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End-stage liver disease: Management of hepatorenal syndrome

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Abstract

Hepatorenal syndrome (HRS) is a serious complication of cirrhosis with high morbidity and mortality rates. Recently, the definition of HRS type 1 has been updated and is now called HRS-AKI. This new definition reduces the risk of delaying HRS treatment and eliminates the need to establish a minimum creatinine cut-off for the diagnosis of HRS-AKI. From a pathophysiological point of view, newly identified mechanisms involved in the development of HRS are related to the inflammatory response, conditioning the development of extrahepatic organ dysfunction in patients with cirrhosis. One of the main challenges for the diagnosis of HRS is the validation of new biomarkers to obtain an early and differential diagnosis of kidney injury (eg HRS vs. ATN). Treatment of HRS is based on the use of vasoconstrictive agents in combination with albumin and terlipressin is the most widely used vasoconstrictor drug, with a high response rate. The effects of a continuous infusion of terlipressin at a dose of 2-12 mg/day was similar to bolus administration, but with lower rates of adverse events. Finally, MELD/MELD-Na which includes creatinine as one of its main determinants gives AKI-HRS patients priority on the waiting list (WL) for liver transplant (LT). However, the MELD and MELD-Na scores are reduced in responding patients, resulting a longer waiting time in these patients than in non-responders. Thus, the initial MELD/MELD-Na score (pre-treatment value) should be used to prioritize patients on the WL for LT in these cases.

KEYWORDS

AKI, cirrhosis, HRS, liver Transplant

1 | INTRODUCTION

Hepatorenal syndrome (HRS) is a serious complication of cirrhosis that is associated with high morbidity and mortality rates. Its development is associated with functional circulatory changes in the kidneys which are a maladaptive response of physiological compensatory mechanisms leading to a significant decrease in the estimated glomerular filtration rate (eGFR).[1] Moreover, this circulatory condition is reversible if renal blood flow is reestablished, either by liver transplantation or by the use of vasoconstrictor therapy.[2] The terminology, definition, and classification of HRS have changed considerably in the last 10 years, mainly due to changes in the diagnosis and staging of acute kidney injury (AKI) and improved characterization of the natural history of

Abbreviations: ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; ATN, acute tubular necrosis; CCM, Cirrhotic cardiomyopathy; CKD, chronic kidney disease; CSPH, clinically significant portal hypertension; CysC, Cystatin C; eGFR, estimated glomerular filtration rate; FENa, fractional excretion of sodium; HRS, hepatorenal syndrome; HRS-AKD, HRS Acute kidney disease; HRS-CKD, HRS Chronic kidney disease; ICA, International Club of Ascitis; LT, liver transplant; N-GAL, neutrophil gelatinase-associated lipocalin; RRT, renal replacement therapy; SBP, spontaneous bacterial peritonitis; SLKT, simultaneous liver-kidney transplant; TLR4, Toll-like receptor 4; WL, waiting list.

acute kidney disease in patients with cirrhosis.[3,4] Thus, one of the main challenges of clinical practice is to differentiate HRS from acute tubular necrosis (ATN), which is important because the use of vasoconstrictors is not indicated in the latter patients. Also, one of the main topics of debate is whether HRS and ATN should be considered a continuum instead of different entities.[5,6] Emerging biomarkers can help differentiate these two conditions and even provide prognostic information on the recovery of kidney function after liver transplantation (LT), as well as help decide on the need for simultaneous liver-kidney transplant (SLKT).[7] The present review describes the recent advances that have shaped the current definitions, diagnosis and management of HRS.

