Monitoring Renal Function and Therapy of Hepatorenal Syndrome Patients with Cirrhosis

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KEYWORDS

• Cirrhosis • Acute kidney injury • Hepatorenal syndrome • Terlipressin • Biomarkers • Liver transplantation

KEY POINTS

- Differential diagnosis of the causes of acute kidney injury (AKI) in cirrhosis is essential to start correct treatment as soon as possible and improve outcomes.
- The diagnostic criteria of HRS-AKI recently have been modified and the cutoff value of serum creatinine has been removed, thus leading to earlier identification and start of treatment.
- Vasoconstrictors, in particular terlipressin, together with intravenous albumin is the first-line pharmacologic treatment of patients with hepatorenal syndrome (HRS)-AKI and should be started as soon as possible after its diagnosis.
- Liver transplantation represents the definitive treatment of patients with HRS-AKI. Therefore, if there are no contraindications, all patients with HRS-AKI should be evaluated for liver transplantation.

Funding: Part of the work discussed in this article was supported by grant funding from Plan Nacional I+D+I and cofunded by ISCIII–Subdirección General de Evaluación and European Regional Development Fund FEDER (PI16/00043 and PI18/00727). The European Commission Horizon 2020 program, grant LIVERHOPE: 731875. Some of the investigators involved have been supported by the AGAUR 2017-SGR-01281. A.J. is funded by Contratos Río Hortega (CM19/00044) granted by Instituto de Salud Carlos III and by the Award 'Emili Letang' granted by Hospital Clínic de Barcelona.

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Clin Liver Dis 25 (2021) 441–460
https://doi.org/10.1016/j.cld.2021.01.011
liver.theclinics.com

ACUTE KIDNEY INJURY IN CIRRHOSIS: RELEVANCE OF THE PROBLEM

Acute kidney injury (AKI) is a common complication of patients with cirrhosis, occurring in up to 20% to 50% of hospitalized patients for an acute decompensation of cirrhosis.[1–6] The development of AKI is associated with very high short-term and long-term mortality that directly correlates with the severity of AKI.[2,3,7] A systematic review of 74 studies showed that the overall median mortality in patients with cirrhosis and AKI was 67%, 30-day mortality was 58%, and at 1 year mortality was 63%.[8] In addition, there is accumulating evidence showing that AKI predisposes to development of chronic kidney disease (CKD) in patients with cirrhosis, which is associated with higher risk of new episodes of AKI and worse outcomes.[6,9]

DEFINITION OF ACUTE KIDNEY INJURY IN CIRRHOSIS

Traditionally, the diagnosis of renal failure in patients with cirrhosis was defined as an increase in serum creatinine (SCr) of greater than or equal to 50% from baseline to a final value of greater than 1.5 mg/dL (133 μmol/L).[10,11] Using this definition, however, at the time of diagnosis, most patients already had severely reduced glomerular filtration rate (GFR) (<30 mL/min), and the use of a fixed threshold did not capture the dynamic changes in SCr, limiting the differentiation between acute and chronic renal failure.[12] Consequently, the diagnosis of renal failure in patients with cirrhosis was modified according to Acute Kidney Injury Network criteria by the International Club of Ascites (ICA) in 2015.[13] According to the ICA-AKI criteria, AKI in cirrhosis is defined as an increase in SCr of greater than or equal to 0.3 mg/dL (≥26.5 μmol/L) within 48 hours or a percentage increase in SCr of greater than or equal to 50% from baseline, which is known, or presumed, to have occurred within the prior 7 days.[13] These criteria also classify AKI into different stages (AKI 1, AKI 2, and AKI 3) depending on the magnitude of change in SCr (**Table 1**) and provide definitions for the concepts of progression and regression of AKI and response to treatment. Several studies have validated the usefulness of AKI criteria in patients with cirrhosis and describe that AKI stages are useful for prognosis stratification because they correlate with mortality.[2,3,14,15]

Results from different studies have shown that the population of patients included in AKI stage 1 is heterogeneous and should be divided into 2 subgroups with different prognoses. These studies showed that patients with stage 1 and SCr at diagnosis less than 1.5 mg/dL, named AKI stage 1A, had significantly better prognosis than that of patients with stage 1 and SCr at diagnosis greater than or equal to 1.5 mg/

Table 1
Diagnostic criteria and acute kidney injury stages

Definition of acute kidney injury	
Increase in SCr ≥0.3 mg/dL (≥26.5 μmol/L) within 48 h; or, a percentage increase in SCr ≥50% from baseline, which is known, or presumed, to have occurred within the prior 7 d	
Acute kidney injury stages	
1A	Increase in SCr ≥0.3 mg/dL (26.5 μmol/L) from baseline to a value <1.5 mg/dL (133 μmol/L)
1B	Increase in SCr ≥0.3 mg/dL (26.5 μmol/L) from baseline to a value ≥1.5 mg/dL (133 μmol/L)
2	Increase in SCr >2-fold to 3-fold from baseline
3	Increase in 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

dL, named AKI stage 1B.[2,3,14] Patients with AKI stage 1A have significantly higher 90-day survival rates compared with that of patients with AKI stage 1B (82% vs 55%, respectively; $P = .001$). In addition, progression of AKI and development of acute-on-chronic liver failure (ACLF) are significantly more common in patients with AKI stage 1B compared with those with AKI stage 1A. In view of these results, it currently is recommended that patients with cirrhosis AKI stage 1 should be divided into 2 groups for better prognosis stratification.[16]

An important point derived from the new definition is the need of a baseline value of SCr. The ICA-AKI criteria arbitrarily defined baseline SCr for the diagnosis of AKI as the closest SCr value within 3 months before hospital admission.[13] In patients without a previous value available before hospitalization, the value at admission should be used. It should be taken into account that in this latter subgroup of patients, a diagnosis of AKI may be missed. Therefore, the management of that specific group of patients should be based not only on the AKI definition but also on clinical experience; if there is a precipitant event and SCr is greater than or equal to 1.5 mg/dL, it is reasonable to assume that these patients probably have an AKI episode and should be treated accordingly.

