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Role of Terlipressin and Albumin for Hepatorenal Syndrome in Liver Transplantation

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Abbreviations:

Acute Kidney Injury	**AKI**
Acute Tubular Necrosis	**ATN**
Chronic Kidney Disease	**CKD**
Hepatorenal syndrome	**HRS**
Kidney Disease Improving Global Outcomes	**KDIGO**
Liver Transplantation	**LT**
Model for End-stage Liver Disease	**MELD**
Renal Replacement Therapy	**RRT**

Abstract

Hepatorenal syndrome is one of the most ominous complications of portal hypertension in patients with decompensated cirrhosis and ascites. It is associated with very high mortality on the waiting list. Liver transplantation is the most successful therapeutic option for patients with hepatorenal syndrome. However, not all the liver transplant candidates with hepatorenal syndrome are able to receive a deceased donor allograft in a timely manner because it is a scarce resource and patients may need alternative best supportive treatment with systemic splanchnic vasoconstrictors and albumin as a bridge to transplant. The combination of terlipressin and albumin is efficacious in the reversal of hepatorenal syndrome and is used worldwide. More recently, the CONFIRM trial demonstrated the efficacy of terlipressin and albumin in the reversal of hepatorenal syndrome in North America. The aim of this article is to review the role of terlipressin and albumin in liver transplant candidates with hepatorenal syndrome in the United States.

Introduction:

Liver transplantation (LT) is a life-saving procedure and standard of care for patients with decompensated liver disease. There were 8896 LT performed in the United States in 2019(1) with 12,922 candidates awaiting LT as of February 17th, 2020.(2) Model for End

stage Liver Disease (MELD) based policy has revolutionized the allocation of livers from deceased donors in the United States.(3) Since serum creatinine is one of the heavily-weighted components of MELD score(4), the proportion for patients receiving LT with serum creatinine ≥ 2 mg/dl or on renal replacement therapy (RRT) has increased significantly in the MELD era (5, 6) with a clear survival benefit for this cohort of very sick patients.(6) Moreover, the use of combined liver and kidney transplants has also increased significantly in MELD era.(7)

Acute kidney injury (AKI) is observed in 20% of hospitalized patients with decompensated cirrhosis and ascites.(8) It is associated with high morbidity and mortality.(8) AKI can be reversible or irreversible whether it is pre-renal, renal or post-renal. In a cohort study, post-renal AKI was diagnosed in <1% of patients.(8) Hepatorenal syndrome (HRS) is a form of pre-renal AKI that is non-responsive to plasma volume expansion alone. As defined by International Ascites Club in 1994, it is of two types, has limited treatment options and carries a high mortality. Progressive worsening of HRS may lead to acute tubular necrosis (ATN) in a minority of patients. More recently, HRS-1 is renamed as HRS-AKI and HRS-2 is renamed as HRS-NAKI based on Kidney Disease Improving Global Outcomes (KDIGO) criteria (Table 1). (9, 10)

Terlipressin, a vasopressin analogue, together with albumin has been shown to improve renal function in patients with HRS-1.(11-16) However, terlipressin is not available in the United States. Recently, the CONFIRM trial showed the efficacy and safety of terlipressin and albumin in HRS-1 reversal in North America.(17) The aim of this article is to review the role of terlipressin and albumin for patients with HRS-1 listed for LT in the United States.

HRS: Pathophysiology and definition

HRS, as originally defined with a serum creatinine cut-off of 2.5 mg/dl, occurs in 4% of hospitalized patients with decompensated cirrhosis and ascites.(8, 18) The probability of developing HRS is 18% at one year and up to 40% at 5 years.(19, 20) The new definition of HRS does not include a final cut-off value of serum creatinine; thus, allowing the diagnosis to be made and pharmacologic treatment be initiated at early stages. (9, 10)

The pathogenesis of HRS is multi-factorial triggered by splanchnic vasodilatation leading to central hypovolemia, circulatory dysfunction and systemic inflammation (Figure 1a). Splanchnic and systemic vasodilation cause a lowering of mean arterial pressure and central blood volume.(21) (22). Such vasodilation and lowering of vascular resistance would

normally be corrected by auto-regulatory responses. However, both the baroreflex and cardiovascular responses to angiotensin II, norepinephrine, and vasopressin are abnormal with portal hypertension, causing further blood pressure dysregulation. In response to the splanchnic vasodilation and central hypovolemia in advanced cirrhosis, the various systemic endogenous vasoconstrictor systems are activated.(23) (24)

