS-1 and HRS-2	Gr A: Norepinephrine plus albumin Gr B: Midodrine	Norepinephrine-IV infusion of 0.1–0.7 µg/kg/min		HRS recurrence in 18% of Gr A. vs. 25% of Gr B	No ischemic event reported	Norepinephrine has same efficacy, safety and outcome as Midodrine plus octreotide group	

Table 2 (continued)

Table 2 (continued)

Table 2 (Continued)									
				F/U- 14 days		Survival rate better in HRS reversal group (47%) vs those not achieving reversal (4%) respectively.			regardless of therapy or success or failure of HRS reversal Patients not undergoing transplantation, HRS reversal with Terlipressin plus albumin improved survival.
Rice <i>et al.</i> [22] (Retrospective; 2011; n=43)	To determine post-Liver transplant outcome in patients receiving pre-liver transplant triple therapy with Midodrine, octreotide and albumin	HRS-1 and HRS-2	Cases: Patients who received pre-liver transplant triple therapy Controls: Patients who did not receive triple therapy before transplant				After liver transplant, mean GFR similar between cases (56.9mL/min) and controls (52.6 mL/min) Long term HD after liver transplant was required in 7.7% of cases and 12.5% of controls		Liver transplant improved renal function in patients with HRS. Triple therapy not associated with additional benefit in GFR after liver transplant.
Wong <i>et al.</i>[132] (Observational; 2010; n=6)	To assess the efficacy of MARS in improving systemic and renal hemodynamics in patients not responding to vasoconstrictor	HRS-1	MARS dialysis	5 days of 6-8 hours of MARS dialysis	4 out of 6 patients died following MARS treatment	No significant changes in systemic hemodynamics and GFR following MARS treatment. Transient reduction in S Cr, CPS score and MELD score with MARS but no difference for cytokine level			MARS is ineffective in improving systemic hemodynamics and renal function. Transient reduction in serum creatinine indicates direct removal by MARS and may not represent improved renal function.

Table 2 (continued)

Munoz <i>et al.</i> [87] (Clinical trial; 2009; n=13)	To evaluate the effectiveness and adverse effect of Terlipressin plus albumin in treatment of HRS	HRS-1	Terlipressin plus albumin F/U- 18 days	Gr A: Responders (n=8) Gr B: Non-responder (n=5)	Survival 115 days in responder vs. 12 days for non-responders	61%. No relapse of HRS after withdrawal of Terlipressin		No ischemic event observed.	Terlipressin plus albumin effective therapy to improve renal function
Kalkreuth <i>et al.</i> [93] (Retrospective study; 2009; n=30)	Effect of duration and dose of Terlipressin plus albumin therapy for positive response to treatment	HRS-1 and HRS-2					Complete response in 66% of treatment episodes. Predictive for positive response included duration of treatment, cumulative Terlipressin dose, HRS-2, baseline S Cr and MELD score. Complete response 52% at day 7 and 84% at day 17		Median duration of therapy 6-8 days. Median dose- 3.9 ±1.3 mg/day. Terlipressin plus albumin effective in two-third of patients. Prolongation of treatment from 7 to 20 days increased response rate.
Skagen <i>et al.</i> [114] (Observational study; 2009; n=162)	To examine the effect of Octreotide, midodrine plus albumin on survival and renal function	HRS-1 and HRS-2	Treatment group: Octreotide plus Midodrine plus albumin (n=75) Control group: Did not receive (n=87)		Transplant free survival higher in treatment group (101 days vs 18 days) Survival significantly better in both groups.		Transplantation performed in 45% of patients in treatment group vs 26% in control group and most difference observed in HRS-2. Renal function at 1 month significantly improved for treatment group		Therapeutic regimen with Octreotide plus Midodrine plus albumin improved short-term survival and renal function for both types of HRS. Prevent progression of HRS-2 to HRS-1
Sharma <i>et al.</i> [117] (RCT; 2008; n=40)	To compare efficacy Norepinephrine plus albumin with	HRS-1	Gr A: Norepinephrine plus albumin (n=20)	Norepinephrine: 0.5–3 mg/h	55% survival in both groups	HRS reversal	Significant decrease in S. Cr from baseline, increase in CrCl, MAP		Lower MELD, high CrCl, MAP, and lower plasma renin activity

Table 2 (continued)