As discussed previously, AKI is defined by increase in SCr levels. It is well known, however, that SCr is an inaccurate marker of renal function in cirrhosis, because SCr could be underestimated due to sarcopenia found in patients with advanced cirrhosis.[17] Along the same lines, equations to estimate GFR are based on SCr and tend to overestimate true GFR.

In recent years, the use of plasma cystatin C has gained interest and could represent an alternative maker of renal function, not only for estimating GFR but also for predicting kidney dysfunction and mortality in patients with acute decompensation of cirrhosis.[9,18] Nevertheless, a reference method for cystatin C dosage is lacking, and genetic variability in cystatin C production or metabolism has been reported.[17] Thus, further investigation on cystatin C and new methods for an accurate assessment of renal dysfunction in patients with decompensated liver cirrhosis are needed.

DIFFERENTIAL DIAGNOSIS OF ACUTE KIDNEY INJURY: ROLE OF URINE BIOMARKERS

Hepatorenal syndrome (HRS)-AKI is a particular type of AKI that occurs only in patients with advanced cirrhosis. Patients with cirrhosis, however, may develop other causes of AKI, with hypovolemia-induced AKI and acute tubular necrosis (ATN) the most common, whereas others, such as nephrotoxicity, glomerulonephritis, and urinary tract obstruction, are less common.[1,10,19] Recently, different studies in hospitalized patients with cirrhosis have shown that the most frequent cause of AKI is hypovolemia (ranging between 48% and 75%), followed by ATN (12%–31%) and HRS-AKI (11%–29%).[5,9,20] Importantly, the etiology of AKI is associated with prognosis, with ATN and HRS the causes associated with the lowest 3-month survival.[3] Recent data showed that in patients with AKI stage 1A and 1B, the frequency of hypovolemia-induced AKI was higher than in patients with AKI stage 2 and 3, whereas the frequency of HRS and ATN was significantly higher in patients with AKI stage 2 and 3 compared with those with lower AKI stages.[14]

Hepatorenal Syndrome: Definition and New Diagnostic Criteria

HRS-AKI is a unique type of renal failure that occurs in patients with advanced cirrhosis characterized by severe impairment of kidney function due to marked vasoconstriction of renal arteries secondary to marked splanchnic vasodilation existing in patients with advanced cirrhosis. In addition, a systemic inflammatory response may

be involved in the pathophysiology of the syndrome (discussed later).[11,21,22] Traditionally, HRS was classified into 2 clinical types: (1) type 1 HRS, a rapidly progressive form of acute renal failure with very poor short-term prognosis, defined when SCr value doubled from the baseline to a final value greater than or equal to 2.5 mg/dL in less than 2 weeks; and (2) type 2 HRS, a steadily progressive form of renal failure SCr values, usually ranging between 1.5 mg/dL and 2.5 mg/dL, that was associated with better short-term prognosis.[11,21] The new definition of AKI in cirrhosis led to changes in the diagnostic criteria of HRS. The new diagnostic criteria of HRS-AKI are shown in **Box 1**.[13] The only change with respect to the classical definition of HRS is the removal of the cutoff value of SCr that leads to early diagnosis and treatment of AKI-HRS. Therefore, the new definition includes not only patients with classic type 1 HRS (SCr >2.5 mg/dL) but also patients with SCr less than 2.5 mg/dL, fulfilling the new HRS-AKI criteria. The characteristics and outcomes of the latter patients are unknown and should be evaluated in future studies. The classic term type 2 HRS is not included in the current concept of HRS-AKI, because it is not an acute impairment but rather a chronic impairment of kidney function, and these patients do not fulfill AKI criteria. Therefore, type 2 HRS currently is considered a form of CKD (HRS-CKD) that is characteristic of cirrhosis.[13,16,23]

Differential Diagnosis of the Cause of Acute Kidney Injury

Differential diagnosis between the different causes of AKI is essential because they need different treatment approaches that should be initiated as soon as possible. To date, there is no specific laboratory test or marker for the diagnosis of HRS-AKI, and its diagnosis remains a diagnosis of exclusion of other causes of AKI. In many cases, a detailed clinical history (existence of infections, fluid losses, and gastrointestinal bleeding), physical examination (hemodynamics and volume status), blood tests and cultures, and evaluation of urine electrolytes are sufficient for establishing the cause. Nevertheless, in some cases, the differential diagnosis of the cause of AKI in daily clinical practice may be challenging, in particular, the differential diagnosis between AKI-HRS and ATN, because both usually occur in critically ill patients that frequently associate other complications that may act as confounders to establishing a correct clinical differential diagnosis.[16,22]

Box 1
Diagnostic criteria of hepatorenal syndrome according to International Club of Ascites - Acute Kidney Injury criteria

Cirrhosis with ascites

Diagnosis of AKI according to ICA-AKI criteria: acute increase in SCr $\geq$0.3 mg/dL ($\geq$26.5 μmol/L) within 48 hours; or, a percentage increase in SCr $\geq$50% from baseline, which is known, or presumed, to have occurred within the prior 7 days

No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin (1 g per kg of body weight)

Absence of shock

No current or recent use of nephrotoxic drugs (NSAIDs, aminoglycosides, iodinated contrast media, etc.)

