Role of Terlipressin and Albumin for Hepatorenal Syndrome in Liver Transplantation

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Hepatorenal syndrome (HRS) 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 wait list. Liver transplantation (LT) is the most successful therapeutic option for patients with HRS. However, not all the LT candidates with HRS 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 HRS and is used worldwide. More recently, the multicenter, randomized, placebo-controlled double-blind study to confirm efficacy and safety of terlipressin in subjects with hepatorenal syndrome type 1 (the CONFIRM study) trial demonstrated the efficacy of terlipressin and albumin in the reversal of HRS in a North American cohort. The aim of this article is to review the role of terlipressin and albumin in LT candidates with HRS in the United States.

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Liver transplantation (LT) is a lifesaving procedure and the standard of care for patients with decompensated liver disease. There were 8896 LTs performed in the United States in 2019[(1)] with 12,922 candidates awaiting LT as of February 17, 2020.[(2)] Policies based on the Model for End-Stage Liver Disease (MELD) score have revolutionized the allocation of livers from deceased donors in the United States.[(3)] Because serum creatinine (sCr) is one of the heavily weighted components of MELD score,[(4)] the proportion for patients receiving LT with sCr ≥2 mg/dL or while 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 simultaneous liver and kidney transplants (SLKT) has also increased significantly in the 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 prerenal, renal, or postrenal AKI. In a cohort study, postrenal AKI was diagnosed in <1% of patients.[(8)] Hepatorenal syndrome (HRS) is a form of prerenal AKI that is nonresponsive to plasma volume expansion alone. As defined by the International Club of Ascites (ICA) in 1994, it is of 2 types, has limited treatment options, and carries a high mortality. Progressive worsening of HRS may lead to acute tubular necrosis in a minority of patients. More recently, HRS type 1 was renamed as HRS-AKI and HRS type 2 was renamed as HRS-non-AKI (NAKI) based on the Kidney Disease: Improving Global Outcomes (KDIGO) criteria (Table 1).[(9,10)]

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ACLF, acute-on-chronic liver failure; ADH, anti diuretic hormone axis; AKI, acute kidney injury; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HRS, hepatorenal syndrome; IAC, International Ascites Club; KDIGO, Kidney Disease: Improving Global Outcomes; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; NSAID, nonsteroidal anti-inflammatory drug; RAS, renin angiotension system; RBC, red blood cell; RRT, renal replacement therapy; SBP, spontaneous bacterial peritonitis; sCr, serum creatinine; SLKT, simultaneous liver-kidney transplantation; SNS, sympathetic nervous system.

TABLE 1. New Classification of HRS

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

NOTE: Adapted from Angeli et al.[9]

Terlipressin, a vasopressin analogue, together with albumin has been shown to improve renal function in patients with HRS type 1.[11-16] However, terlipressin is not available in the United States. Recently, the multicenter, randomized, placebo-controlled double-blind study to confirm efficacy and safety of terlipressin in subjects with hepatorenal syndrome type 1 (the CONFIRM study) trial showed the efficacy and safety of terlipressin and albumin in HRS type 1 reversal in North America.[17] The aim of this article is to review the role of terlipressin and albumin for patients with HRS type 1 listed for LT in the United States.

HRS: Pathophysiology and Definition

HRS, as originally defined with a sCr cutoff 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 1 year and up to 40% at 5 years.[19,20] The new definition of HRS does not include a final cutoff value of sCr, thus allowing the diagnosis to be made and pharmacological treatment to be initiated at early stages.[9,10]

The pathogenesis of HRS is multifactorial, triggered by splanchnic vasodilatation leading to central hypovolemia, circulatory dysfunction, and systemic inflammation (Fig. 1A). Splanchnic and systemic vasodilation cause a lowering of mean arterial pressure and central blood volume.[22,23] Such vasodilation and lowering of vascular resistance would normally be corrected by autoregulatory 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.[24,25]

Cirrhotic cardiomyopathy, a phenomenon that affects both systolic and diastolic cardiac function, further exacerbates the circulatory dysfunction. Although 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 physiological stress stimulus.[18,23,26,27]

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.[28,29] A low-grade systemic proinflammatory state exists with elevated levels of cytokines, including interleukin 6 and tumor necrosis factor α, which may be associated with the translocation of enteric bacteria. Spontaneous bacterial peritonitis (SBP) is the most frequent infectious precipitant of HRS.[30] A total of 35% of patients with cirrhosis and ascites who develop SBP also develop AKI. Other bacterial infections can precipitate HRS, such as urinary tract or biliary tract infections.[8,14,18,23,27]