Table 2 (continued)										
	Terlipressin plus albumin		Gr B: Terlipressin plus albumin (n=20)	Terlipressin: 0.5–2 mg/6h		50% in both groups.	and urine output for both groups		predicted response to therapy.	
Sanyal <i>et al.</i> [88] (RCT; 2008; n=112)	To evaluate the efficacy and safety of Terlipressin	HRS-1	Gr A: Terlipressin plus albumin (n=56) Gr B: Placebo plus albumin (n=56) F/U- 14 days	Terlipressin- IV 1mg/6h and dose doubled on day 4 if S Cr do not decrease by 30%	Overall and transplantation-free survival similar between the groups HRS reversal improved survival at 180 days.	HRS reversal 34% in Gr A vs 13% in Gr B.		Total adverse effect similar in both groups. Non fata MI in group A.	Terlipressin effective treatment for HRS.	Norepinephrine inexpensive, safe and effective alternative to Terlipressin
Testro <i>et al.</i> [160] (Retrospective cohort; 2008; n=69)	Factors predicting response to therapy and long-term outcome in patients with HRS	HRS-1 and HRS-2	F/U- 5 years		30% patients survived of which 81% had HRS-1 and 19% had HRS-2		59% response to Terlipressin		HRS-1 and age predicted renal function improvement and HRS-1 predicted transplant-free survival. No patients with type 2 HRS survived without transplantation	
Neri <i>et al.</i> [161] (Prospective cohort; 2007; n=52)	To investigate the improvement of renal function in patients receiving Terlipressin plus albumin compared to albumin alone	HRS-1	Gr A: Terlipressin plus albumin (n=26) Gr B: Albumin (n=26)	Terlipressin- IV bolus of 1mg/8h for 5 days followed by 0.5 mg/8h for two weeks	In Gr A- 87% survival at day 15 and 42% at day 180		Significant improvement of renal function in group A vs. group B. Complete response (Decrease in S. Cr to≤ 1.5 mg/dl)	Incidence of adverse event very low in Terlipressin group	Terlipressin plus albumin improves renal function in patients with HRS	

Table 2 (continued)

Esraïlian <i>et al.</i> [113] (Retrospective study; 2007; n=81)	To evaluate efficacy of Midodrine plus Octreotide plus albumin	HRS-1	F/U- 14 days	Albumin- 1g/kg body weight on day 1 followed by 20-40g/day F/U- Up to 3 months after discharge	In Gr B- 53% survival at day 15 and 16% at day 180	in 80% of Gr A vs. 19% in Gr B. Partial response ($\geq 50\%$ decrease in S. Cr) in 15% of Gr A vs. 16% of Gr B		30-day survival better in Midodrine plus Octreotide plus albumin group
Alessandria <i>et al.</i> [118] (RCT; 2007; n=22)	To assess efficacy and safety of Norepinephrine compared to Terlipressin	HRS-1 and HRS-2	Gr A: Norepinephrine plus albumin (n=10) Gr B: Terlipressin plus albumin (n=12) F/U- 14 days	Norepinephrine – 0.1–0.7 $\mu\text{g/kg/min}$ Terlipressin- 1-2 mg/4h Albumin to maintain CVP between 10–15 cm of H_2O Albumin for Gr A- 40–75 g/day Albumin for Gr B- 35–65 g/day	No difference in survival between the groups	HRS reversal in 70% of Gr A vs 83% of Gr B	No ischemic events for either group. Most patient with Terlipressin with abdominal pain and watery diarrhea	Reversal of HRS associated with improved survival Norepinephrine as effective and safe as Terlipressin
Kiser <i>et al.</i> [120] (Retrospective cohort; 2005; n=43)	To evaluate the efficacy of Vasopressin compared to Octreotide	HRS-1 and HRS-2	Gr A: Vasopressin (n=8)	Mean vasopressin dose (0.01–0.8 U/min for responders vs. 0.01–	Patients who responded to therapy had significantly lower mortality	Vasopressin alone (42%) and Vasopressin plus Octreotide (38%) had significantly greater recovery rate	No adverse effect reported	Therapy with vasopressin an independent predictor of recovery

Table 2 (continued)

Management of HRS-AKI (formerly HRS-1)

The role of available therapeutic modalities on different stages of underlying pathophysiological pathways leading to HRS over time is depicted in cirrhosis-HRS network shown in Figure 2. Although the treatment strategies are not organized sequentially or in order of priority but together they play a vital role both in preventing the progression to HRS as well as HRS reversal.