No macroscopic signs of structural kidney injury, defined as
- Absence of proteinuria (<500 mg/d)
- Absence of microhematuria (<50 red blood cells per high power field)
- Normal findings on renal ultrasonography

Urine biomarkers

In recent years, several urinary biomarkers have been studied for the differential diagnosis of AKI in patients with cirrhosis, especially to differentiate HRS-AKI from ATN.[24] In this context, classic urinary markers, such as urine sodium, fractional excretion of sodium (FeNa), and urine osmolality, generally are considered not useful in patients with cirrhosis because these can be influenced by diuretics. In addition, urinary sodium in advanced cirrhosis may be markedly low due to increased sodium retention.

In past decades, urinary biomarkers of tubular damage have been shown to be useful for the differential diagnosis of ATN, characterized by injury of tubular epithelial cells, from HRS, which is characterized by functional renal vasoconstriction with minimal renal abnormalities. Several urinary biomarkers have been studied in this setting, including urinary neutrophil gelatinase-associated lipocalin (NGAL), interleukin (IL)-18, albumin, kidney injury molecule-1 (KIM-1), and liver fatty acid–binding protein (L-FABP). Several studies consistently have shown that patients with hypovolemia-induced AKI have lower levels of NGAL, IL-18, albumin, and L-FABP compared with those of patients with HRS and ATN. On the contrary, patients with ATN have the highest levels of these biomarkers, and patients with HRS have intermediate levels but significantly lower levels than patients with ATN and significantly higher than levels of patients with hypovolemia-induced AKI.[5,25–28]

Among these biomarkers, urinary NGAL is the one that has shown most promising results. NGAL is a low-molecular-weight protein produced by tubular renal cells that also is expressed in neutrophils and cells of the liver/gastrointestinal tract.[29] Urinary NGAL levels rise significantly during AKI, prior to SCr elevation.[30] In 2012, 2 initial studies demonstrated the usefulness of urinary NGAL for the differential diagnosis of AKI in cirrhosis. Both studies showed that patients with ATN had the highest levels of NGAL compared with other causes of AKI (hypovolemia, HRS, and CKD).[26,31] Studies that have investigated several urinary biomarkers in addition to NGAL (ie, IL-18, KIM-1, L-FABP, and albumin, among others) have shown that these biomarkers are useful for the differential diagnosis of ATN from nontubular causes of AKI, but NGAL was the one performing the best.[27,28] Moreover, in a meta-analysis, including more than 1000 patients with cirrhosis, urine NGAL and IL-18 showed good accuracy to differentiate between ATN and other types of AKI (areas under the receiver operating characteristic [AUROCs] 0.89 and 0.88, respectively).[32]

Finally, a recent large prospective study, including 320 consecutive cases of AKI in hospitalized patients for decompensated cirrhosis, supports the use of urinary NGAL in clinical practice. This study showed that among different urinary biomarkers measured (NGAL, IL-18, albumin, FeNa, and β2-microglobulin), NGAL measured at day 3 of AKI after albumin administration had the greatest accuracy for the differential diagnosis between ATN and other types of AKI (AUROC 0.87 at a cutoff value of 220-μg/g creatinine).[5]

In addition, urinary biomarkers not only are useful for differential diagnosis of the cause of AKI but also can be useful to predict kidney and clinical outcomes of patients with cirrhosis. There are data derived from prospective studies and a meta-analyses showing that NGAL independently predicts short-term mortality in patients with cirrhosis and AKI.[5,32] Urine biomarkers also may detect AKI earlier than SCr and they also may predict the recovery of renal function after liver transplantation (LT). This should be confirmed, however, in future studies.[24,33,34]

In summary, there is large body of evidence showing that urine biomarkers are useful for the differential diagnosis and prognosis of patients with cirrhosis and AKI. Results suggest that NGAL can be used in clinical practice to help distinguish between ATN and HRS.[16]

PATHOPHYSIOLOGY OF HEPATORENAL SYNDROME

HRS represents the end stage of a circulatory dysfunction that occurs late in the natural history of decompensated cirrhosis.[22] Traditionally, HRS has been considered a type of renal failure of functional origin. The hallmark of HRS is the existence of marked renal vasoconstriction that leads to a reduction in renal blood flow that finally turns into a decrease in GFR with consequent functional AKI.[22] This functional nature of renal dysfunction in HRS with absence of renal parenchymal damages has been based on the decrease in renal blood flow assessed by Doppler ultrasound in patients with cirrhosis and ascites, the absence of significant histologic changes in renal postmortem studies after pharmacologic treatment, and the reversibility of renal dysfunction after LT.[22,35,36]

Impairment of systemic arterial circulation and activation of systemic and renal vasoconstrictor factors leading to HRS are the main physiologic responses to portal hypertension.[37,38] In addition to systemic circulatory dysfunction, impairment in cardiac function and systemic inflammation are factors that may play an important role in the development of HRS (Fig. 1).

