Management of Hepatorenal Syndrome: A Review

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Abstract

Acute kidney injury (AKI) occurs frequently in patients with cirrhosis, and hepatorenal syndrome (HRS) is second most common etiology of AKI after volume responsible pre-re nal etiology. AKI in these patients negatively impacts pre- and post-transplant patient survival and healthcare burden. Reduced effective blood volume with consequent reduced renal blood flow, along with systemic inflammation in patients with decompensated cirrhosis, result in susceptibility to HRS. In this article, we will review updates over the last 5 years on the changing definition with diagnostic criteria and nomenclature of AKI and HRS, data on medical treatment with vasoconstrictors, and urinary biomarkers in diagnosis of etiology of AKI. We will also discuss the significance of liver transplantation evaluation once the diagnosis of HRS is established and the post-transplant immunosuppression management. We will also review one of the challenging issues that remains among transplant-eligible patients, that of allocation of simultaneous liver kidney transplant. Finally, we will review the new implemented policy from the Organ Procurement Transplant Network on simultaneous liver kidney allocation.

Citation of this article: Tariq R, Singal AK. Management of hepatorenal syndrome: A review. J Clin Transl Hepatol 2020;8(2):192–199. doi: 10.14218/JCTH.2020.00011.

Introduction

Hepatorenal syndrome (HRS) among patients with cirrhosis is one of the most devastating complications, with high mortality if not promptly recognized and properly treated.1,2 Portal hypertension in cirrhosis leads to splanchic arterial vasodilation, which results in reduced systemic vascular resistance and effective circulating blood volume.3 Compensatory increase in cardiac output by activation of the renin-angiotensin-aldosterone and sympathetic nervous systems results in vasoconstriction of renal arteries with reduced renal blood flow. These physiological changes combined with hypoalbuminemia from reduced synthetic function of liver lead to sodium and water retention, manifesting as ascites and edema and setting the stage for development of acute kidney injury (AKI) and HRS. Inflammation with systemic inflammatory response syndrome in acute on chronic liver failure (ACLF) and decompensated cirrhosis is emerging as another major mechanism for the development of HRS.

In this article, we will review recent updates on the definition and terminology, criteria for diagnosis, emerging biomarkers in differentiating HRS from intra-renal cause of AKI, especially acute tubular necrosis (ATN), medical management, and role of liver transplantation (LT), especially for criteria for allocation of simultaneous liver kidney (SLK) transplantation.

Prevalence and healthcare burden

HRS is common among patients with cirrhosis and its occurrence increases with its severity and duration. For example, in a prospective study, the incidence of HRS was 18% at 1 year and 39% at 5 years of follow-up.4 Another study described the prevalence of HRS in about 48% of patients listed for LT.5 Apart from negative impact on patient survival and outcomes, HRS is associated with huge healthcare cost and significant socioeconomic burden.6 For example, in a retrospective study on 2542 patients hospitalized with HRS, mean length of hospital stay per patient was 30.5 days, with $91,504 per admission.7

Definition of AKI and HRS

Serum creatinine estimation in patients with cirrhosis may not provide true renal function, due to a) malnutrition and muscle atrophy that occur with reduced synthesis of creatinine, b) increased renal tubular secretion of creatinine, c) dilution of serum creatinine due to increased volume of distribution in cirrhotic patients, and d) measurement error when there is cholestasis with elevation of serum bilirubin levels.8,9 However, in routine practice, serum creatinine continues to be used for monitoring renal function and diagnosing AKI and HRS. This is because the test is simple, inexpensive, readily performed, widely available, and can be repeated frequently during the day. Over the last 10-15 years, the old definition of AKI using serum creatinine cut-off at 1.5 mg/dL has been changed, since even a minor change from baseline of as little as 0.3 mg/dL has been found to be associated with worse patient survival among hospitalized patients.10 Currently, AKI is defined as increase in serum creatinine of ≥0.3 mg/dL within 48 h among hospitalized patients, or ≥50% increase over baseline level within the last 3 months among outpatients, or urine volume <0.5 mL/kg/h for about 6 h. Further, severity of AKI is stratified into three stages: stage 1 defined by increase in serum creatinine ≥0.3 mg/dL or 1.5- to 2-fold from baseline; stage 2 defined by increase by 2- to 3-fold; and, stage 3 defined by >3-fold increase by 2- to 3-fold.
Volume 16 In early stages of cirrhosis, compensatory increase in splanchnic vasodilation, with pooling of blood and reduced effective circulating blood volume. In contrast, type 2 HRS, which presents as indolent decrease in renal function is often associated with refractory ascites, with median survival of about 6 months. Recently, the nomenclature of HRS types has been modified with ‘HRS-AKI’ replacing HRS type 1 and ‘HRS-CKD’ replacing HRS type 2 (Table 1). Being most common, the current review will focus on the HRS-AKI type.