Key points

- Hepatorenal syndrome (HRS) is a deterioration of renal function caused mainly by the presence of systemic circulatory dysfunction. However, it has recently been discovered that systemic inflammation and the presence of cirrhotic cardiomyopathy also play a role in its pathogenesis. The development of HRS is associated with poor survival.
- The diagnosis of HRS is based on the new criteria of the International Club of Ascites-Acute Kidney Injury (ICA-AKI) and Hepatorenal Syndrome-Acute Kidney Injury (HRS-AKI), which are essential to exclude the presence of intrinsic kidney disease (hematuria, proteinuria or abnormal renal ultrasound).
- Currently, two types of hepatorenal syndrome are recognized depending on the time of presentation and the progression of kidney injury. The first, HRS-AKI, represents the acute deterioration of renal function, while the second represents exacerbated chronic kidney dysfunction, HRS-CKD.
- The treatment of HRS includes the early use of terlipressin with albumin. However, liver transplantation continues to be the treatment with the greatest benefit to survival, and therefore, timely referral for transplant evaluation is crucial in preventing permanent kidney damage and if necessary to determine the need for a simultaneous liver and kidney transplant.
- The use of new renal biomarkers in clinical practice can improve both the diagnosis and prognosis of this population. In particular, NGAL is a promising biomarker in cirrhosis with a significant impact in clinical practice for the differentiation between ATN and HRS, showing that improved prognostic accuracy has significant implications in organ allocation.

2 | DEFINITIONS

Acute deterioration of renal function, determined by an increase in serum creatinine, is a prevalent condition (19%-26%) in hospitalized patients with cirrhosis.[8] Although it is widely used, serum creatinine is known to have serious limitations in patients with decompensated cirrhosis. Creatinine synthesis is reduced in patients with cirrhosis, either because of reduced muscle mass or reduced protein intake. Moreover, there is a gender bias.[9] Therefore, creatinine is a sub-optimal biomarker for risk stratification in this population. New, alternative, more precise biomarkers such as cystatin C (CysC), are promising in patients with cirrhosis both because of the possibility of early diagnosis and their ability to establish a prognosis.[10] Nevertheless and despite its limitations, serum creatinine continues to be the most affordable and available biomarker for eGFR and thus, the definition of acute renal failure has evolved in the last two decades due to the variability of this serological biomarker. Recent modifications in the diagnostic criteria for AKI by the International Club of Ascites (ICA), based on an absolute increase in serum creatinine of at least 0.3 mg/dl or 50% from baseline, have been shown to be more effective for the early detection of patients at a higher risk of a longer hospital stay, multiple organ failure, admission to intensive care units, in-hospital mortality, and mortality at 90 days.[11-13] (Table 1).

Recently, the ICA also updated the definition of type 1 HRS, which is now called HRS-AKI. One of the main changes of this new definition is that the two-week interval required to double the serum creatinine in the previous definition has been modified because it creates a risk of delaying the beginning of treatment for hepatorenal syndrome. It has also been shown that the higher the serum creatinine at the start of vasoconstrictor treatment, the lower the probability of reversing HRS.[14] Thus, this new definition has eliminated the need for establishing a minimum creatinine cut-off for the diagnosis of HRS-AKI.[3] In contrast, the new ICA definition states that functional kidney injury which does not meet HRS-AKI criteria is now called HRS-NAKI (that is, not AKI) and is defined by eGFR instead of serum creatinine. The presence of NAKI is divided into HRS Acute kidney disease (HRS-AKD) if the eGFR is less than 60 ml/min/1.73 m2 for less than three months and HRS Chronic kidney disease (HRS-CKD) if it is less than this for more than three months (Table 1).

3 | PATHOGENESIS OF HEPATORENAL SYNDROME

3.1 | Circulatory dysfunction

The main driver in the development of the complications of cirrhosis is clinically significant portal hypertension (CSPH). The consequent splanchnic arteriolar vasodilation is a key factor in the pathophysiology of HRS-AKI.[2] In the early stages of cirrhosis, the increase in intraportal hypertension is modest along with