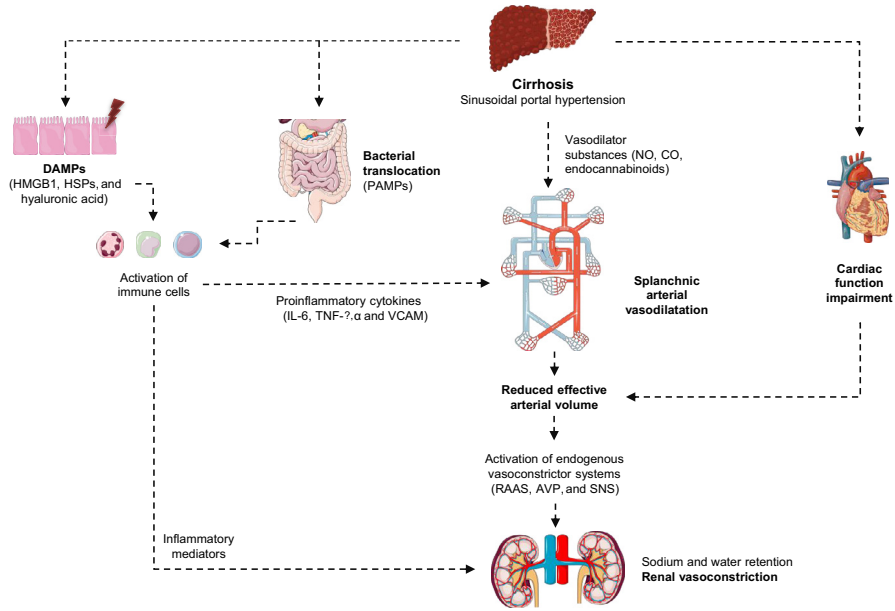

Fig. 1. Pathophysiology of HRS. Patients with advanced cirrhosis have a marked splanchnic arterial vasodilation triggered by portal hypertension. Splanchnic vasodilation leads to a decreased systemic vascular resistance with the development of effective arterial hypovolemia. The activation of vasoconstrictor systems leads to a marked renal vasoconstriction, low GFR, and development of HRS. In this advanced stage, there is a reduced cardiac output and decreased effective arterial blood volume. Systemic inflammation seems to play a role in the pathophysiology of complications of cirrhosis. PAMPs and DAMPs from bacterial translocation and injured liver, respectively, may lead to a marked inflammatory response. Inflammatory mediators lead to further systemic vasodilatation and also could cause direct kidney tissue damage. CO, carbon monoxide; HMGB1, high-mobility group box 1; HSPs, heat shock proteins; NO, nitric oxide. (*Adapted from* Ginès P, Solà E, Angeli P, Wong F, Nadim MK, Kamath PS. Hepatorenal syndrome. Nat Rev Dis Prim 2018;4:23. https://doi.org/10.1038/s41572-018-0022-7; with permission.)

Systemic Circulatory Dysfunction

Liver cirrhosis is characterized by the development of regenerative nodules that modify the normal architecture of the liver and cause an increase of intrahepatic vascular resistance and, consequently, portal pressure.[39] The increasing portal pressure is counteracted by the release of nitric oxide and other vasodilators substances (ie, carbon monoxide and endogenous cannabinoids) that induce splanchnic vasodilatation.[40] The accumulation of plasma volume in the splanchnic bed causes a decrease in the effective blood volume and mean arterial pressure (MAP) that initiates a compensatory response. This compensatory homeostatic response is mediated by the activation of the renin-angiotensin-aldosterone system (RAAS), the sympathetic nervous system (SNS), and arginine vasopressin (AVP).[41–43] The release of these vasoconstrictors systems is aimed at maintaining effective arterial blood volume and MAP within normal limits. The activation of systemic vasoconstrictor systems, however, leads to detrimental effects in the kidney, in particular sodium and water retention and, at advanced stages of the disease, renal vasoconstriction. In early stages of cirrhosis, the activation of vasoconstrictor systems is moderate, and local renal vasodilators can counteract the vasoconstrictor effect of RAAS, SNS, and AVP. The increasing amount of these vasoconstrictor hormones as the cirrhosis progress, however, finally leads to severe kidney vasoconstriction, leading to a decrease in GFR and the development of HRS.[38,44]

Reduced Cardiac Output

There are data suggesting that impaired cardiac function also plays an important role in the development of HRS.[45] As described previously, cirrhosis progression is associated with a decrease in effective arterial blood volume. In this context, cardiac output tends to increase to maintain systemic hemodynamic homeostasis.[46,47] In advanced cirrhosis, patients may develop systolic and diastolic cardiac dysfunction and conductance abnormalities that lead to a decrease in cardiac output. This cardiac dysfunction is known as cirrhotic cardiomyopathy.[48] Cirrhotic cardiomyopathy has been associated with a decrease in renal blood flow, decreased GFR, a higher probability of developing HRS among patients with advanced cirrhosis, and also lower 3-month and 12-month survival rates.[49,50]

Kidney Factors

Together with the increase of vasoconstrictor factors, an additional mechanism that may play a role in the development of HRS is a decrease in the production of renal vasodilators, in particular prostaglandins.[51] Prostaglandins are lipid mediators that have a vasodilator effect on the kidney circulation and may act by compensating the enhanced vasoconstrictor effects of the RAAS and the SNS. This mechanism is supported by the fact that treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), which inhibit prostaglandin synthesis, may lead to the development of AKI, resembling HRS, in patients with cirrhosis and ascites.[52]

In addition, abnormalities in renal autoregulation can play a role. In healthy individuals, renal autoregulation maintains a constant renal blood flow independently of arterial pressure fluctuations. Patients with advanced cirrhosis, however, have a shift to the right of the renal autoregulation curve, meaning that for the same renal perfusion pressure, renal blood flow is lower than that of healthy subjects. This effect, which probably is related to the increased activity of the SNS, may increase the risk that patients with advanced cirrhosis have of developing AKI, in particular HRS.[53]

Systemic Inflammation

In recent years, there has been accumulating evidence showing that systemic inflammation may play an important role in the progression of cirrhosis and development of complications, including HRS.[54] Cirrhosis is associated with systemic inflammation that increases progressively with the severity of liver, circulatory, and renal dysfunction.[54,55]

Patients with decompensated cirrhosis develop bacterial translocation from the gut to mesenteric lymph nodes, which is associated with increased levels of proinflammatory cytokines.[56] It currently is accepted that systemic inflammation results from the activation of immune cells secondary to pathogen-associated molecular patterns (PAMPs) derived from bacterial translocation and/or damage-associated molecular patterns (DAMPs) released from the injured liver.[54,55]