The interplay of various hemodynamic changes in patients with advanced cirrhosis and ascites as described here create the perfect storm when patients

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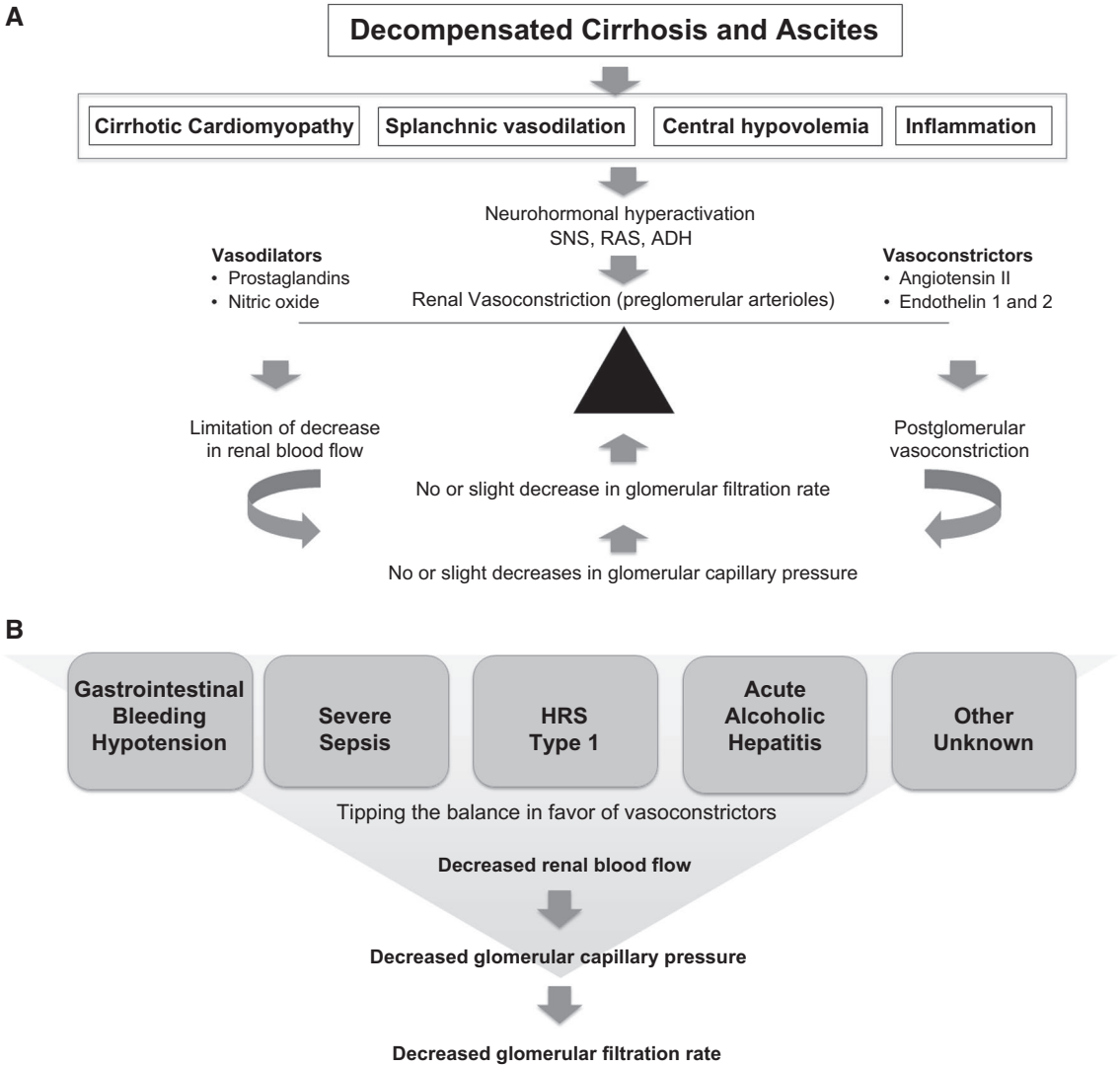

FIG. 1. (A) The relationship of renal blood flow and preserved glomerular filtration rate in patients with decompensated cirrhosis and ascites. (B) The second hit leading to AKI in patients with decompensated cirrhosis and ascites. Adapted from Moreau and Labrec[21] (2003).