A. Supportive management

Patients with HRS-AKI are ideally managed in the hospital or in the intensive care setting (ICU) [68]. Supportive measures should be started early after the disease diagnosis. All effort should be made to detect underlying triggers of HRS especially underlying infections and a diagnostic paracentesis should be performed to exclude SBP [68, 69]. All diuretics should be withdrawn especially spironolactone due its risk of causing life threatening hyperkalemia. There are no data to support the discontinuation versus the continuation of beta-blockers in HRS patients but consideration for discontinuation of these medications should be made in those with severe or symptomatic hypotension.

Regular monitoring of vital status, renal and liver functions, arterial blood pressure, assessment of the intravascular volume status using either a central venous pressure (CVP) or assessment of inferior vena cava (IVC) using bed side ultrasound to monitor fluid balance and volume status. The administration of albumin plays a vital role in the survival of patients with HRS[10]. In majority of well-designed prospective and randomized controlled trials, albumin in combination with various vasoconstrictors has been found to increase

MAP, serum sodium, renal perfusion and function and HRS reversal [70]. According to the American association for the study of liver disease (AASLD) and European society for liver disease, albumin infusion with vasoconstrictive drugs is a treatment of choice for HRS-1 [68, 71]. Although the dosage for albumin varied but according to the European society for liver disease, the initial dose of albumin for HRS-1 is 1g/kg on day 1 followed by 20-40 g/day until serum creatinine normalizes to less than 1.5mg/dL [68].

B. Pharmacological management

Hallmark of HRS is peripheral vasodilation with renal vasoconstriction. Although previously advocated, renal vasodilators including angiotensin converting enzyme inhibitors, Dopamine, oral prostaglandin E1 analog Misoprostol, endothelin antagonist are no longer treatment of choice for HRS due to adverse effects and lack of therapeutic benefit [3]. Vasoconstrictors in conjunction with albumin are the cornerstone of therapy to revert the cascade of events preceding HRS as well as a bridge to definitive treatment which is liver transplantation (LT) [72]. The possible role of intravenous albumin in HRS has been postulated to be related to its ability to reduce NO level as well as level of other cytokines including TNF [73]. Currently 3 classes of vasoconstrictors are available for the treatment of HRS namely vasopressin receptor agonists (Vasopressin, Terlipressin and Ornipressin), alpha adrenergic receptor agonist (Noradrenaline, Midodrine) and Somatostatin receptor agonist (Octreotide) [74]. Of the vasoconstrictors, the best studied agent is Terlipressin followed by Noradrenaline, Midodrine and Octreotide.

Figure 2. Cirrhosis-HRS network showing various management strategies in relation to pathophysiology of Hepatorenal syndrome. Abbreviations: LT = liver transplantation, SLKT = simultaneous liver-kidney transplantation, MARS = Molecular Adsorbent Recirculator System, TIPS = transjugular intrahepatic portosystemic shunt, RRT = renal replacement therapy.

(i) Terlipressin – which is not available in North America, is the most extensively studied vasopressin receptor agonist in the treatment of HRS. Terlipressin is metabolized to lysine vasopressin by exopeptidase which subsequently works by stimulating V1a vasopressin receptors which are preferentially expressed in the vascular smooth muscles of the splanchnic circulation [75]. Terlipressin works by causing splanchnic vasoconstriction, restoration of effective circulating blood volume, increase in effective MAP, amelioration of neurohumoral abnormalities, increased renal perfusion, improvement of renal function and reversal of HRS [74, 75]. In North America, there were three major randomized controlled trials in the last 15 years namely OT-0401 study (2004–2006), REVERSE study (2010–2013) and CONFIRM (2016–2019) study which were done on similar population and with similar treatment regimen and indicated the relative efficacy of Terlipressin in reversing HRS, reducing ICU stay and improving renal replacement therapy (RRT) [76–78]. There were multiple studies that assessed the efficacy of Terlipressin and albumin in reversing HRS outside of the North American studies. A brief review of trials published within the last 15 years looking at the efficacy of Terlipressin can be classified into 4 groups as: (a) efficacy of Terlipressin plus albumin as compared to placebo or albumin; (b) studies comparing the efficacy of Terlipressin with other vasoconstrictors such as norepinephrine; (c) studies looking at the dosage and route of administration of Terlipressin and (d) studies looking at the efficacy of Terlipressin in selected group of HRS patients such as those with sepsis, variceal bleeding, or with myocardial dysfunction. These studies are summarized in Table 2. Majority of the randomized and nonrandomized single center or multicenter studies have indicated that Terlipressin treatment is effective in 40–70% of patients in reversing HRS and is associated with improvement of short-term survival especially in those who achieved HRS reversal [68, 79]. Most studies used Terlipressin in conjunction with albumin and demonstrated that response to therapy (Terlipressin plus albumin) was heralded by an increase in MAP and reduction in serum creatinine (sCr) to below 1.5 mg/dL [68], [80–88].