Patients with decompensated cirrhosis show increased levels of white blood cells, plasma C-reactive protein, and circulating proinflammatory cytokines, such as IL-6, IL-8, and tumor necrosis factor (TNF)-α.[55,57–60] In addition, decompensated cirrhosis is associated with activated circulating neutrophils and monocytes.[55,61] Levels of inflammatory markers increase in parallel with disease severity and are markedly high in patients with ACLF, a syndrome that is characterized by the presence of multiple organ failures, including the kidney.[58–60,62] There are recent data showing that HRS-AKI is associated with marked systemic inflammation. Results from a recent study describe that HRS-AKI is associated with increased serum levels of proinflammatory cytokines, in particular IL-6, TNF-α, and vascular cell adhesion molecule 1 (VCAM-1), regardless of the presence of a bacterial infection. Levels of proinflammatory cytokines were markedly higher compared with patients with hypovolemia-related AKI and patients with decompensated cirrhosis without AKI. In addition, levels of VCAM were associated with increased short-term mortality.[63]

Bacterial infections, in particular spontaneous bacterial peritonitis (SBP), are leading triggers of HRS. There are data showing that patients with SBP who develop HRS-AKI have higher levels of IL-6 and TNF-α compared with those patients with SBP who do not develop HRS.[57]

MANAGEMENT OF HEPATORENAL SYNDROME–ACUTE KIDNEY INJURY

General Management of Acute Kidney Injury in Cirrhosis

The management of patients with cirrhosis and AKI depends on the cause. As described previously, early identification of the cause of AKI is the most important step in the management of AKI in cirrhosis. Management of AKI should be started as soon as possible, according to AKI stage, even in the absence of a definitive recognized etiology of AKI (**Fig. 2**).[16] Diuretic treatment should be discontinued and the potential precipitating factors of AKI should be identified and treated: screening and treatment of infections, volume expansion in case of fluid loss, and discontinuation of all nephrotoxic drugs (ie, NSAIDs).[13] Patients with fluid loss secondary to diarrhea or excessive diuresis due to diuretic treatment should be treated with crystalloids. Patients with acute gastrointestinal bleeding should be given packed red blood cells to maintain hemoglobin levels between 7 g/dL and 9 g/dL.[64,65] Patients with initial AKI stage 1B or greater and patients with initial AKI stage 1A that progresses to greater than or equal to AKI stage 1B despite initial management should receive volume expansion with intravenous albumin (1 g of albumin/kg of body weight; maximum dose of 100 g) for 2 consecutive days. At that step, if there is no response to albumin administration, a diagnosis of HRS-AKI should be considered. An algorithm for diagnosis and management of AKI in cirrhosis is shown in **Fig. 2**.

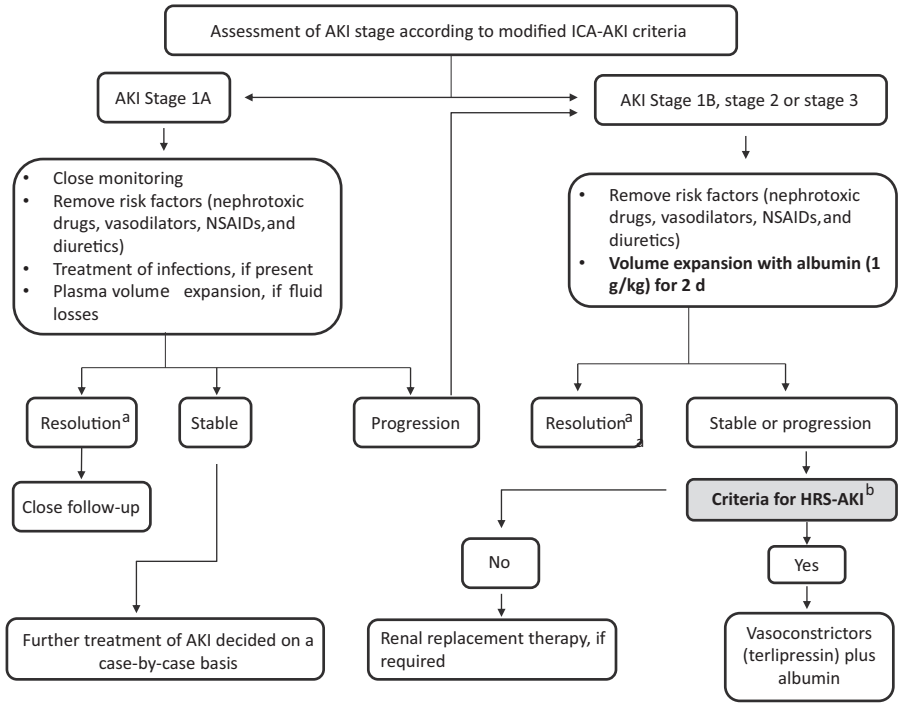

Fig. 2. Algorithm for the management of AKI in patients with cirrhosis. [a]Return of SCr levels to less than 0.3 mg/dL from baseline. [b]At this point, the use of new urine biomarkers, in particular NGAL, may help in the differential diagnosis of the type of AKI. (*Adapted from* Ginès P, Solà E, Angeli P, Wong F, Nadim MK, Kamath PS. Hepatorenal syndrome. Nat Rev Dis Prim 2018;4:23. https://doi.org/10.1038/s41572-018-0022-7; with permission. (Figure 4 in original).)