Pathophysiology of HRS

Portal hypertension in cirrhosis results in splanchnic vasodilation, with pooling of blood and reduced effective circulating blood volume. In early stages of cirrhosis, compensatory increase in cardiac output maintains the circulatory volume. However, the susceptibility of such afflicted patients to reduced renal blood flow and AKI is increased with a) hypovolemia (nausea, vomiting, diarrhea, poor oral intake, diuretics, gastrointestinal bleeding, use of non-steroidal anti-inflammatory drugs or radiocontrast agents), b) progressive disease with increasing severity and decompensation of cirrhosis, and c) cirrhotic cardiomyopathy in 40–50% of patients with cirrhosis and diastolic dysfunction. The reduced circulating blood volume results in activation of the renin-angiotensin-aldosterone and sympathetic nervous systems, with sodium water retention and reduced renal blood flow occurring due to the vasoconstriction of renal arteries, with development of HRS-AKI (Fig. 1).

Recently, there is a growing line of evidence on the role of inflammation and systemic inflammatory response syndrome in the development of HRS. Systemic inflammation induced either by pathogen-associated molecular patterns or by damage-associated molecular patterns plays a key role in the development of acute decompensation in patients with cirrhosis.

Bacterial translocation from the gut due to increased intestinal permeability with activation of Toll-like receptor 4 (commonly known as TLR4) on hepatic macrophages results in inflammatory response. Additionally, studies have suggested the up-regulation of renal tubular TLR4, which is associated with the development of renal dysfunction and tubular damage.

The activated inflammatory cascade leads to release of proinflammatory cytokines (tumor necrosis factor-alpha or interleukin-6) and vasodilators [nitric oxide (commonly referred to as NO)]. Studies have also suggested that bacterial translocation plays a predominant role in causing the arterial vasodilation that is seen in advanced liver cirrhosis, occurring by stimulation of NO production and up-regulation mediated by tumor necrosis factor-alpha. About 30% of patients with HRS have systemic inflammatory response syndrome, due to sterile inflammation in the absence of bacterial infection.

Diagnosis of HRS

As soon as the diagnosis of AKI is established, steps are taken to expand the intravascular circulating blood volume, including withholding diuretics and administering intravenous fluid (1.5 L of normal saline or 1 gm/kg of albumin). Simultaneously, efforts should be made to determine specific intrarenal or post-renal etiology with urine examination and renal ultrasound respectively (Fig. 2). Additionally, patients with ATN versus HRS could be distinguished based on fractional excretion of sodium. It appears that fractional excretion of sodium less than 0.2% may be clinically useful for distinguishing HRS from ATN.

There is emerging data on the utility of plasma and urine biomarkers of renal injury, such as neutrophil gelatinase-associated lipocalin, human endothelin-1, uromodulin, fatty acid binding protein, epidermal growth factor kidney injury molecule-1, and interleukin-18. In a prospective study, urinary concentration of neutrophil gelatinase-associated lipocalin measured at day 3 of development of AKI was found to be accurate for differentiating ATN from other causes of AKI, with c-statistic of 0.87 (95% confidence interval of 0.78-0.95). In this study, neutrophil gelatinase-associated lipocalin was also found to independently predict AKI progression and 28-day mortality. Further studies are needed to validate the utility of neutrophil gelatinase-associated lipocalin before implementing this in routine management of patients with AKI.