In majority of the studies, the usual dosage for albumin was 1g/kg body weight followed by 20–40 g/day [68]. Terlipressin was initiated as IV bolus at a dose of 1mg/4–6h and increased to 2mg/4–6 h if

there was no reduction of serum Cr. by at least 25% of baseline at day 3 of treatment [67, 68, 89]. Terlipressin is administered until Cr level decreases to <1.5mg/dL or for a maximum of 14 days [67, 90]. In absence of response, the Terlipressin dose was increased in a stepwise fashion every 3rd day [67]. A study by Wan *et al* looking at high (1 mg/6–8h) versus low (1mg/24h) dose Terlipressin found comparable beneficial effect of both doses while the high dose patients demonstrated lasting efficacy at 14 days with no marked difference in 14-day survival between the groups [91]. A study comparing Terlipressin administered as IV bolus (0.5–1 mg every 4–6h to 2 mg every 4 h) to continuous IV infusion (2 mg/day to 12 mg/day) found similar efficacy but at a lower dose and with lower incidence of severe side effect in the continuous IV infusion group [92].

Median time to HRS reversal and response was found to be between 7 to 14 days [89]. Von Kalckreuth *et al.* found that prolongation of treatment from 7 to 20 days increased response rate from 52% to more than 84% [93]. Various independent predictors of response included baseline Child-Turcotte score, baseline MELD score, baseline Cr, Bilirubin, Urinary Na, absence of hyperkalemia and portal vein thrombosis, MAP and age [17, 86, 94–101]. Factors affecting survival included age, etiology of liver disease, duration of treatment, improvement of renal function, baseline ESLD, high bilirubin, low Na [64, 65, 102–104]. Recurrence rate following treatment discontinuation was found to be between 20–40% that usually responded to re-introduction of Terlipressin [6, 105]. Frequent reported side effects of Terlipressin included abdominal pain, diarrhea, arrhythmia and ischemic events including peripheral gangrene, osteomyelitis [89, 106]. Majority of the side effects of Terlipressin was related to ischemic events and required treatment suspension in 7% of the cases [107]. Patients on Terlipressin therapy should be monitored for the development of ischemic events including splanchnic and digital ischemia, fluid overload, cardiac arrhythmia and treatment modified and managed accordingly [68]. Contraindication to Terlipressin treatment included presence of coronary, vascular or peripheral arterial ischemic diseases [89]. Thus, although not approved for use in North America, Terlipressin used along with albumin is a drug of choice for HRS reversal with significant efficacy and mortality benefit. In HRS-1 complicated with

sepsis or variceal bleeding, early treatment with Terlipressin plus albumin was found to be safe and effective [103, 108, 109].

(ii) Norepinephrine – is an alpha 1 adrenergic agonist with potential to be used in the reversal of HRS-1. Norepinephrine binds with alpha 1 receptor and causes vasoconstriction of splanchnic vessels with limited effect on myocardium [3]. A study by Gupta *et al.* found Norepinephrine plus albumin administered for 14 days was associated with 73% response rate as evidenced by significant decrease in sCr, increase in creatinine clearance (Cr Cl), urine output, MAP and serum Na [110]. Several trials although limited by sample size found similar efficacy in terms of HRS reversal and 30-day mortality between Norepinephrine plus albumin and Terlipressin plus albumin [67]. The mean effective dose of Norepinephrine was 0.5 mg/h which can be titrated by 0.5 mg/h every 4 hours until a maximum dose of 3 mg/h with the aim of achieving a >10 mm Hg increase in basal MAP [96, 111, 112]. Norepinephrine is readily available in US and Canada with side effect profile and cost less than Terlipressin plus albumin but the use is limited by requirement of continuous monitoring in intensive care unit [67, 112]. Thus, in ICU setting Norepinephrine plus albumin can be used as an alternative to Terlipressin plus albumin.