Management of Hepatorenal Syndrome–Acute Kidney Injury

The initial goal in the management of patient with HRS is to optimize the clinical status, with adequate management of fluid balance and close monitoring of blood pressure and other vital signs.[13,64] Patients need to be hospitalized and monitored closely. Intravenous fluids should be administered with caution to prevent pulmonary edema and development or worsening of hypervolemic hyponatremia. Patients with HRS-AKI are prone to developing other complications of cirrhosis, in particular bacterial infections; therefore, early identification and management of concurrent complications are essential. The use of a central venous catheter is recommended in patients who are going to receive pharmacologic therapy, because it involves the administration of volume expansion with albumin. The use of a bladder catheter is not recommended in all patients because it is associated with increased risk of urinary tract infections. Bladder catheterization is recommended only in patients with marked oliguria. Given that patients with advanced cirrhosis frequently are malnourished and require a sodium-restricted diet, a nutritionist should be a part of the team taking care of the patient.[16,66]

Specific treatment of HRS-AKI should be started as soon as possible. The only definitive treatment of HRS-AKI is LT. Therefore, all patients with HRS-AKI should be evaluated for LT. In candidates for LT, all efforts should be made to normalize renal function before transplantation. The treatment of choice for the management of AKI-HRS is vasoconstrictors and albumin.[16]

Pharmacologic therapy

Previous to the new definition of HRS-AKI, the type of HRS (type 1 vs type 2) was taken into account when considering treatment. All clinical trials evaluating the efficacy of vasoconstrictors and albumin available to date are based on those criteria. With the new definition of HRS-AKI, these criteria no longer are applied. As described previously, patients with type 1 HRS are included within the term HRS-AKI, whereas type 2 HRS is considered a type of CKD. Therefore, according to the new definition, there is no specific cutoff value of SCr for a diagnosis of HRS-AKI and to start pharmacologic treatment.[13,16] According to new definition and algorithm (see **Fig. 2**), vasoconstrictor therapy is recommended for those individuals with AKI stage 1B criteria or greater who meet HRS-AKI criteria.[16] These new criteria will lead to start pharmacologic treatment earlier. To date, there is no information on the efficacy and safety of treatment in this setting and these need to be evaluated in future trials.

Vasoconstrictors together with albumin currently is the most effective pharmacologic therapy for the management of AKI-HRS.[16] A combination of vasoconstrictors and albumin counteracts the intense vasodilation of the splanchnic circulation and improves effective arterial blood volume, leading to suppression of endogenous vasoconstrictor factors responsible for the development of HRS. Vasoconstrictors that have been evaluated for the management of HRS include terlipressin, noradrenaline, and the combination of midodrine and octreotide.[67–78]

Terlipressin. Terlipressin is the most widely studied drug for the management of HRS. It is a synthetic analog of vasopressin with a marked vasoconstrictor effect by acting on vasopressin V1 receptors, predominantly. Several studies, including randomized controlled trials and some meta-analyses, have shown that terlipressin in combination with albumin is significantly associated with improvement of kidney function in patients with type 1 HRS.[67–69,71–73] According to previous trials, overall reversal of type 1 HRS is achieved in approximately 40% to 60% of patients. In contrast to results from previous trials, a recent large, randomized, placebo-controlled, double-blind trial aimed at assessing the efficacy of terlipressin in the reversal of type 1 HRS conducted in North America (REVERSE Trial [NCT01143246]) did not show significant differences in the reversal of type 1 HRS between terlipressin plus albumin and placebo arms.[71] The study described some positive findings, however, in particular, a greater improvement of kidney function in patients treated with terlipressin, and survival was highly correlated with changes in SCr levels.

There are some reasons that could explain the negative results of this study in contrast to previous trials. First, the duration of treatment with terlipressin was relatively short in this study because up to one-third of patients received less than or equal to 3 days of treatment and only 6% completed the 14 days of therapy. In addition, renal replacement therapy (RRT) was used as a rescue therapy in a high proportion of patients in the early stages of treatment, considered one of the main reasons for treatment failure.[79]

Finally, recent results from a large North American randomized, placebo-controlled trial, including 300 patients with type 1 HRS, have been reported (CONFIRM Study [NCT02770716]). In this study patients were randomized 2:1 to receive terlipressin plus albumin versus placebo plus albumin. Results show that in patients treated with terlipressin plus albumin the reversal rate of type 1 HRS was significantly higher than in those patients treated with placebo plus albumin (36% vs 17%, respectively; $P<.001$).[80]

Classically, terlipressin has been administered by repeated intravenous boluses (starting dose of 0.5–1 mg every 4–6 h and increasing to a maximum of 2 mg every

4–6 h in cases of reduction of baseline SCr <25%). Recently, a randomized trial compared the efficacy and safety of terlipressin given by continuous intravenous infusion (dose 2 mg/d up to 12 mg/d) compared with intravenous boluses. Results of these trials showed that response rates between both groups were similar. Mean effective dose of terlipressin was significantly lower in the continuous infusion group, however, and, importantly, that was associated with a lower rate of adverse events.[69]

Treatment with terlipressin always should be associated with intravenous albumin. There is evidence showing that the combination terlipressin and albumin is more effective than terlipressin alone.[70] Although the dose of albumin has not been well established, a dose of 20 g/d to 40 g/d is recommended.[16]

The most common side effects associated with terlipressin are diarrhea and abdominal cramps. Severe adverse events, such as ischemic and cardiovascular events or arrhythmias, also may occur. The administration of albumin may be associated with circulatory overload and, therefore, should be administered with caution. Patients with established ischemic heart disease or peripheral vascular disease probably should not be treated with terlipressin.