are exposed to a "second hit" (hypovolemia, gastrointestinal bleed, dehydration, infection, etc.; Fig. 1B). The second hit typically leads to a further impairment of circulatory dysfunction and worsening renal perfusion.[26] The kidneys autoregulate renal blood flow at blood pressures above 70 mm Hg. However, overactivation 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.[25] Stimulation of the renin-angiotensin-aldosterone axis is further increased because of the inability of the cirrhotic liver to degrade renin.[25,31]

Historically, HRS was considered to be a single entity. In 1994, the ICA held a meeting at the American Association for the Study of Liver Diseases (AASLD) meeting in Chicago, and it was recognized that there were 2 forms of HRS, type 1 and type 2 based on the severity and acuity of renal dysfunction.[32] This distinction was made to improve the greater understanding of the pathophysiology of HRS and to aid the design of clinical trials with consistent efficacy endpoints. The more aggressive HRS type 1 (now called HRS-AKI), defined as a doubling of baseline sCr to a level >2.5 mg/dL

in less than 2 weeks, has a 2-week median survival if left untreated. HRS type 2 (now called HRS-NAKI) has a more insidious onset in patients with refractory ascites and moderate renal dysfunction (sCr ≥1.5 mg/dL), and it has a median survival of 4-6 months.[33] These cutoffs for baseline creatinine were arbitrary values that were determined partly to ensure homogeneity and to avoid inclusion of patients with prerenal AKI.

The ICA revised the definition of HRS in 2015[10] (Fig. 2A,B), and more recently in 2019[9] (Table 1) to incorporate it into a broad definition of AKI based on KDIGO criteria. These criteria define AKI in cirrhosis as an increase in sCr ≥0.3 mg/dL within 48 hours or a percentage increase in sCr ≥50% from baseline, which is known, or presumed, to have occurred within the past 7 days.[9,10] The subclassifications of HRS type 1 and HRS type 2 with the limiting threshold of a sCr concentration of 2.5 mg/dL and the time limit of 2 weeks to diagnosis for HRS type 1 were removed because the evidence suggests that a higher pretreatment sCr is associated with a lower probability of response to terlipressin and albumin in patients with HRS type 1.[34,35]

It is important to distinguish between the phenotypes of AKI given the therapeutic and prognostic implications. This newer classification describes a new phenotypic classification of HRS in patients with cirrhosis

A

ICA-AKI new definitions for the diagnosis and management of AKI in patients with cirrhosis

Subject	Definition		
Baseline sCr	• A value of sCr obtained in the previous 3 months, when available, can be used as baseline sCr. In patients with more than one value within the previous 3 months, the value closest to the admission time to the hospital should be used. • In patients without a previous sCr value, the sCr on admission should be used as baseline.		
Definition of AKI	• Increase in sCr ≥0.3 mg/dL (≥26.5 µmol/L) within 48 hours; or, • A percentage increase sCr ≥50% from baseline which is known, or presumed, to have occurred within the prior 7 days.		
Staging of AKI	• **Stage 1:** increase in sCr ≥0.3 mg/dL (26.5 µmol/L) or an increase in sCr ≥1.5-fold to 2-fold from baseline • **Stage 2:** increase in sCr >2-fold to 3-fold from baseline. • **Stage 3:** increase of sCr >3-fold from baseline or sCr ≥4.0 mg/dL (353.6 µmol/L) with an acute increase ≥0.3 mg/dL (26.5 µmol/L) or initiation of RRT.		
Progression of AKI	**Progression** • Progression of AKI to a higher stage and/or need for RRT	**Regression** • Regression of AKI to a lower stage	
Response to treatment	**No response** • No regression of AKI	**Partial response** • Regression of AKI stage with a reduction of sCr to ≥0.3 mg/dL (26.5 µmol/L) above the baseline value	**Full response** • Return of sCr to a value within 0.3 mg/dL (26.5 µmol/L) of the baseline value

B

Box 1. Diagnostic criteria of HRS type of AKI in patients with cirrhosis

HRS-AKI
- Diagnosis of cirrhosis and ascites
- Diagnosis of AKI according to ICA-AKI criteria
- No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin 1 g/kg of body weight
- Absence of shock
- No current or recent use of nephrotoxic drugs (NSAIDs, aminoglycosides, iodinated contrast media, or others)
- No macroscopic signs of structural kidney injury,* defined as
  - Absence of proteinuria (>500 mg/day)
  - Absence of microhaematuria (>50 RBCs per high-power field),
  - Normal findings on renal ultrasonography