TABLE 1 Definition of AKI according to international club of ascites

ICA AKI in Cirrhosis	Increase in sCr>= 0.3 mg/Dl (26.5 umol/L) within 48 hours OR sCr percentage increase >= 50% x baseline, which is known or presumed to have occurred within the prior 7 days
ICA Determining Baseline sCr in Cirrhosis	SCr value obtained in the previous 3 months should be used, when available if multiple sCr values within previous 3 months, value closest to admission sCr should be used. If no previous sCr available, admission sCr serves as baseline value
ICA AKI Staging in Cirrhosis	Stage 1: Increase in sCr >= 0.3 mg/Dl (26.5 umol/L) within 48 hours OR increase in sCr 1.5-2 x baseline
	Stage 2: Increase in sCr 2-3 x baseline
	Stage 3: Increase in sCr > 3 x baseline OR sCr > 4 mg/dl (353.6 umol/L) with an acute rise > 0.5 mg/dl (44 umol/L) OR initiation of RRT
OLD NAME **HRS type 1**	**NEW NAME** **HRS-AKI**
- Doubling of serum creatinine to a concentration >= 2.5 mg/dL within 2 weeks	- Increase In serum creatinine of >= 0.3 mg/Dl within 48 hours OR - Increase in serum creatinine >= 1.5 times from baseline (creatinine value within previous 3 months, when available, may be used as baseline, and value closest to presentation should be use)
- No response to diuretic withdrawal and 2-day fluid challenge with 1 g/kg/day of albumin 20%-25%	- No response to diuretic withdrawal and 2-day fluid challenge with 1 g/kg/day of albumin 20%-25%
- Cirrhosis with ascities	- Cirrhosis with ascities
- Absence of shock	- Absence of shock
- No current or recent use of nephrotoxic drugs (NSAIDs, contrast dye, etc)	- No current or recent use of nephrotoxic drugs (NSAIDs, contrast dye, etc)
No signs of structural kidney injury - Absence of proteinuria (> 500 mg/day) - Absence of hematuria (> 50 RBCs per high power field) - Normal findings on renal ultrasonography	No signs of structural kidney injury - Absence of proteinuria (> 500 mg/day) - Absence of hematuria (> 50 RBCs per high power field) - Normal findings on renal ultrasonography
HRS type 2 - Gradual increase in serum creatinine, not meeting criteria above	HRS-NAKI *HRS-AKD* - Estimated glomerular filtration rate < 60 mL/min/1.73 m^2 for < 3 months in absence of other potential causes of kidney disease. - Percentage increase in serum creatinine < 50% using last available value of outpatient serum creatinine within 3 months baseline value *HRS-CKD* - Estimated glomerular filtration rate < 60 mL/min/1.73 m^2 for >= 3 months in absence of other potential causes of kidney disease

a decrease in systemic resistance caused by vasodilation. This vasodilation, which is the main cause of HRS, is triggered by the overproduction of vasodilator substances (nitric oxide, carbon monoxide and endocannabinoids) and their reduced degradation due to increased portal hypertension and the leaking of these substances into the general circulation. Increased cardiac output, heart rate and the activation of powerful vasoconstrictor systems and the renin-angiotensin-aldosterone system are triggered as compensatory physiological measures. In the same way, the development of liver complications shows that these initially adaptive measures are no longer efficient, causing deterioration of renal blood flow.[15] These consequences are associated with the retention of sodium and free water with the accumulation of ascites and oedema.[16] Later, renal vasoconstriction becomes even more pronounced, eGFR decreases, and SHR may develop. Finally, if extreme renal vasoconstriction is not corrected in time, it may lead to the development of acute tubular necrosis, although this evolution is still controversial.[5,6] (Figure 1).