Pre-transplant management of HRS

The medical management of HRS has been shown to improve short-term outcomes; however, long-term outcomes are poor without LT. The aim of the medical therapy is to stabilize the patient until LT and to optimize their pre-transplant condition. The medical therapy includes early treatment of AKI and use of vasoconstrictors.

Early treatment of AKI

Early recognition and treatment is key to improving both pre- and post-transplant outcomes of patients with cirrhosis. The

Table 1. New definition and nomenclature of HRS

| Old name | Old definition | New name | New definition |
|----------|---------------|----------|---------------|
| Type 1 HRS | ➢ ≥50% increase in serum creatinine from baseline | HRS-AKI | ➢ Increase in serum creatinine within <48 h |
| | ➢ Cut-off serum creatinine value ≥1.5 mg/dL | | ➢ ≥50% increase in serum creatinine from baseline within ≤3 months |
| Type 2 HRS | ➢ Smoldering increase in serum creatinine to ≥1.5 mg/dL | HRS-CKD* | ➢ Estimated glomerular filtration rate <60 mL/min per 1.73 m² for ≥3 months in the absence of other (structural) causes |

*Acute kidney disease if increase in serum creatinine is <50% from baseline and/or estimated glomerular filtration rate <60 mL/min for <3 months. Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; HRS, hepatorenal syndrome.
main aim is to identify and treat reversible factors, like dehydration, nephrotoxic medications (diuretics, non-steroidal anti-inflammatory drugs, aminoglycosides, and angiotensin-converting enzyme inhibitors), infection and sepsis, and gastrointestinal bleeding. If large volume paracentesis is needed, especially over 3-5 L, intravenous...
alcohol replacement should be used with 6-8 g of albumin for every 1 L of ascitic fluid removed. Patients with spontaneous bacterial peritonitis should also receive intravenous albumin (1.5 g/kg on day 1, followed by 1 g/kg on day 3), along with antibiotic to improve outcome of these patients. HRS is a common complication that can occur during acute alcohol hepatitis, having a mortality of about 90% within 3 months, unless the patient receives liver transplant. Hence, early recognition and treatment for acute alcohol hepatitis is needed with alcohol abstinence supplemental nutrition, and, for select patients, pentoxifylline or corticosteroids.

**Prevention of HRS**

Physicians managing patients with cirrhosis should be cognizant of reduced effective circulatory blood volume and renal blood flow, especially with the onset of portal hypertension. These patients should avoid nephrotoxic medications, especially non-steroidal anti-inflammatory drugs. Radiocontrast agents should be used judiciously. Optimization of diuretics should be performed with close follow up of basic metabolic panel and renal function. Further, early identification and treatment of AKI prevents progression and improves patient outcomes. The threshold should be low in using intravenous albumin for expanding fluid volume, especially in hospitalized patients with AKI and spontaneous bacterial peritonitis. For example, in a randomized controlled trial, use of intravenous albumin prevented type-1 HRS in patients with spontaneous bacterial peritonitis; the trial suggested decreased incidence of HRS (28% vs. 41%) and an improvement in 3-month survival (94% vs. 62%) in this population, when compared to placebo.

**Vasoconstrictor therapy**

Vasoconstrictors cause constriction of splanchnic vessels, resulting in increasing the effective circulating blood volume, which in turn increases renal perfusion and glomerular filtration. Vasoconstrictors work better when used with intravenous albumin. Terlipressin is the most common vasopressor used and acts on the V1 receptors on vascular smooth muscle cells. In a systematic review and meta-analysis of eight randomized trials, terlipressin was associated with 15% and 9% reduction of overall and HRS-related mortality respectively. Another meta-analysis of 309 patients showed mortality benefit with terlipressin, with relative risk of 0.76 (95% confidence interval of 0.61-0.95). Although, used extensively throughout the world, terlipressin is not yet approved by the FDA for use in the USA. A recent randomized placebo controlled trial from North America (CONFIRM trial) involving 300 participants (199 receiving terlipressin), HRS reversal was documented in 29.1% of terlipressin patients compared to 15.8% of patients receiving placebo (p=0.012). Major side effects of terlipressin included abdominal cramps and diarrhea in about 20% patients and tachyarrhythmias or chest pain in 6% of patients. Rarely, ischemia of bowel or skin and extremities can occur. These side effects are less frequent with use of terlipressin as continuous intravenous infusion, as compared to when the drug is applied in intravenous boluses, due to the less daily total dose needed when used as an infusion.