Cirrhotic cardiomyopathy, a phenomenon that affects both systolic and diastolic cardiac function, further exacerbates the circulatory dysfunction. While cardiac output is often high in absolute terms because of the decreased systemic vascular resistance, the impaired function becomes apparent when either the resistance is normalized or there is a physiologic stress stimulus.(18, 22, 25, 26)

Systemic inflammation as a result of pathogen-associated molecular patterns or damage-associated molecular patterns plays a key role in the development of organ failure and acute decompensation.(27) (28)A low-grade systemic pro-inflammatory state exists with elevated levels of cytokines, including IL-6 and TNF-α, which may be associated with translocation of enteric bacteria. Spontaneous bacterial peritonitis is the most frequent infectious precipitant of HRS. (29) Thirty five percent of patients with cirrhosis and ascites who develop SBP also develop AKI. Other bacterial infection can precipitate HRS include urinary tract or biliary tract infections. (8, 14, 18, 22, 26)

These interplay of various hemodynamic changes in patients with advanced cirrhosis and ascites as described above create the perfect storm when patients are exposed to a second hit (hypovolemia, GI bleed, dehydration or infection) (Figure 1b). The second hit typically leads to a further impairment of circulatory dysfunction and worsening renal perfusion. (25)The kidneys auto-regulate renal blood flow at blood pressures above 70 mm Hg; however, over-activation of the sympathetic system increases the kidneys' reliance on an adequate blood pressure to maintain renal perfusion. Constriction of the afferent and efferent arterioles is caused by stimulation of α-adrenergic receptors and renin release both by reduced blood flow and β-adrenergic receptors.(24) Stimulation of the renin–angiotensin–aldosterone axis is further increased because of the inability of the cirrhotic liver to degrade renin.(24, 30)

Historically, HRS was considered to be a single entity. In 1994 the International Ascites Club held a meeting at the AASLD in Chicago, when it was recognised that there were two forms of HRS, type 1 and type 2 based upon the severity and acuity of renal dysfunction.(31) This distinction was made in order to improve the greater understanding of pathophysiology of HRS and to design of clinical trials with consistent efficacy endpoints.

The more aggressive HRS-1 (HRS-AKI), defined as a doubling of baseline serum creatinine to a level >2.5 mg/dL in less than 2 weeks, has a 2-week median survival, if left untreated. HRS-2 (HRS-NAKI) has a more insidious onset in patients with refractory ascites and moderate renal dysfunction (serum creatinine ≥1.5 mg/dL), and has a median survival of 4-6 month.(32) These cut-offs for baseline creatinine were arbitrary values that were determined partly to ensure homogeneity and to avoid inclusion of patients with pre-renal AKI.

The International Ascites Club, revised the definition of HRS in 2015(10) (Figure 2a and 2b) and more recently in 2019(9) (Table 1) to incorporate it into broad definition of AKI based on KDIGO criteria. These criteria define AKI in cirrhosis as (i) an increase in serum creatinine ≥ 0.3 mg/dL within 48 hours; or, (ii) a percentage increase in serum creatinine ≥ 50% from baseline which is known, or presumed, to have occurred within the past 7 days. (10) (9) The sub-classifications of HRS-1 and HRS-2 with the limiting threshold of a serum creatinine concentration of 2.5 mg/dL and the time limit of 2 weeks to diagnose HRS-1 were removed because the evidence suggest that a higher pre-treatment serum creatinine is associated with a lower probability of response to terlipressin and albumin in patients with HRS-1.(33, 34)

It is important to distinguish between the phenotypes of AKI given the therapeutic and prognostic implication. This newer classification describes a new phenotypic classification of HRS in cirrhotic patients based on pathophysiologic characteristics (Table 1).(9) Non-HRS AKI now includes other causes of AKI in cirrhotic patients such as bile salt nephropathy, pre-renal hypovolemia caused by bleeding, excessive diuretic use, or any excessive fluid loss, acute tubular injury and necrosis, and AKI caused by intrinsic renal causes such as acute interstitial nephritis. Despite the newer definition,(9, 10) the majority of clinical trials examining the drug efficacy for HRS used the historical HRS-1 and HRS-2 definition. The downside of the use of arbitrary but relatively high cut-offs for serum creatinine is because patients with early stage HRS-AKI were never entered into controlled clinical studies. As a result, patients being randomized into such clinical trials always had advanced AKI using current criteria.(10)

Management of HRS-AKI: Terlipressin and albumin

LT is the only definitive therapeutic option for HRS in listed patients with decompensated cirrhosis. Successful LT eliminates portal hypertension and advanced liver disease, the underlying clinical "milieu" within which HRS develops and usually results in

renal recovery after transplant. (35-37) However, only a minority of HRS patients are eligible for or able to undergo timely LT. In addition, because deceased donor organs are a scarce resource, patients may need to be optimized with various treatment strategies until an organ becomes available. Therapy with splanchnic vasoconstrictors and albumin is an effective option to improve renal dysfunction and may improve short-term waitlist survival.