3.2 | Systemic inflammation

The presence of a systemic inflammatory response syndrome was identified in almost half the patients with HRS-AKI, independently from the presence of infection.[17] Systemic inflammation occurs as a result of increased intestinal permeability which leads to pathological bacterial translocation from the intestine to the systemic circulation, changes in the quantity and quality of microbiome and immune dysfunction associated with cirrhosis.[18]

Bacterial translocation induces a broad spectrum of genes that encode molecules responsible for triggering an inflammatory response through specific receptors called pattern

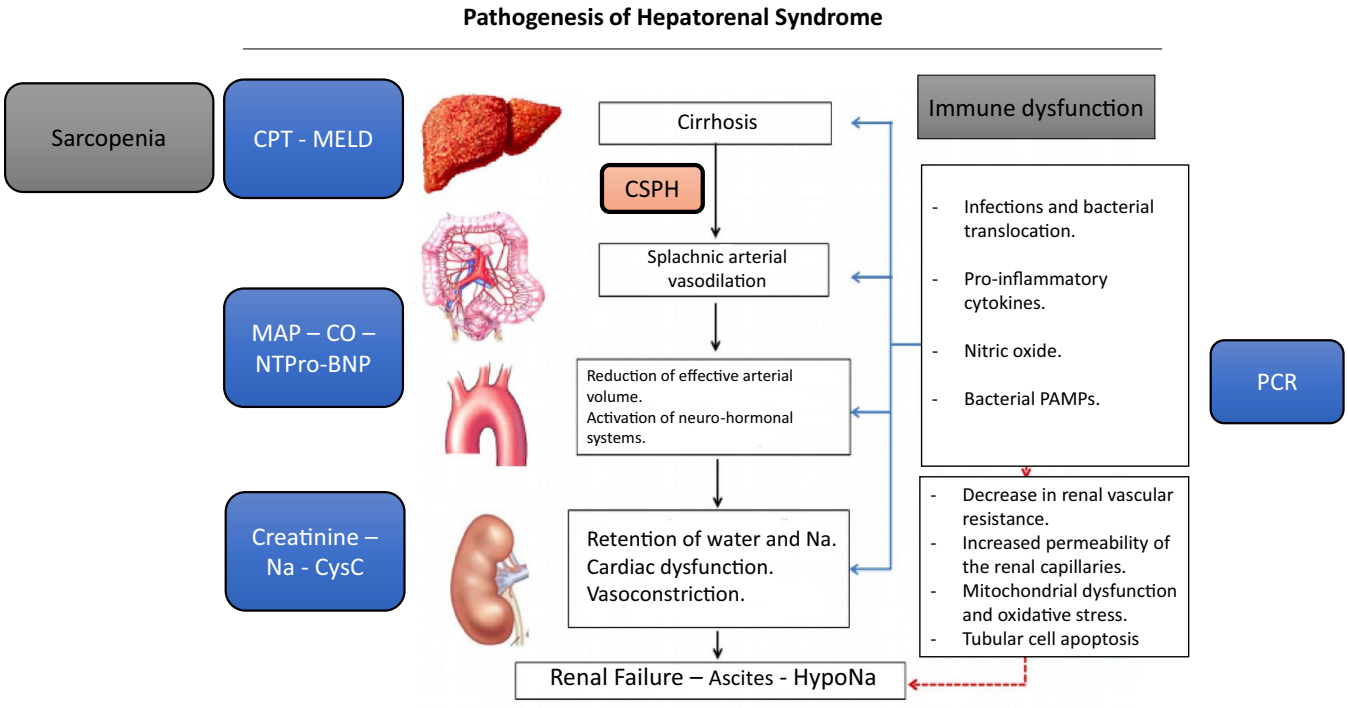

FIGURE 1 Pathophysiology of hepatorenal syndrome

recognition receptors.[19] The Toll-like receptor 4 (TLR4) is the main pattern recognition receptor that has been studied. Tubular TLR4 overexpression has been described in patients with cirrhosis and renal dysfunction.[20] A subset of patients diagnosed with hepatorenal syndrome showed TLR4 overexpression in tubular cells and evidence of tubular cell damage, suggesting an overlap in the pattern of kidney damage and not a pure form of HRS-AKI.[20] The inflammatory components can spread to the systemic circulation and peripheral organs, conditioning the development of dysfunction of extrahepatic organs, including the kidney. Immune dysfunction and changes in systemic inflammation can contribute to systemic circulatory changes associated with the development of HRS. Clear evidence of this situation is represented by high levels of pro-inflammatory cytokines (TNF-a and IL-6).[21] (Figure 1).