As terlipressin is currently not available in the USA, other vasoconstrictors like norepinephrine, midodrine, and octreotide, are used for the treatment of HRS. Norepinephrine, a catecholamine with predominantly alpha-adrenergic activity, is an inexpensive alternative and widely used as an infusion for the treatment of HRS. In a meta-analysis of seven trials of norepinephrine compared with terlipressin, the drugs were found to be equally effective in reversal of HRS (53 vs. 55%, p indicated non-significance). Midodrine, an alpha-adrenergic agent administered orally in combination with subcutaneous octreotide, is another alternative. In a case-control study, use of this combination on 75 HRS patients improved transplant-free survival, overall survival, with better renal function at 1 month compared to historical cohort of 87 HRS patients who did not receive this specific pharmacologic vasoconstrictor therapy.

In the most recent meta-analysis of 13 randomized controlled trials on use of vasoconstrictors for HRS, terlipressin was the most effective agent for HRS reversal and norepinephrine was as effective as terlipressin. However, both these drugs were superior to midodrine and octreotide combination for HRS survival. None of the drugs showed any benefit on HRS relapse or on patient survival. Based on these data, until terlipressin is available for use in the USA, norepinephrine remains the drug of choice, especially for patients treated in the intensive care unit, and the midodrine/octreotide combination is reserved for patients treated on the medical floor (Table 2).

Most patients are treated for 2 weeks at least before declaring non-response and discontinuation of the specific medication. As mentioned earlier, to achieve maximum efficacy, vasoconstrictors are used in combination with intravenous albumin infusion. Among responders, midodrine is usually continued indefinitely or until LT. In one study, outpatient terlipressin infusion as a bridge to LT has been reported in six patients after HRS reversal was documented, with three patients successfully bridged to LT. Further prospective studies are needed to evaluate the role and regimen of this approach as basis for maintaining renal function and bridging patients to LT. The role of vasoconstrictors for type 2 HRS or HRS-CKD remains unclear and most studies have been performed on HRS-AKI patients. In a non-randomized study, terlipressin was associated with improved renal function in patients with type 2 HRS. Further good quality randomized data is needed to evaluate the efficacy and long-term safety of these agents in patients with HRS-CKD.

**Miscellaneous therapies**

Few studies have evaluated the efficacy of transjugular intraportal portosystemic stent-shunt for HRS. Two small case series found improvement in renal function and survival in patients who underwent transjugular intraportal portosystemic stent-shunt for HRS. However, transjugular intraportal portosystemic stent-shunt is a risky procedure and patients with HRS are usually too sick to undergo this procedure. Until benefit of transjugular intraportal portosystemic stent-shunt is documented in randomized controlled trials, the procedure is not recommended in the management of HRS. Renal replacement therapy can be used as a bridge to LT in patients who fail medical therapy. The indications for renal replacement therapy in these patients are the same as for any other cause of AKI and include volume overload with 10% or more weight gain, hyperkalemia, symptomatic uremia, pericarditis, and acidosis. Risks of dialysis include hypotension, infection, and bleeding. Additionally, the exact mode of dialysis for these patients remains unknown. There is
no evidence on survival benefit with renal replacement therapy among patients not eligible for LT. Molecular absorbent recirculating system by extra-corporeal albumin dialysis has been proposed as a treatment of refractory ACLF. In a randomized study of 166 patients, survival was similar in patients receiving standard of care (n=81) and patients treated with extra-corporeal albumin dialysis (n=85). However, extra-corporeal albumin dialysis was superior in improving encephalopathy, reducing bilirubin, and improving serum creatinine. Based on these data, extra-cor-poreal albumin dialysis may be an alternative option to bridge patients with HRS to LT.