FIG. 2. (A) IAC–AKI definitions for the diagnosis and management of AKI in patients with cirrhosis. (B) Diagnostic criteria of HRS-AKI in patients with cirrhosis. *Patients who fulfill these criteria may still have structural damage such as tubular damage. Urine biomarkers will become an important element in making a more accurate differential diagnosis between HRS and acute tubular necrosis. Adapted from Angeli et al.[9,10] (2015, 2017).

based on pathophysiological characteristics (Table 1).[9] Non-HRS-AKI now includes other causes of AKI in patients with cirrhosis, such as bile salt nephropathy, prerenal hypovolemia caused by bleeding, excessive diuretic use, or any excessive fluid loss, acute tubular injury, and necrosis as well as 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 definitions for HRS type 1 and type 2. The downside of the use of arbitrary but relatively high cutoffs for sCr is that patients with early stage HRS were never entered into controlled clinical studies. As a result, patients being randomized into such clinical trials always had advanced AKI due to HRS using current criteria.[9,10]

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, which is the underlying clinical milieu within which HRS develops and usually results in renal recovery after transplant.[36-38] 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 wait-list survival.

Albumin is the preferred plasma expander for volume expansion in patients with decompensated cirrhosis.[39] It is used in conjunction with splanchnic vasoconstrictors for the treatment for HRS and in combination with antibiotics for the treatment of SBP for the prevention of HRS.[40] It is increasingly clear that the beneficial effects of albumin derive from a combination of the oncotic and nononcotic properties including its role as pleotropic scavenger, antioxidant, and immunomodulatory molecule.[41] Albumin infusion improves circulatory volume, increases plasma renin activity, and may reduce the severity of inflammation by binding to lipopolysaccharides and other bacterial products.[42] Compared with albumin, alternative plasma expanders are less effective.[43] The recommended dose is 1 g of albumin per kilogram of body weight, with a maximum dose of 100 g/day. A meta-analysis of 19 studies suggested a significant dose-response benefit with albumin, with a 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 with 24.8% survival with a cumulative dose of 200-g albumin.[44]

Splanchnic vasoconstrictors like terlipressin exert their effect through vascular vasopressin V1 receptors in the splanchnic blood vessels, resulting in a 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 that baseline sCr and total bilirubin levels, grade of acute-on-chronic liver failure (ACLF), and mean arterial pressure were independent predictors of the response to terlipressin in HRS.[15,34]

Because terlipressin is not approved by the US Food and Drug Administration, the therapeutic options for patients with HRS in the United States are limited to either a combination of octreotide and midodrine with albumin[12,16] in noncritically ill patients or noradrenaline and albumin[45,46] 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, which may serve as a 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 it is not recommended in the European Association for the Study of the Liver guidelines.[47]

Several randomized controlled trials have evaluated the therapeutic effect of terlipressin with albumin and found that it is more effective in improving renal function in patients with HRS compared with other drugs or placebo.[11-15,48] Current data show that a terlipressin and albumin combination is superior to noradrenaline and albumin in patients with ACLF and HRS-AKI.[49] In a recent systematic review and meta-analysis, 18 randomized controlled trials including 1011 patients were analyzed. The HRS reversal rate was 42.0% in the terlipressin group and 26.2% in the nonterlipressin group. Terlipressin and albumin had a 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 a significant reversal in HRS in the terlipressin and albumin arm compared with placebo (29.1% versus 15.8%; $P = 0.012$).[17] The baseline characteristics of the enrolled patients were similar in both groups including the mean MELD scores (32.7 versus 33; P = not significant) and Sequential Organ Failure Assessment scores (10.4 versus 10.8; P = not significant). The durability of HRS reversal, defined as no RRT up to day 30, was significantly higher in the terlipressin and albumin arm compared with the placebo arm (31.7% versus 15.8%; $P = 0.003$).[17] Furthermore, the proportion of HRS patients needing RRT after LT was significantly lower in the terlipressin and albumin arm compared with placebo (19.6% versus 44.8%; $P = 0.04$).[17] Similar findings were reported from a European study where terlipressin-treated patients had a lower incidence of pretransplant and posttransplant RRT and a lower rate of chronic kidney disease (CKD) at 1 year.[32]