3.3 | Cirrhotic cardiomyopathy

Cirrhotic cardiomyopathy (CCM) is a silent condition that is difficult to identify in a stable setting but can become symptomatic during a decompensating event and is clearly involved in the pathophysiology of HRS, mainly because it greatly alters renal perfusion. Recent studies have shown that the presence of CCM, either based on echocardiographic parameters or biomarkers such as NT-proBNP (Diaz JM et AASLD 2020 - Poster number 1846), is directly related to the development of HRS through its dynamics and decreased cardiac output.[22] (Figure 1).

4 | CLINICAL APPLICATION OF KIDNEY BIOMARKERS

Despite the numerous limitations of creatinine as a renal biomarker, it continues to be the most widely accepted parameter worldwide. However, the development of new, more clinically useful, renal biomarkers is promising.[9] One of the main uses of urinary biomarkers is to clarify the aetiology of renal failure, more specifically by differentiating ATN from HRS-AKI. The most extensively investigated biomarker thus far is neutrophil gelatinase-associated lipocalin (N-GAL), which has been shown to be robust in differentiating ATN from HRS-AKI and thus to be useful when deciding on vasoconstrictor therapy.[7] The best diagnostic performance of N-GAL for differentiating ATN has been found at a cut-off of 220 ug/g with approximately 86% of the diagnoses of ATN with values above this threshold, while 88% of those with HRS-AKI and 93% of prerenal-AKI had values below this cut-off.[23,24] (Figure 2A) However, despite its discriminative capacity, this urinary biomarker is not easily accessible in daily practice worldwide, thus, more readily available, simpler tools are needed.

The use of the fractional excretion of sodium (FENa) continues to be useful in differentiating between functional and structural damage. In case of functional damage, the tubules are usually intact, allowing greater Na reabsorption due to renal hypoperfusion. However, circulatory disorders, especially in patients with advanced cirrhosis, could cause chronic renal hypoperfusion and therefore affect the estimated values of FENa < 1%. Despite this, different studies in HRS-AKI have shown that FENa values < 0.2% adequately