Albumin is the preferred plasma expander for volume expansion in patients with decompensated cirrhosis.(38) It is used in conjunction with splanchnic vasoconstrictors for the treatment, and in combination with antibiotics for the treatment of spontaneous bacterial peritonitis for the prevention of HRS.(39) It is increasingly clear that the beneficial effects of albumin derive from a combination of the oncotic and non-oncotic properties including its role as pleotropic scavenger, antioxidant and immunomodulatory molecule.(40) Albumin infusion improves circulatory volume, increases plasma renin activity and may reduce the severity of inflammation by binding to lipopolysaccharides and other bacterial products.(41) Compared to albumin, alternative plasma expanders are less effective(42). The recommended dose is 1 g of albumin/kg of body weight, with a maximum dose of 100gms/day. Meta-analysis of 19 studies suggested a significant dose–response benefit with albumin, with 600 g cumulative dose of albumin (equivalent to 50 g/day given over a 12-day period) providing a 90-day survival of 41% compared to 24.8% survival with a cumulative dose of 200 g of albumin.(43)

Splanchnic vasoconstrictors like terlipressin exert their effect through vascular vasopressin V1 receptors in the splanchnic blood vessels resulting in reduction of portal pressure. The combination of terlipressin and albumin is efficacious in the reversal of HRS and is used worldwide. Previous studies have shown baseline serum creatinine and total bilirubin levels, grade of acute-on-chronic liver failure, and mean arterial pressure were independent predictors of the response to terlipressin in HRS.(15, 33)

Since terlipressin is not approved by Food and Drug Administration, the therapeutic options for patients with HRS in United States are limited to either a combination of octreotide and midodrine with albumin (12, 16) in non-critically ill or noradrenaline and albumin(44, 45) in critically ill patients with decompensated cirrhosis. Both of these combinations result in plasma expansion and systemic vasoconstriction leading to an increase in effective blood volume and a partial or more limited improvement of renal function and may serve as bridge to LT. However, the efficacy of midodrine and octreotide with albumin in achieving complete reversal of HRS is low.(12). Midodrine and octreotide is thus rarely used in Europe for HRS, and not recommended in the EASL guidelines (46).

Several randomized controlled trials have evaluated the therapeutic effect of terlipressin with albumin and found it is more effective in improving renal function in patients with HRS, compared to other drugs or placebo. (11-15, 47) Current data show that terlipressin and albumin combination is superior to noradrenaline and albumin in patients with ACLF and HRS-AKI. (48)In a recent systematic review and meta-analysis, 18 randomized controlled trials including 1011 patients were analysed. HRS reversal rate was 42.0% in the terlipressin group and 26.2% in the non-terlipressin group. Terlipressin and albumin had greater HRS reversal rate and renal function improvement rate than placebo, or midodrine/octreotide in the management of HRS(16).

More recently, the results of the CONFIRM trial, presented at the AASLD meeting in Boston in 2019, showed significant reversal in HRS in the terlipressin and albumin arm compared to placebo (29.1% vs. 15.8%; p=0.012).(17) The baseline characteristics of the enrolled subjects were similar in both groups including the mean MELD scores (32.7 vs. 33; P=NS)) and SOFA scores (10.4 vs. 10.8; p=NS). The durability of HRS reversal, defined as no RRT up to day 30, was significantly higher in terlipressin and albumin arm compared to placebo arm (31.7% vs. 15.8%; P=0.003).(17) Furthermore, the proportion of HRS patient needing RRT after LT was significantly lower in the terlipressin arm compared to placebo (19.6% vs. 44.8%; p=0.04).(17) Similar findings were reported from a European Study where terlipressin treated subjects had a lower incidence of pre and post-transplant RRT and lower rate of CKD at one year.(31)