Liver transplantation for HRS

Liver transplantation is the definitive treatment for HRS and can be considered as soon as diagnosis of HRS is established. HRS patients, even after successful medical therapy and reversal of HRS, have poorer post-transplant outcomes than patients without HRS. In one study, of 104 patients, 33 with HRS had longer intensive care unit stay with higher use of hospital resources (including dialysis and blood transfusion), poorer renal function at 1 year, and worse patient survival. However, the patient survival rate at 5 years was satisfactory, at about 80%, justifying its use in these HRS. It should be recognized that HRS patients with longer duration of renal dysfunction prior to LT may not recover renal function after LT. In another study, about 6% increased risk of non-recovery of renal function was shown with each additional day of pre-transplant dialysis.

Simultaneous liver kidney allocation

Since the introduction of the model for end-stage liver disease scoring system, a proportion of all LT receiving simultaneous liver kidney (SLK) has increased from 4% in 2002 to 10% in 2016. Selection of candidates for SLK is a challenge for the hepatology and nephrology transplant community, as there are no good predictors for recovery of renal function after LT alone. In general, SLK transplantation provides survival benefit over LT alone to patients with serum creatinine >2 mg/dL and/or patients on hemodialysis. However, the data are scanty on the duration of renal dysfunction or of dialysis in predicting recovery of renal function after LT alone. Criteria for SLK allocation are therefore based on consensus recommendations and without good scientific data, which explains the increasing use of SLK and also the heterogeneity of their use across the regions and also between centers within the region (Table 3).

The Organ Procurement Transplant Network introduced a new policy in 2016 for SLK allocation, with the following criteria: A) for chronic kidney disease: a) glomerular filtration rate of <60 mL/min for 90 days and subsequent glomerular filtration rate of <30 mL/min or initiation of dialysis, b) chronic kidney disease due to metabolic disease that can be corrected with a liver transplant (hyperoxaluria, atypical hemolytic uremic syndrome, familial non-neuropathic systemic amyloidosis, and methylmalonic aciduria); and B) for AKI: a) duration of AKI >6 weeks with persistent glomerular filtration rate of <20 mL/min, b) need of dialysis for >6 weeks, or combination of both the criteria meeting 5 weeks duration. Under this policy, the respective criteria need to be documented every 7 days to maintain listing for SLK. A recent study examined the effects of the implementation of the Organ Procurement Transplant Network policy on 40,979 candidates, of which 1683 met the new criteria, 2452 met the old criteria, and 1878 met both the criteria. They found that patients meeting the new criteria were less likely to die post-transplant. Further studies are needed for continuous

| Study name | Type of study | Intervention | Outcome assessed |
|------------|--------------|--------------|------------------|
| Hiremanth et al. | Meta-analysis | Terlipressin | 15% reduction in overall mortality. |
| Gludd et al. | Meta-analysis | Terlipressin | Overall reduction in mortality 0.76 (95% CI: 0.61-0.95). |
| Israelsen et al. | Meta-analysis | Norepinephrine vs. terlipressin | Equally effective in reversal of HRS (53 vs. 55%, p=NS). |
| CONFIRM trial | RCT | Terlipressin vs. placebo | HRS reversal was documented in 29.1% of terlipressin-treated patients vs. 15.8% patients receiving placebo (p<0.012). |
| Skagen et al. | Case control | Midodrine and octreotide | Transplant-free survival was higher compared with the control arm (median survival 101 days vs. 18 days, p<0.0001). |
| Nanda et al. | Meta-analysis | All drugs available for HRS | Terlipressin plus albumin was more efficacious than placebo plus albumin (OR=4.72; 95% CI: 1.72-12.93; p=0.003) or midodrine plus albumin and octreotide (OR=5.94; 95% CI: 1.69-20.85; p=0.005), for HRS reversal. No significant difference was noted comparing terlipressin plus albumin versus noradrenaline plus albumin. |

Abbreviations: CI, confidence interval; HRS, hepatorenal syndrome; NS, non-significant; OR, odds ratio.
monitoring of SLK outcomes with the implementation of the new policy.