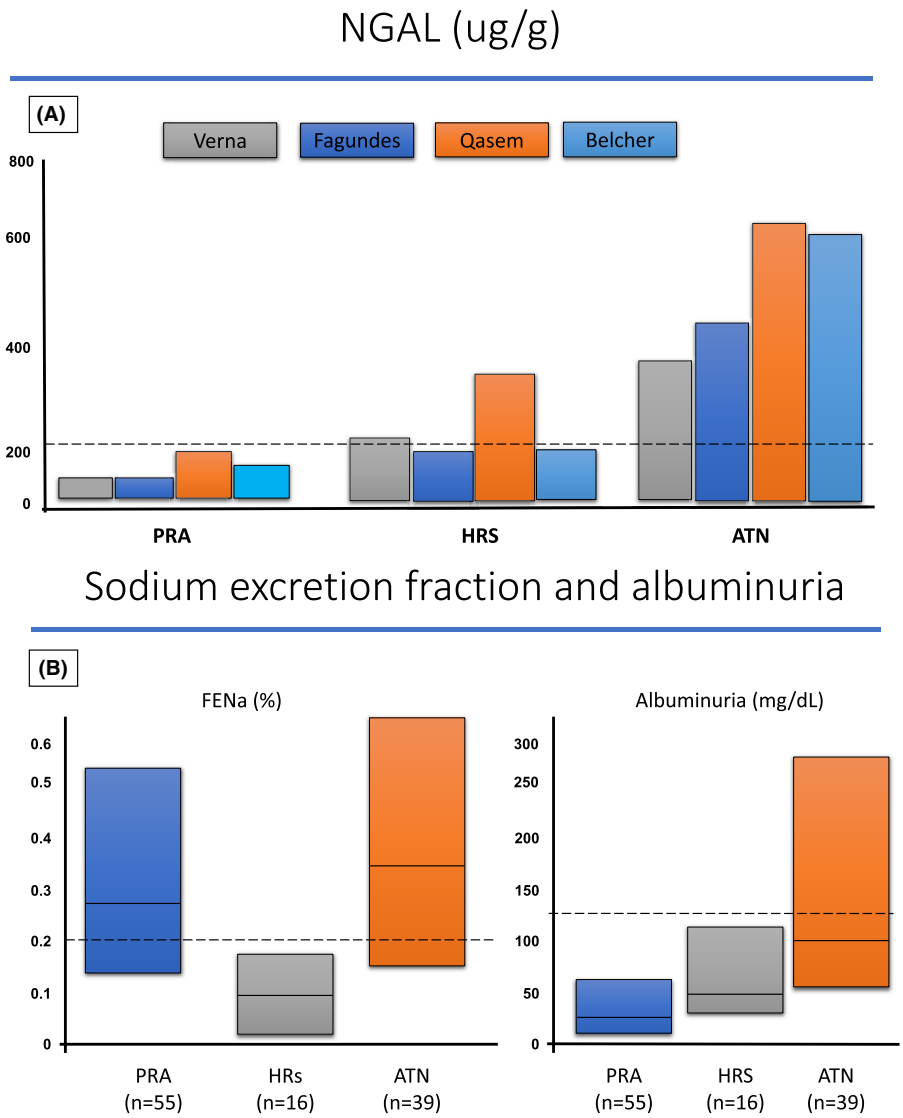

FIGURE 2 Urinary biomarkers in the differential diagnosis of hepatorenal syndrome vs. acute tubular necrosis

differentiate HRS-AKI from ATN.[23,25] (Figure 2B) Moreover, recent studies have shown similar results in the diagnosis of ATN based on high levels of albuminuria.[26]

Finally, the use of serum CysC has become more relevant to identify patients at risk of developing renal events independently of muscle mass or sex, as well as for its predictive value for the development of acute on chronic liver failure (ACLF) and mortality on the waiting list (WL) for LT.[10] Figure 3.

5 | PREVENTION OF HEPATORENAL SYNDROME

5.1 | Prevention of circulatory dysfunction

Numerous predictors have been described for the development of HRS: hyponatremia, high plasma renin activity,[27] the degree of ascites,[28] and elevated CysC values.[29] However, the main factors associated with HRS-AKI are the acute hemodynamic changes associated with infections and large volume paracentesis without albumin administration, while the development of AKI without a clear triggering factor is very rare (1.8%).[28]

The prevalence of HRS-AKI in the presence of spontaneous bacterial peritonitis (SBP) or other bacterial infections is 30% and is a sign of a poorer short-term prognosis.[30-33]

Post-paracentesis circulatory dysfunction occurs after large-volume paracentesis (≥5 L) and is associated with hypotension, hyponatremia, and an increased risk of HRS-AKI. Albumin administration after large-volume paracentesis significantly reduces this risk and improves overall survival in these patients.[1] This protective effect appears to be unique to albumin, compared to other volume expanders, suggesting that albumin has an additional benefit other than as a plasma expander.[34]

Moreover, the development of HRS-AKI can be prevented by the administration of intravenous albumin in addition to the early initiation of effective antibiotic treatment in the presence of SBP (8.3%