Terlipressin is a splanchnic vasoconstrictor, therefore, monitoring for ischemic events such as gut ischemia, coronary ischemia and digit ischemia is required, similar to noradrenaline. In the CONFIRM trial, 9 out of 200 subjects (4.5%) had ischemic adverse effects.(17) Patient selection for this therapy is the key given the potential for ischemia-related adverse effects with terlipressin(11-13, 15, 17, 32, 45, 47) Patients on the transplant waiting list are highly selected and screened for coronary artery disease and are usually low risk for coronary artery disease. Terlipressin as a continuous intravenous infusion appears to be as effective as bolus injection with less adverse events. (49)

Reversibility of HRS: Role of LT

It is clear from multiple studies that HRS is a largely functional pre-renal disorder and is potentially reversible. This comes from the experience in transplantation medicine, whereby kidneys from patients with cirrhosis and HRS exhibited excellent allograft function following transplantation into patients with end-stage renal disease (ESRD).(35) Conversely,

LT in patients with HRS frequently leads to normalization of kidney function after LT alone.(36, 37, 50, 51) One study (N=2112) reported the cumulative incidence of renal non-recovery, defined as transition to chronic dialysis within 6 months of LT as 8.9% among those who were on acute renal replacement therapy (<90 days) before LT. (37)The predictors of renal non-recovery were longer duration of pre-LT RRT, diabetes, re-LT and older age.(36, 37, 51)

Many observational studies have shown that patients with HRS-AKI usually have a very high MELD score with a high risk of death on the waiting list.(36, 37, 51) Additionally, their early post-transplant mortality is around 20%.(37) None of the randomized controlled trial examining the efficacy of terlipressin and albumin specifically enrolled LT candidates(12, 13, 15). Furthermore, the available data from the randomized trials do not address the transplant rates and post-transplant renal outcomes and survival among those treated with terlipressin and albumin for HRS prior to transplant. The window of opportunity for these patients to undergo LT is very narrow because of high waitlist mortality and timely transplant is not always available. Therefore, it is important to have treatment strategies that may serve as bridge to transplant score and improve post-transplant outcomes of waitlisted candidates with high MELD.

HRS: Role of simultaneous liver and kidney transplant (SLKT)

SLKT is an important option for LT candidates with CKD and inherited metabolic diseases such as primary hyperoxaluria, as well as those with sustained AKI deemed unlikely to recover after LT alone. It is difficult to assess how many of sustained AKI patients will have renal recovery after LT alone. Previous studies suggest that advanced age, diabetes, re-LT and prolonged duration of renal replacement therapy before LT are the significant predictors of renal non recovery after LT alone. (36, 51, 52) The recent SLKT policy, implemented in August 2017, has medical eligibility criteria and option of "safety net".(53) "Safety net" is for those LT recipients who do not recover renal function after LT alone, or subsequently develop advanced, persistent renal dysfunction within 60–365 days of LT. These candidates receive significant priority in the kidney allocation system in order to receive an expedited kidney after LT. SLKT for sustained AKI constitutes on 6.5% of all SLKT performed in 2018 (Unpublished data; Source: Scientific Registry of Transplant Recipients). Patients with sustained AKI who get transplanted and do not recover their renal function will benefit from safety net option and this led to a decreased number of SLKT and an increase in kidney after liver transplantation in 2018.

HRS reversibility: Impact on MELD score

Patients with HRS have worse survival for any given MELD score when compared to other patients with cirrhosis on LT waiting list. Reversal of HRS due to response to terlipressin and albumin will reduce the MELD score transiently and can affect their priority on transplant waiting list. Therefore, a "rescue" prioritization strategy should be developed for patients requiring treatment with terlipressin and albumin since recurrence of HRS occurs in 20% of the responders. Updating the MELD score in patients on the transplant waiting list is a dynamic process. For example, those with a MELD score >24 need to get the MELD score updated every 7 days. Recurrence of HRS occurs in up to 20% of responders to terlipressin and albumin (10) and organ availability is not universal for all the listed candidates. Since reduction of MELD score can affect the priority on the waiting list, a "rescue" prioritization strategy should be developed for patients requiring long term treatment with terlipressin and albumin due to recurrence of HRS.

HRS reversal on terlipressin and albumin may reduce MELD score transiently. There should be a mechanism so that these patients do not get disadvantaged by transient reduction in MELD score because of improvement in serum creatinine. In order to maintain the priority of treated HRS patients on the waiting list, the Liver and Intestine Transplant Committee should consider either a weighted pre-treatment serum creatinine value (similar to when RRT is used) or an exception MELD score mechanism until we get the real world experience in the United States following its anticipated approval by Food and Drugs Administration. This is very important to ensure the optimal pre-transplant management of HRS in the listed candidates without the concerns as to whether such treatment might decrease their prioritization for LT.