(iii) Midodrine, Octreotide plus albumin (MOA)

Midodrine administered in combination with Octreotide and albumin represent current standard of care in the US [67]. Midodrine is an alpha1 adrenergic agonist with vasoconstrictive properties that works primarily on the systemic circulation. When used as monotherapy, it caused modest improvement of blood pressure with no effect on improvement of renal function in HRS patients [17]. However, when combined with Octreotide (a somatostatin analog) and albumin (MOA) it was associated with improvement in renal function and HRS reversal in small number of patients. Midodrine is inexpensive, has favorable side effect profile and its oral dosing makes it an attractive option for the outpatient management of HRS. Midodrine can be started at a dose of 2.5 mg thrice daily and then increased to 15 mg thrice daily as needed [102]. Octreotide is also relatively cheap and is injected subcutaneously and therefore can also be used in

the outpatient management of HRS. The starting dose for Octreotide is 50µg thrice daily that can be increased to a maximum dose of 200 µg thrice daily as needed [102]. Although MOA combination was found to be safe and user friendly, its beneficial effect on survival and improvement of renal function was not found to be consistent across trials [22, 113, 114]. Recent studies however questioned the efficacy of MOA in reversing HRS. In a randomized controlled study by Cavallin M *et al.*, complete or partial remission of HRS occurred in 30% of MOA treated patients as compared 70% in Terlipressin treated patients[102].

(iv) Comparative efficacy of different vasoconstrictors in the treatment of HRS-1

Currently moderate to higher quality of evidence is available for efficacy of Terlipressin in HRS reversal and improved survival as compared to low quality of evidence for other pharmacological agents [115]. Among the studies published in the last 15 years, majority of the studies found that in terms of HRS reversal and 30-day mortality, Terlipressin and Norepinephrine had similar efficacy with Norepinephrine being cheaper with less side effects [95, 96, 99, 112, 116-118]. A study by Arora *et al.*, in patients with acute on chronic liver disease, Terlipressin was more effective than Norepinephrine in HRS reversal and decreased renal replacement therapy (RRT) requirement [111]. Use of Dobutamine in addition to Terlipressin plus albumin might reverse the cardiosuppressive effect of Terlipressin [79]. Triple therapy with dopamine (2 µg/kg/min), Furosemide (0.01 mg/kg/h) and albumin (20 g/day) had similar improvement of renal function as Terlipressin plus albumin [119]. Both Terlipressin and Vasopressin had significantly higher recovery rate and improved survival and renal function compared to Midodrine plus Octreotide [102, 120]. Tavakkoli *et al.* found similar efficacy and safety between Norepinephrine and Midodrine plus Octreotide [121]. A network metanalysis was done looking at RCTs comparing the efficacy of various pharmacological therapies either used singly or in combination [122]. Compared to placebo, Terlipressin plus albumin and Norepinephrine plus albumin were found to be ranked best and second best in reversal of HRS followed by Terlipressin alone, albumin with placebo, albumin alone and Octreotide plus Midodrine plus albumin

respectively [122]. Placebo and Octreotide were ranked least effective with no difference between the two. For decreasing sCr, Dopamine combined with Furosemide and albumin was found to rank best followed by Terlipressin plus albumin, Norepinephrine plus albumin, Octreotide plus Midodrine plus albumin Terlipressin alone albumin plus albumin respectively [122].

As such, it is found that Terlipressin plus albumin had overall comprehensive effect in HRS reversal and reduction of serum creatinine.

C. Non-Pharmacological Management

Non-pharmacological management for HRS includes trans jugular intrahepatic portosystemic shunting (TIPS), peritoneovenous shunt, molecular absorbent recirculating system (MARS) and renal replacement therapy (RRT).