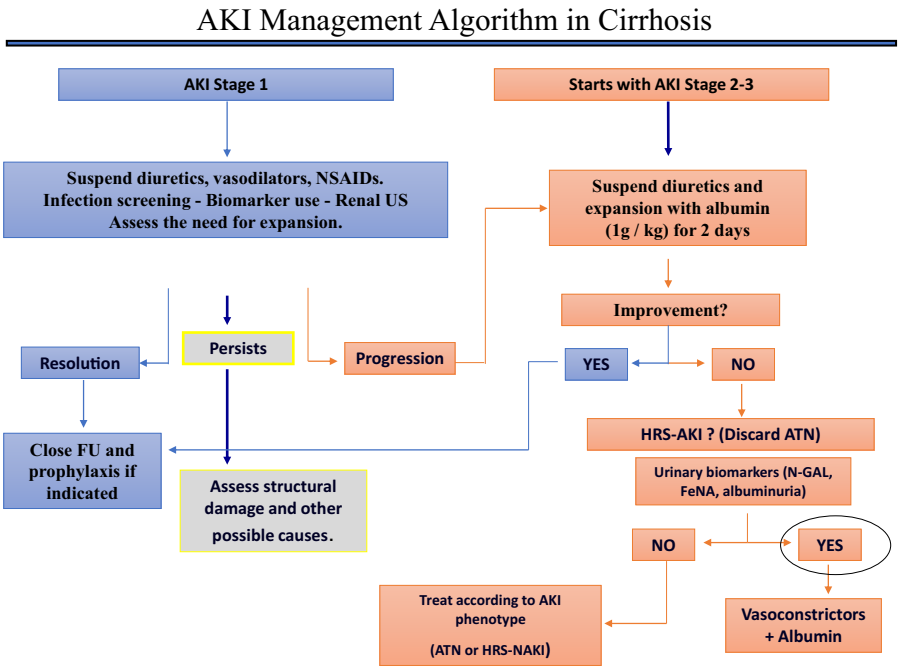

FIGURE 3 Algorithm for management of acute kidney injury in patients with cirrhosis

vs 30.6% with antibiotics alone; $P = .01$), leading to a reduction in overall mortality (16% vs 35.4%; OR: 0.34).[30,35] In contrast, although the administration of albumin to patients with non-SBP infections can improve circulatory function and delay the development of renal dysfunction,[36] it has not been shown to prevent the development of HRS-AKI or improve survival.[37]

The evidence on the prolonged use of albumin as a preventive strategy in decompensated cirrhosis is controversial. This hypothesis has been evaluated in a recent RCT in which weekly albumin administration was added to standard treatment for 18 months and was shown to improve overall survival (77% vs 66%; $P = .028$) as well as to reduce the incidence of HRS-AKI (OR:0.39).[38] In contrast, a similar trial evaluating the long-term use of albumin and midodrine in 196 patients with decompensated cirrhosis on the WL for LT did not show a one-year survival benefit, or any prevention of the complications of cirrhosis.[39] In conclusion, although there is biological plausibility for the use of albumin, future trials such as PRECIOSA12 or ATTIRE trial, are expected to shed light on long-term albumin in this population.

5.2 | Antibiotic prophylaxis

Prophylactic antibiotics to prevent SBP and after gastrointestinal bleeding, have been shown to decrease the incidence of HRS-AKI. The risk of SBP is identified by lower concentrations of protein in ascites fluid (<1.5 mg/dl) associated with liver and/or kidney dysfunction (bilirubin > 3 mg/dl, serum sodium < 130 mEq/L, Child-Pugh score > 10, and/or serum creatinine > 1.2 mg/dl) In these cases antibiotic prophylaxis prevents both the development of SBP as well as significantly reducing the risk of HRS-AKI and overall mortality.[40]

6 | MANAGEMENT AND TREATMENT OF HEPATORENAL SYNDROME

At present, vasoconstrictor agents in combination with albumin are the first-line treatment for HRS-AKI.[41-45] Terlipressin, a vasopressin analogue, is the most commonly prescribed drug. The efficacy of terlipressin plus albumin in the treatment of hepatorenal syndrome has been evaluated in a large number of patients, with a response rate ranging from 25% to 75%. Terlipressin can first be administered intravenously at 0.5-1 mg every 4-6 hours, then gradually increased to a maximum dose of 2 mg every 4 hours. Treatment should be maintained until a complete response is obtained or for a maximum of 14 days. The side effects of terlipressin are related to vasoconstriction, with a risk of myocardial infarction and intestinal or peripheral ischemia.