Whether urinary or plasma biomarkers of tubular injury can improve optimal allocation of SLK was tested in a small open study. However, none of the biomarkers tested within 30 days prior to LT among patients with cirrhosis and AKI were useful in predicting recovery of renal function after LT alone.\(^\text{53}\) There remains unmet need of accurate biomarkers for differentiation of HRS from ATN and predictors using clinical variables or biomarkers or combination of both for recovery of renal function after LT alone, as basis for optimal SLK allocation and use of already scarce donor kidney pool.

**Post-transplant management**

Common risk factors for the development of end-stage renal disease during the post-transplant period include calcineurin inhibitor nephrotoxicity, pre-transplant HRS, pre-existing renal insufficiency, and diabetes mellitus.\(^\text{54–56}\) Additionally, episodes of acute renal failure, renal replacement therapy pre- and post-transplantation, hepatitis C infection, and increasing age have been shown to be associated with risk of chronic kidney disease in the post-transplant period.\(^\text{57–59}\)

Given the significant nephrotoxic effects of calcineurin inhibitor, renal-sparing regimens have been used for preserving renal function in the post-transplant period among patients receiving LT for HRS. For example, use of renal-sparing approaches have been effective to preserve renal function during the post-transplant period, such as with a) interleukin-2 receptor antagonists (daclizumab, or basiliximab) or polyclonal antibodies (rabbit anti-thymocyte globulin) for induction of immunosuppression and delaying the introduction of calcineurin inhibitor, and b) mTOR inhibitors, such as everolimus or low-dose calcineurin inhibitor, with other agents, like mycophenolate, for maintaining the immunosuppression.\(^\text{60–62}\)

**Role of palliative care**

Patients with progressive HRS and those ineligible for LT have high short-term mortality with huge healthcare burden. For example, in a study using the national in-patient sample on hospitalized cirrhosis patients who were denied LT, multiple somatic symptoms were experienced with poor quality of life, and this was associated with prolonged hospitalization and higher use of hospital resources. Only 11% of these patients received palliative care consultation.\(^\text{63}\) Consideration should be given on a case-by-case basis, to discuss the goals of care with the patient and families.\(^\text{64}\) Future research should evaluate timing and effects of palliative care on quality of end-of-life care in this population.

**Conclusions**

HRS is a serious complication among patients with liver cirrhosis and is associated with poor prognosis. With recent advances in therapeutic strategies due to better understanding of pathophysiology, there is a hope to reduce its prevalence and improve patient outcomes. Terlipressin and norepinephrine infusion are effective vasoconstrictors, and midodrine combined with octreotide is an alternative option. With the encouraging data from a recently completed multicenter trial in the USA, it is hoped that terlipressin will be approved by the Federal Drug Administration for clinical use in the USA. Vasoconstrictors provide better efficacy when combined with intravenous albumin. Neutrophil gelatinase-associated lipocalin at day 3 of onset of AKI is a promising tool for differentiating intrarenal etiology from HRS; however, larger prospective data are needed as basis for validation before implementing into routine clinical practice. Lack of accurate models for predicting renal function recovery after LT has resulted in increase in the use of SLK in these patients. It is hopeful that the recently introduced Organ Procurement Transplant Network policy for SLK allocation and listing would optimize the use of SLK and help the already scarce kidney donor pool. There remains a clinical unmet need for better and more accurate models predictive of renal function recovery after LT and non-invasive urine or plasma biomarkers for accurate diagnosis of HRS.

**Funding**

None to declare.

**Conflict of interest**

The authors have no conflict of interests related to this publication.

**Author contributions**

Drafted the first version of the manuscript (RT), edited and revised the manuscript, and contributed to conceptual development of the study (AKS).

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Tariq R. et al: Hepatorenal syndrome: A review
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