(i) TIPS- Data supporting using TIPS in HRS is limited and is based on old studies as there are no studies that assessed TIPS use in HRS in the last 15 years. Previous studies have demonstrated that TIPS insertion was associated with reduction in portal pressure and restoration of some of the hemodynamic and neurohumoral abnormalities observed in HRS through reduction in the RAAS and SNS activities with resultant improvement of hemodynamic parameters, amelioration of cardiac function and gradual improvement of GFR, BUN and Creatinine [89]. In general, the effect of TIPS on kidney function is delayed with majority studies indicating a 2–4 weeks lag period for improvement of Cr Clearance, Cr and increase in urinary sodium excretion with reversal of HRS in ensuing 6–8 weeks [123]. Rate of HRS reversal after TIPS insertion varied among studies. At least in one study, the rate of HRS reversal after TIPS insertion was 93% [124]. In terms of survival, studies have indicated greater survival rate in HRS patients who received TIPS versus who did not with average survival rate of approximately 5 months following the procedure with some variation between different groups of patients [125, 126]. Predictive models looking at survival rate after TIPS procedure in HRS-1 found a 25% mortality at 90 days for HRS-1 associated with alcoholic cirrhosis or chronic cholestatic disease and an 80% mortality rate for cirrhosis due to other causes [127]. Another study found short term and 1-year survival rates as high as 72% and 47%, respectively, in HRS

with low procedure related complication [124]. However, the applicability of TIPS in patients with HRS is limited due to difficulties selecting the optimum patient for the procedure and due to the risk of worsening hepatic encephalopathy, worsening liver function and procedure related bleeding complication, cardiac decompensation and risk of contrast induced nephropathy [128]. Thus, there is a need for more well-designed controlled trials to assess the effect of TIPS on HRS reversal in the modern era. Meanwhile, TIPS should be used only in selected patients with HRS specially in those with preserved liver function and as a bridge to liver transplant or to try to avoid renal replacement therapy (RRT) for those who are not candidate for liver transplant.

(ii) MARS – Molecular absorbent recirculating system (MARS) is an extracorporeal, cell free modified dialysis technique for liver support that is responsible for temporary removal of various water-soluble and albumin bound molecules by combination of continuous RRT (CRRT) technique with albumin enriched dialysate [129]. MARS is currently approved for the treatment of hepatic encephalopathy. The majority of studies that assessed the effect of MARS in HRS were published before 2005 and showed mixed results regarding the survival benefit of MARS as compared to standard therapy in HRS patients [129–131]. MARS removes various molecules which accumulate in liver and renal failure including bilirubin, ammonium, urea, creatinine, fatty acid, bile salt inflammatory cytokines including TNF α and IL6 [89] and vasoactive mediators such as NO, renin, angiotensin, aldosterone, which in turn will lead to restoration of the hemodynamic derangements observed in HRS [130]. Indeed, 2 studies confirmed that MARS therapy reduced Cr as compared to standard medical treatment [129, 131]. However, a study by Wong *et al.* looking at efficacy of 5 days MARS therapy for a period of 6–8 hours/day in 6 HRS patients who failed vasoconstrictor therapy demonstrated that although MARS reduced NO level, the level of other cytokines and neurohumoral factors were unchanged and MARS was ineffective in improving systemic hemodynamics or renal function and concluded that the transient reduction in Cr post MARS was due to the direct removal of Cr rather than improvement of renal function [132]. Thus, at present there is limited

evidence that MARS therapy is beneficial in HRS reversal or prolonging survival in HRS patients. Meanwhile, MARS may be still used as bridge to LT in selected patients especially those with severe hepatic encephalopathy.

(iii) Renal replacement therapy (RRT) – In HRS patients, who progress despite supportive care and pharmacological management, RRT might become indicated. Indication for RRT include volume overload, uremia, encephalopathy, intractable metabolic acidosis and electrolyte imbalance [67, 68]. RRT in itself is not a treatment as it does not help recover kidney function and it should be viewed as a bridge to liver transplant for patients with intractable HRS. Initiation of RRT however is controversial specially in HRS patients who are not candidates for LT especially that earlier studies documented prolonged hospital stay, higher rates of complications especially bleeding and high mortality rate in those patients after RRT initiation [133]. A recent study by Allegretti and colleagues found that the 6-month mortality for HRS patients on RRT who were listed for LT to be 39% as compared to 84% for those not listed for LT [134]. In those listed for LT, RRT is helpful in optimizing the electrolyte balance and volume status of prior to LT. Thus, RRT should be advocated for HRS patients who are candidates for LT and should be individualized depending on the patient's condition and hemodynamic status and therapeutic goal in those not candidates for transplantation.