Continuous infusion of terlipressin at a dose of 2-12 mg/d has been shown to have effects similar to a bolus administration but with lower rates of adverse events in one study.[46] Baseline serum creatinine and the degree of ACLF (the higher the degree, the greater the inflammation) are inversely associated with the response to terlipressin.[43,47] Other vasoconstrictive agents have been proposed in combination with albumin. Although norepinephrine at a dose of 0.5-3 mg/h, IV is an alternative treatment that has been shown to be effective in small studies[48-50] a recent controlled trial suggests that this agent is not as effective as terlipressin in reversing HRS-AKI, renal replacement therapy (RRT)

requirements, or overall survival in ACLF.[45] The combination of midodrine plus octreotide, used in countries where terlipressin is not yet available, has been shown to be less effective than terlipressin in a single-centre study.[41]

7 | IMPLICATIONS OF HRS-AKI TREATMENT IN LIVER TRANSPLANTATION

Although the response to vasoconstrictor therapy plus albumin has clearly been found to be beneficial in restoring renal function, LT is the therapy with the greatest benefit to survival.[51] On one hand, the fact that MELD/MELD-Na includes creatinine as one of its main determinants, means that patients with HRS-AKI are prioritized on the WL for LT. However, responding patients present with a reduction in the MELD and MELD-Na scores, and thus have to wait for a graft about twice as long as those who do not respond, and have a lower possibility of LT in the short term.[52] This issue has been addressed by experts in the field who suggest using the baseline MELD/MELD-Na score (pre-treatment value) for giving priority on the LT WL to responders to terlipressin and albumin. This strategy is reasonable, especially because for any given MELD score value, patients with HRS have shorter expected survival than candidates for LT with chronic liver disease.[12]

Patients responding to terlipressin and albumin present with less severe AKI episodes after LT and less need for RRT than those who do not respond to vasoconstrictor therapy, which lowers post-LT survival rates.[52] The most widely accepted hypothesis on the impact of the lack of response to vasoconstrictor therapy in pre-LT and the consequences after LT, is based on the presence and/or the progression to ATN, where tubular injury markers are frequently higher or which increase over time as HRS-AKI evolves. However, the lack of robust data supporting the hypothesis of a progression from AKI-HRS to AKI-ATN shows the need for additional well-designed studies, possibly with new biomarkers of tubular injury.[5,6]

Finally, although the response to treatment with terlipressin plus albumin reduces the risk of CKD one year after LT in patients with HRS-AKI, strategies are needed to improve prioritization for responders on the WL for LT to prevent long-term kidney damage and thus its impact on post-LT survival.

8 | THE DIFFICULT DECISION BETWEEN LIVER OR SIMULTANEOUS LIVER–KIDNEY TRANSPLANTATION

Predicting the outcome of kidney function after LT is a challenge because it is difficult to accurately evaluate the relative contribution of kidney disease itself, perioperative events, and post-LT immunosuppression on kidney dysfunction after LT.

The presence of AKI before LT has been shown to be associated with a higher risk of long term chronic kidney disease (CKD) after LT as well as an increased risk of mortality.[53]

The treatment of choice for patients with HRS-AKI is liver transplantation, and in case of pure HRS without any other renal disease, kidney function should be fully restored post-LT. However, there are several issues that should be taken into account when deciding on transplantation. First, kidney recovery after LT in patients with HRS-AKI is less probable in the presence of associated ATN. Moreover, this complication is associated with decreased survival. In addition, other intrinsic CKD could also play a role. Thus, the decision to perform SLKT rather than LT alone is based not only on the increased risk of post-LT mortality, but also on the risk that the kidney might not recover.

The decision is clearly not easy. The duration of AKI and dialysis and any evidence of CKD are factors that can help. In the most difficult cases, a (usually transjugular) kidney biopsy should be performed to reach the best decision.

CONFLICT OF INTEREST

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