Terlipressin is a splanchnic vasoconstrictor, therefore, monitoring for ischemic events, such as gut ischemia, coronary ischemia, and digit ischemia, is required, which is similar to noradrenaline. In the CONFIRM trial, 9 out of 200 (4.5%) patients had ischemic adverse effects.[17] Patient selection for this therapy is the key given the potential for ischemia-related adverse effects with terlipressin.[11-13,15,17,33,46,48] Patients on the transplant wait 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 a bolus injection with less adverse events.[50]

Reversibility of HRS: Role of LT

It is clear from multiple studies that HRS is a largely functional prerenal 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.[36] Conversely, LT in patients with HRS frequently leads to normalization of kidney function after LT alone.[37,38,51,52] One study (n = 2112) reported the cumulative incidence of renal nonrecovery, which is defined as a transition to chronic dialysis within 6 months of LT, as 8.9% among those who were on acute RRT (<90 days) before LT.[38] The predictors of renal nonrecovery were longer duration of pre-LT RRT, diabetes, re-LT, and older age.[37,38,52]

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 wait list.[37,38,52] Additionally, their early posttransplant mortality is approximately 20%.[38] None of the randomized controlled trials 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, posttransplant 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 wait-list mortality, and timely transplant is not always available. Therefore, it is important to have treatment strategies that may serve as a bridge to transplant and could improve posttransplant outcomes of wait-listed candidates with high MELD scores.

HRS: Role of SLKT

Simultaneous liver-kidney transplantation 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 patients with sustained AKI will have renal recovery after LT alone. Previous studies suggest that advanced age, diabetes, re-LT, and prolonged duration of RRT before LT are the significant predictors of renal nonrecovery after LT alone.[37,52,53] The recent SLKT policy, implemented in August 2017, has medical eligibility criteria and the option of a safety net.[54] The safety net is for those LT recipients who do not recover renal function after LT alone or who 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 6.5% of all SLKT performed in 2018 (unpublished data from the Scientific Registry of Transplant Recipients). Patients with sustained AKI who were transplanted and did not recover their renal function benefited from the safety net option, which

led to a decreased number of SLKTs and an increase in kidney transplants after LT in 2018.

HRS Reversibility: Impact on MELD Score

Patients with HRS have worse survival for any given MELD score when compared with other patients with cirrhosis on the LT wait list. Reversal of HRS due to a response to terlipressin and albumin will reduce the MELD score transiently and can affect a patient's priority on the transplant wait list. Therefore, a rescue prioritization strategy should be developed for patients requiring treatment with terlipressin and albumin because recurrence of HRS occurs in 20% of responders. Updating the MELD scores for patients on the transplant wait list is a dynamic process. For example, those with a MELD score >24 need a MELD score update 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 of the listed candidates. Because the reduction of MELD score can affect the priority on the wait list, a rescue prioritization strategy should be developed for patients requiring longterm treatment with terlipressin and albumin due to the recurrence of HRS.

HRS reversal on terlipressin and albumin may reduce MELD score transiently. There should be a mechanism so that these patients are not disadvantaged by the transient reduction in MELD score because of improvement in sCr. To maintain the priority of treated HRS patients on the wait list, the Liver and Intestine Transplant Committee should consider either a weighted pretreatment sCr 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 terlipressin's anticipated approval by the US Food and Drug Administration. This is very important to ensure the optimal pretransplant management of HRS in the listed candidates without the concerns as to whether such treatments might decrease their prioritization for LT.

Furthermore, poor renal function and the use of RRT increases wait-list and posttransplant mortality.[19,20,53,55,56] Unlike splanchnic vasoconstrictor therapy, RRT does not reverse the underlying process leading to HRS. Furthermore, the downstream adverse effects of RRT, such as venous access bleeding, infections, electrolyte abnormality, fluid overload, and cardiac events, may further increase morbidity, readmissions, and mortality in a wait-listed patient.

Renal failure requiring hemodialysis after transplantation is a major risk factor for death in LT recipients. Patients who require posttransplant dialysis also have significantly worse graft survival compared with those without posttransplant RRT.[53,55] In a single-center study, 75.8% of patients with pretransplant patients had resolution of HRS after LT. Like other studies, those who had higher pretransplant sCr, longer duration of AKI, and RRT before LT were less likely to have renal recovery following LT.[37,38] 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 as well as the need for SLKT, and it should result in better posttransplant outcomes.

Conclusions

HRS is an ominous complication of portal hypertension associated with very high morbidity and mortality. We hope that with the success of the CONFIRM trial in achieving HRS type 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 wait-listed LT candidates and may improve their pretransplant and posttransplant outcomes including renal outcomes.

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