Another controversial issue is the modality of RRT initiation. Both intermittent hemodialysis (IHD), continuous RRT (CRRT) through either continuous veno-venous hemodiafiltration (CVVHD) or hemofiltration (CVVH) have been used in HRS patients [135]. Data is limited where the efficacy, safety and choice of specific modality of RRT has been systemically assessed for proper recommendation. IHD is frequently challenging in HRS due to hypotension resulting in increased risk of hemodialysis related complications including cardiac arrest and death [136]. In such scenarios as well as in patients with cerebral edema and fulminant hepatic failure CRRT has potential advantage over intermittent dialysis through slower removal of fluid in patients with hemodynamic stability, slower control of solute clearance and less variation in intracranial pressure [137]. A study by Nand *et al.* found that CRRT is the best modality for treatment of hemodynamically unstable and critically ill patients with HRS [138] with both forms of CRRT including

CVVHD and continued arteriovenous hemodialysis (CAVHD) were found to be equally effective [138].

D. Definitive therapy

Successful LT is the treatment of choice for HRS patients as it restores hepatic function, is associated with reduction in serum aldosterone and renin level, improvement in systemic blood pressure, normalization of renal resistive indices and increase in renal Na excretion [139]. HRS reversal and normalization of renal function after LT occurs in only two-thirds of patients who had pre-LT HRS. There is a complex interplay of various pre-LT and post-LT factors that affect post-LT renal recovery. One such factor is pre-LT duration of RRT. For each day of dialysis, a 6% increase in the risk of non-resolution of HRS-1 has been observed [89] with patients who have been on RRT for more than 2 weeks having a 9.2 times greater risk of non-resolution of HRS post-LT [140]. The duration of pre-LT RRT is so important that current guidelines recommend simultaneous liver-kidney (SLK) transplantation in HRS patients who have been on RRT for ≥ 6 weeks. Other pre-transplant factors impacting post-LT renal recovery includes history of diabetes mellitus (DM), hypertension (HTN) and older recipients and donor ages [140, 141]. Some of the transplant and post-LT related factors affecting outcome included intraoperative hypotension, intraoperative bleeding, need for surgical re-exploration and post-LT transplant allograft dysfunction [140–142]. It is important to mention that post-LT patient survival is lower in LT recipients who had pre-LT HRS with one study which found that the 1- and 3-year survival rate of HRS transplanted patient to be 80.3% and 76.6%, respectively [143]. The effect of pre-LT Terlipressin use on post-LT survival has been the subject of various studies including RCTs that showed conflicting results. A study by Restuccia *et al.* demonstrated similar comparable post-LT survival in HRS patients treated with Terlipressin compared to those who did not have HRS prior to LT. Recent studies showed that the pre-LT use of vasoconstrictors especially Terlipressin had no clear-cut significant impact on post-LT survival [139, 144]. A study by Boyer *et al.* found that the use of Terlipressin pre-transplant facilitated the use of CNI post-LT and reduced the need for post-LT IL2 receptor blockers [139]. Thus, orthotopic liver transplant is a definitive therapy for HRS-1 patients where SLK transplant should be reserved for patients requiring ≥ 6 weeks of pre-transplant dialysis.

Thus, overall management for HRS-1 includes early start of vasoconstrictors as first line therapeutic agent. Terlipressin plus albumin is the most studied and utilized vasoconstrictor followed by Norepinephrine plus albumin or Midodrine plus Octreotide plus albumin. If pharmacological therapy cannot improve renal function, non-pharmacological therapy including MARS or RRT is initiated as a bridge to definitive therapy including LT or SLK transplant as indicated. An algorithm looking at management protocol for HRS-1 and HRS-2 is described in Figure 3. Although different treatment strategies are available for the treatment of HRS-1, a recent review looking at randomized controlled trials found a pooled survival rate of 34.6% and a pooled HRS reversal rate of 42.8% with little improvement over time emphasizing the need for identification of newer treatment strategies and therapeutic modalities [145].