Treatment with terlipressin plus albumin should be continued until complete response (SCr <1.5 mg/dL or close to the baseline value before diagnosis) or for a maximum of 14 days in patients with partial response or no response. Recurrence of HRS in responders has been reported in up to 20% of cases. Retreatment with terlipressin and albumin usually is effective; however, in some cases, continuous recurrent episodes occur. Patients who respond to treatment with terlipressin plus albumin show a better survival rate than nonresponders. In addition, data from 2 meta-analysis show that treatment of terlipressin and albumin is associated with improvement in short-term survival.[81–83]

Predictors of response to therapy. As described previously, treatment with terlipressin and albumin should be started as soon as possible after diagnosis of HRS-AKI. There are data showing that SCr at the time of starting treatment is an independent predictive factor of response to treatment.[84]

In addition, the improvement of kidney function in patients with HRS treated with vasoconstrictors closely correlates with the increase in MAP. Studies suggest that response to treatment with vasoconstrictors and albumin correlates with the increase in MAP.[84–86] There are data showing that patients who experience a significant increase in MAP during terlipressin treatment have higher probability of recovering kidney function compared with patients without increase in MAP.[87] Therefore, a goal-directed approach to the treatment of HRS based on targeting an increase in MAP during treatment may lead to better outcome. Nevertheless, prospective studies evaluating this approach are needed before incorporating it into clinical practice.

Finally, recent data show that besides SCr values and MAP, the presence and severity of ACLF also have an important impact on treatment response. Patients with ACLF grade 3 have significantly lower probability of response to treatment compared with patients with ACLF grade 1 or grade 2 (29% in ACLF grade 3, compared with 60% and 48% in ACLF grade 1 and ACLF grade 2, respectively; $P<.001$).[88]

Other vasoconstrictors. In countries where terlipressin is not available, the use of other vasoconstrictors represents an alternative for the management of HRS-AKI. Norepinephrine, midodrine, and octreotide have been assessed in this setting.

Noradrenaline is an α-adrenergic and β-adrenergic receptor agonist with vasoconstrictor effect activity on systemic and splanchnic circulation that can improve renal

perfusion. It has been evaluated in several randomized controlled trials for the management of type 1 HRS compared with terlipressin.[74–76,89] In summary, noradrenaline seems as effective as terlipressin for the management of HRS; however, the quality of evidence available to date supporting the use of noradrenaline is low, according to a recent meta-analysis.[81] Therefore, noradrenaline should be considered a good alternative treatment if terlipressin is not available. Noradrenaline should be administered in intensive care units under continuous vital signs monitoring.

Midodrine, a selective α_1-adrenergic receptor agonist, in combination with octreotide, a somatostatin analog, also has been evaluated for the management of HRS. Nonrandomized studies showed an improvement in renal function and GFR together with suppression of vasoconstrictor systems in patients with HRS treated with the combination of midodrine plus octreotide.[85,90] A randomized controlled trial showed, however, that treatment with midodrine, octreotide, and albumin was associated with significantly lower response rate compared with treatment with terlipressin and albumin in patients with HRS (70.4 vs 28.6%, respectively).[91] Therefore, it should not be used as a first-line treatment of HRS.

Nonpharmacologic therapy

Liver transplantation. The most effective therapy for patients with HRS-AKI is LT because it represents the definitive treatment of portal hypertension and liver failure, which are responsible for the development of HRS. Patients with AKI-HRS have a very poor prognosis and, therefore, should be transferred to hospitals with LT programs for LT evaluation. Patients with AKI-HRS have high mortality on the waiting list and, therefore, they should be given higher priority.[92] Considering that sSCr is one of the variables included in the Model for End-stage Liver Disease (MELD) score, the use of MELD score as organ allocation system allows giving high priority to these patients. To avoid a reduction in MELD score in patients who respond to pharmacologic treatment with vasoconstrictors and albumin, which would lead to a delay in LT allocation, it has been suggested to maintain the MELD score calculated with the SCr value before treatment while these patients are on the waiting list (**Fig. 3**).[16,93]

The presence of type 1 HRS has a negative impact on survival after the LT.[94] There are data, however, showing that in patients with complete reversal of type 1 HRS after LT, renal function and survival are excellent at 1-year post-LT and comparable to patients undergoing LT without AKI.[94]

AKI-HRS is reversible after LT in most patients and, therefore, LT alone generally is recommended.[16,93] Nonetheless, renal dysfunction may persist in some patients after transplant. In this context, there is much debate on when simultaneous liver-kidney (SLK) transplantation should be recommended instead of LT alone. Recent recommendations for SLK in the United States are (1) patients with AKI with an estimated GFR of less than or equal to 5 mL/min/1.73 m^2 for 6 weeks or a period of dialysis greater than or equal to 6 weeks; (2) stage greater than or equal to 3B CKD (GFR <44 mL/min/1.73 m^2) for greater than 90 days; and (3) comorbidities and presence of metabolic diseases.[95] European guidelines suggest that SLK should be considered in patients with cirrhosis and CKD in the following conditions: (1) estimated GFR (using Modification of Diet in Renal Disease 6 equation) less than or equal to 40 mL/min or measured GFR using iothalamate clearance less than or equal to 30 mL/min; (2) proteinuria greater than or equal to 2 g/d; (3) kidney biopsy showing greater than 30% global glomerulosclerosis or greater than 30% interstitial fibrosis; and (4) inherited metabolic disease. SLK also should be indicated in patients with cirrhosis and sustained AKI irrespective of its type, including HRS-AKI