Furthermore, poor renal function and use of RRT increases the waitlist and post-transplant mortality.(19, 20, 52, 54, 55) Unlike splanchnic vasoconstrictor therapy, RRT does not reverse the underlying process leading to HRS. Furthermore, the downstream ill effects RRT such as venous access bleeding, infections, electrolyte abnormality, fluid overload and cardiac events may further increase morbidity, readmissions and mortality in a waitlisted patient.

Renal failure requiring hemodialysis after transplantation is a major risk factor for death in LT recipients; patients who require post-transplant dialysis also have significantly

worse graft survival compared to those without post-transplant RRT.(52, 54) In a single center study, 75.8% of patients with pre-transplant patients had resolution of HRS after LT. Like other studies, those who had higher pre-transplant serum creatinine, longer duration of AKI and RRT before LT were less likely to have renal recovery following LT(36, 37). These patients may need a kidney transplant later. Moreover, improving renal function in patients with HRS following treatment with terlipressin and albumin should reduce the cost of post-LT AKI related morbidity and resource utilization, need for SLKT and result in better post-transplant outcomes.

Conclusions

HRS is an ominous complication of portal hypertension associated with very high morbidity and mortality. We hope that with the success of CONFIRM trial in achieving HRS-1 reversal(17), terlipressin may get approved for its use in the management of HRS. This will be an important therapeutic advancement for the patients with decompensated cirrhosis and HRS in the United States. It will most certainly be incorporated in the treatment algorithm for the management of HRS similar to European and Asian HRS management guidelines. The availability of terlipressin and albumin for HRS may serve as a bridge to transplant in waitlisted LT candidates and improve their pre- and post-transplant outcomes including renal outcomes.

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Figure Legend

Figure 1a: Relationship of renal blood flow and preserved glomerular filtration rate in patients with decompensated cirrhosis and ascites
Footnote: Adapted from reference # (56)

Figure 1b: Second hit leading to acute kidney injury in patients with decompensated cirrhosis and ascites
Footnote: Adapted from reference # (56)

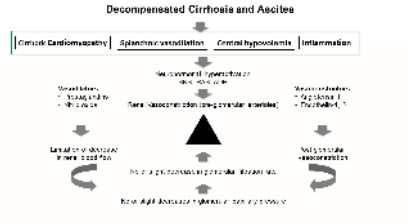
Figure 2a: International Ascites Club-AKI Definitions for the Diagnosis and Management of AKI in Patients with Cirrhosis(10)

Figure 2b: Diagnostic Criteria of HRS-AKI in Patients with Cirrhosis(10)

Table 1: New Classification of Hepatorenal syndrome

Old classification	New Classification		Criteria
HRS-1	HRS-AKI		- Absolute increase in sCr≥ 0.3mg/dl within 48 hours - Urinary output≤ 0.5ml/kg body weight≥ 6 hours - % increase in sCr≥50% based on last outpatient sCr as baseline value
HRS-2	HRS-NAKI	HRS-AKD	- eGFR<60ml/min per 1.73 m^2 for <3 months in the absence of other structural causes - % increase in sCr<50% using the last available value of outpatient sCr within 3 months at baseline value
		HRS-CKD	- eGFR<60 ml/min per 1.73 m^2 for ≥ 3 months in the absence of other structural causes

Abbreviations: sCr, Serum creatinine; HRS, hepatorenal syndrome; AKI Acute kidney injury. Table adapted from Angeli et al. (9)



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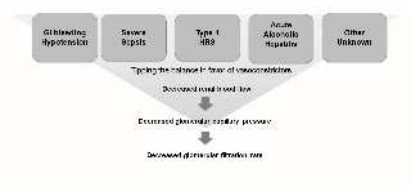

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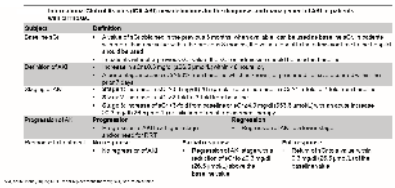

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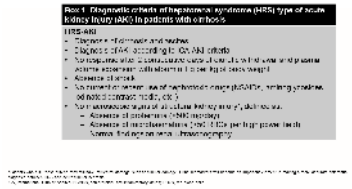

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