A few emerging treatment modalities with therapeutic potential against development of HRS in liver cirrhosis patients included various vasoactive agents as well as anti-inflammatory agents. Animal models as well as human exploratory models found that vasoactive agent,

recombinant human relaxin-2 (Serelaxin) had both vasoprotective as well as anti-fibrotic property, binds with relaxin family peptide receptor-1 (RXFP1) and caused reversal of endothelial dysfunction and increased renal perfusion by about 65% [146]. Although not tested in patients with HRS but Serelaxin was found to be safe and well tolerated with little or no detrimental effect on MAP or hepatic perfusion and had the potential to be used as selective renal vasodilator [146]. The anti-inflammatory drug Pentoxifylline is a potent phosphodiesterase inhibitor with anti-TNF α activity. A study by Stine *et al.* found that the addition of Pentoxifylline with Midodrine plus Octreotide was safe and had the potential to be used as a well-tolerated novel treatment strategy [147]. Another study found that administration of Pentoxifylline 400 mg TDS in patients with acute alcoholic hepatitis or HRS resulted in a 71% decreased risk of development of HRS with significant improvement of survival [71, 148]. As such, there is a need for identification of newer and novel treatment modalities for invigorating the static pipeline of HRS drug development.

Figure 3. Algorithm for diagnosis and treatment of Hepatorenal syndrome.

Management of HRS-CKD (formerly HRS-2)

There are limited data regarding the use of vasoconstrictor in HRS-2. Available studies have reported improvement in renal function in 60–70% of patients with HRS-2 treated with Terlipressin plus albumin [68, 149]. A study looking at efficacy of Terlipressin plus albumin found a comparable reversal rate of HRS between HRS-2 (46%) and HRS-1 (48%) with significantly higher relapse rate for HRS-2 (50% vs 8%) [150]. A 61% response rate was found by another study with no difference in GFR, Cr and mortality rate between responders and non-responders [144]. An important drawback of Terlipressin therapy in HRS-2 is higher rate of recurrence post treatment withdrawal [151]. Triple therapy with Dopamine plus Furosemide plus albumin was well as Norepinephrine were found to be as safe and effective as Terlipressin plus albumin but comparatively less expensive [99, 119]. Baseline creatinine, urine output and urine Na predicted treatment response [99]. Long term treatment in selected patients with recurrent HRS-2 waiting for LT was found to prevent irreversible renal failure and need for dialysis until an organ became available [152]. Among non-pharmacological management, significantly greater benefit was observed with TIPS with around 83% improvement in renal function [89, 124]. Liver transplant is the treatment of choice

for HRS-2. The usefulness of SLKT is ambiguous in HRS-2 due to slow deterioration of renal function which may falsely imply chance of recovery after LT alone [153].

CONCLUSION

AKI specially HRS is common in patients with hepatic cirrhosis and foretells a grim prognosis. Proper diagnosis of HRS through use of modified HRS diagnostic criteria as well as use of evidence derived therapeutics strategically applied for specific management and reversal of HRS has projected an overall improvement of survival. In general vasoconstrictors have been found to be the cornerstone of treatment for HRS followed by definitive treatment with liver transplant or simultaneous liver-kidney transplant as indicated. The pipeline for development of newer treatment strategies as well standardization of current modalities of treatment has been stagnant in the last 15 years. Further studies specially randomized controlled trials are required to properly assess and manage the therapeutic challenges posed by HRS. Also, there is need for head to head trial to compare the vasoconstrictor with nonpharmacological modalities including RRT, MARS and TIPS and to study the impact of various pretransplant therapeutics on post-transplant outcome.

Sindromul hepatorenal (HRS) reprezintă insuficiența renală ce se dezvoltă la pacienții cu ciroză hepatică și ascită, precum și la cei cu insuficiență hepatică fulminantă. Prevalența HRS variază, dar reprezintă a treia cauză de afectare renală la pacienții cu ciroză hepatică, după insuficiența renală prerenală și necroza acută tubulară. HRS are un prognostic prost și o mortalitate de aproape 90% la 3 luni după diagnostic. Există strategii terapeutice, însă ele nu sunt universal eficiente în a restaura funcția renală, dar pot prelungi supraviețuirea până la transplantul hepatic. În ultimele două decenii au fost realizate mai multe descoperiri privind fiziopatologia și managementul HRS. Această lucrare sumarizează ultimele informații privind epidemiologia, fiziopatologia și managementul HRS.

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