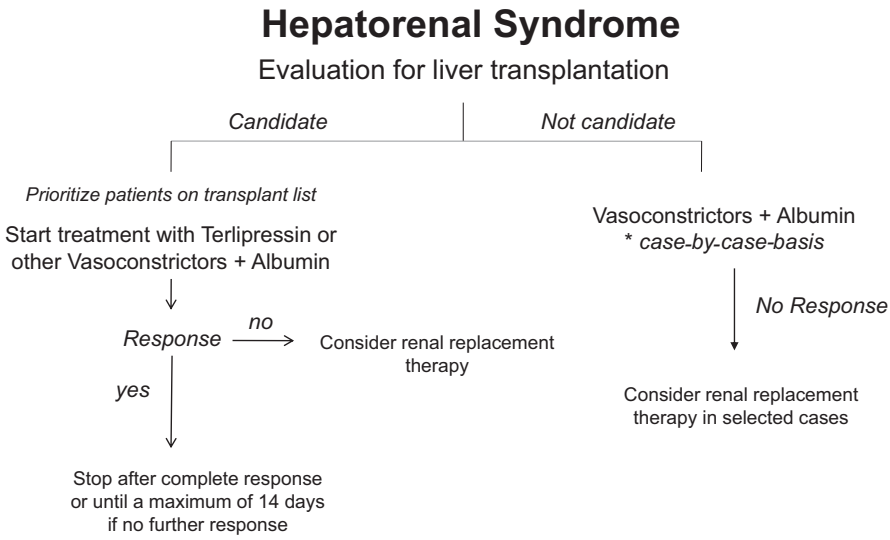

Fig. 3. Proposed algorithm for the management of AKI-HRS considering the evaluation and prioritization of patients for LT. (*Adapted from* Fagundes C, Ginès P. Hepatorenal syndrome: a severe, but treatable, cause of kidney failure in cirrhosis. Am J Kidney Dis. 2012 Jun;59(6):874-85. https://doi.org/10.1053/j.ajkd.2011.12.032. Epub 2012 Apr 4. PMID: 22480795; with permission. *Fagundes, Ginès. Am J Kidney Dis 2012.*[25])

without response to pharmacologic therapy, in the following conditions: (1) AKI on RRT for greater than or equal to 4 weeks and (2) estimated GFR less than or equal to 35 mL/min or measured GFR less than or equal to 25 mL/min greater than or equal to 4 week.[16,96]

Transjugular intrahepatic portosystemic shunt. Transjugular intrahepatic portosystemic shunt (TIPS) has been proposed as an alternative therapy for the management of HRS-AKI, because it reduces portal pressure, leading to an improvement of circulatory dysfunction, suppressing RAAS and SNS activity. The applicability of TIPS in patients with AKI-HRS, who have very advanced liver disease, is limited, however, because many patients have contraindications for the insertion of TIPS. There are data showing that TIPS decreases the activity of endogenous vasoconstrictor systems and, in consequence, improves kidney function in approximately 60% of patients with HRS.[97,98] These studies, however, excluded patients with Child-Pugh score greater than or equal to 12, with serum bilirubin greater than 5 mg/dL, and with previous hepatic encephalopathy. Therefore, considering that existing data are limited and the applicability of TIPS in these patients is very low, TIPS placement should not be recommended in the treatment of HRS-AKI.[16,99,100]

Renal replacement therapy and alternative dialysis methods. RRT should not be considered as the first-line therapy for patients with AKI-HRS. RRT should be considered in nonresponders to pharmacologic therapy. Indications for RRT are the same as in the general population, including severe and/or refractory electrolyte or acid-base imbalance, volume overload, and/or symptomatic azotemia. Published data on RRT in patients with cirrhosis is limited, however, with controversial effects on survival.[101,102]

Alternative dialysis methods, such as the molecular adsorbent recirculating system (MARS), which removes substances from plasma, such as bilirubin, bile acids, and cytokines, have been assessed. In a randomized controlled trial, including patients with type 1 HRS, treatment with MARS showed a significant reduction in SCr and mortality compared with patients treated with standard medical therapy.[103] Data about potential benefits of MARS in this setting still are limited, however, and this strategy should be considered an experimental therapy until further studies are available. Current guidelines do not recommend MARS for the management of AKI-HRS.[16]

PREVENTION

The administration of intravenous albumin together with antibiotics in patients with SBP is indicated to prevent the development of AKI-HRS.[16] Albumin counteracts the marked arterial splanchnic vasodilation triggered by the infection that further impairs the already existing systemic circulatory dysfunction. A randomized controlled trial showed that in patients with SBP receiving intravenous albumin (1.5 g/kg at diagnosis of infection and 1 g/kg at 48 h), the incidence of type 1 HRS was reduced to only 10% compared with 33% patients who received antibiotics alone. Moreover, in-hospital mortality was lower in the group treated with albumin (10% those who recieved albumin, against 29% in those who did not recieved albumin).[104] In infections other than SBP, albumin administration has not shown to prevent the development of AKI-HRS and, therefore, is not indicated. Finally, the administration of norfloxacin (400 mg/d) for prevention of SBP in patients with impaired liver function and low ascitic protein concentration also reduced the incidence of development of HRS-AKI.[105]

CLINICS CARE POINTS

- AKI is a common complication in patients with cirrhosis and has a poor prognosis.
- New diagnostic criteria takes into account slight increases of SCr and, therefore, allow early diagnosis of AKI.
- Treatment and prognosis differs between etiologies, so it is essential to early identify the etiology of AKI.
- Urine biomarkers could have a role in the differential diagnosis between ATN and HRS-AKI.
- HRS-AKI is one of the most common causes of AKI in patients with cirrhosis and has a very poor prognosis.
- In patients with HRS-AKI, vasoactive drugs, preferably Terlipressin, in combination with albumin, should be initiated as soon as possible.
- Liver transplantation should be considered in all patients developing HRS-AKI.
- The use of albumin in patients with SBP, or the prophylaxis with Norfloxacin in patients with advanced liver disease and low ascitic fluid protein concentration, prevent the development of HRS-AKI.

DISCLOSURES

Authors have nothing to disclose.

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