Renal Insufficiency in Patients with Cirrhosis

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KEYWORDS

• Acute kidney injury • Renal insufficiency • Cirrhosis • Hepatorenal syndrome
• International ascites club

KEY POINTS

- Acute kidney injury (AKI), including hepatorenal syndrome, is a common complication in patients with cirrhosis and is associated with high morbidity and mortality.
- The International Club of Ascites has defined AKI in cirrhosis based predominantly on the percentage of serum creatinine increase from the baseline.
- The use of urinary biomarkers of tubular damage may aid in the differential diagnosis of AKI in cirrhosis.
- Advances in our understanding of the pathophysiology of AKI and cirrhosis have led to changes in our approach to renal insufficiency in patients with cirrhosis.

INTRODUCTION

Acute kidney injury (AKI) is a frequent complication in patients hospitalized with complications of cirrhosis and is associated with high morbidity and mortality. Prerenal azotemia, hepatorenal syndrome (HRS)–AKI and acute tubular necrosis (ATN) represent the most common etiologies of AKI in patients with advanced liver disease. Differentiating these conditions may be challenging, but is required due to the differences in the treatment of each etiology. HRS–AKI is characterized by functional circulatory changes that ultimately lead to impairment in kidney function. There have been recent advances in defining this clinical entity and addressing optimal management. This review highlights the contemporary criteria, pathophysiology, diagnosis, and management of renal failure and HRS in patients with cirrhosis.

EPIDEMIOLOGY AND DEFINITIONS

The reported incidence of AKI ranges from 20% to 50% in patients with cirrhosis admitted to the hospital.[1–3] The traditional definition of AKI in cirrhosis was based

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Clin Liver Dis 27 (2023) 57–70
https://doi.org/10.1016/j.cld.2022.08.010 **liver.theclinics.com**

on an increased serum creatinine value of greater than 1.5 mg/dl.[4] This definition had limitations in that it relied on a fixed threshold that did not account for dynamic changes in serum creatinine that are essential in distinguishing acute from chronic renal insufficiency.[5]

The definition of AKI has gone through many updates over the last 2 decades as enumerated in **Table 1**. In 2004, the Consensus Conference of the Acute Dialysis Quality Initiative Group defined the risk, injury, failure, loss, and end-stage kidney disease (RIFLE) classification, which was based on changes in serum creatinine or glomerular filtration rate (GFR) and urine output.[6] Three years later (2007) this classification was refined by the Acute Kidney Injury Network (AKIN) to include the full spectrum of acute renal injury and adjusted the definition of AKI to include an absolute increase in baseline serum creatinine of 0.3 mg/dL within 48 hours.[7] In 2012, the Kidney Disease Improving Global Outcome (KDIGO) further refined the RIFLE and AKIN criteria for defining AKI as an increase in serum creatinine by at least 0.3 mg/dL within 48 hours, an increase in serum creatinine to at least 1.5 times the baseline within the last 7 days, or urine volume less than 0.5 mL/kg/h for 6 hours.[8]

The International Club of Ascites (ICA) modified the definition of AKI with a prognostic significance for cirrhosis and formed the ICA–AKI criteria (**Box 1**).[9] This classification system is based predominately on the percentage of serum creatinine increase from the baseline. The ICA also eliminated urine output from the revised definition of AKI, owing to the expected reduced urine output in patients with cirrhosis due to avid sodium retention.

The definition of HRS has also evolved over time. Formerly, HRS was categorized into two major types: type 1, defined by rapid impairment of renal function manifested in less than 2 weeks by doubling of initial serum creatinine to a level greater than 2.5 mg/dL or a 50% reduction of the initial 24 h creatinine clearance to a level lower than 20 mL/min; and type 2, defined by a less rapid course of renal impairment.[4] The changes proposed by the KDIGO guidelines prompted the ICA in 2015 to reclassify the previous HRS type 1 as the acute form of HRS–AKI,[9] and in 2019, HRS type 2 as HRS–NAKI (ie, non-AKI) (**Table 2**).[10] The updated definition of HRS–AKI removed the 2 week interval required for doubling of serum creatinine and the 2.5 mg/dL level cut-off, facilitating earlier diagnosis and treatment. HRS–NAKI is defined by estimated GFR (eGFR) rather than by serum creatinine and divided into HRS–acute kidney disease (HRS–AKD) if the eGFR is less than 60 mL/min/1.73 m^2 for less than 3 months, and HRS–chronic kidney disease (HRS–CKD) if the eGFR is less than this for greater than 3 months.[11]

PATHOPHYSIOLOGY OF HEPATORENAL SYNDROME

HRS refers to renal dysfunction specific to patients with liver disease and has unique pathophysiology.[12] There has been notable evolution in our understanding of the pathophysiologic mechanisms of HRS in the last several decades.

The *arterial vasodilation theory* has been the leading hypothesis for the development of HRS for the last 20 years. Cirrhosis results in increased intrahepatic vascular resistance associated with overproduction and release of vasodilators (nitric oxide, prostaglandins, endocannabinoids) in the splanchnic and systemic circulation.[13] Splanchnic and systemic vasodilation lead to reduced effective arterial blood volume and systemic arterial hypotension, which in turn lead to a compensatory increase in cardiac output and activation of systemic vasoconstrictor pathways, such as the renin–angiotensin–aldosterone system and the sympathetic nervous system. These mechanisms are typically effective in maintaining circulatory volume in compensated

Table 1
Consensus definitions for acute kidney injury

Criteria	Stage	Definition	
		sCr or GFR Criteria	UOP Criteria
Acute Dialysis Quality Initiative Group -RIFLE criteria in 2004	Stage 1 (risk) Stage 2 (injury) Stage 3 (failure) Loss End-stage	Increased sCr $\geq$ 1.5 $\times$ baseline or GFR decreased > 25% Increased sCr $\geq$ 2 $\times$ baseline or GFR decreased > 50% Increased sCr $\geq$ 3 $\times$ baseline or GFR decreased > 75% Persistent acute renal failure >4 wk Complete loss of kidney function > 3 moths	UOP < .5 mL/kg/h for $\geq$ 6 h UOP < .5 mL/kg/h for $\geq$12 h UOP < .3 mL/kg/h for $\geq$ 24 h
Acute Kidney Injury Network (AKIN) in 2007	Stage 1 Stage 2 Stage 3	Increased sCr $\geq$ 1.5 $\times$ baseline or $\geq$ 0.3 mg/dL within 48 h Increased sCr $\geq$ 2 $\times$ baseline Increased sCr $\geq$ 3 $\times$ baseline	UOP < .5 mL/kg/h for $\geq$ 6 h UOP < .5 mL/kg/h for $\geq$ 12 h UOP < .3 mL/kg/h for $\geq$ 24 h or anuria $\geq$ 12 h
KDIGO in 2012	Stage 1 Stage 2 Stage 3	Increased sCr $\geq$ 1.5–2 $\times$ baseline or $\geq$ 0.3 mg/dL Increased sCr $\geq$ 2–3 $\times$ baseline Increased sCr $\geq$ 3 $\times$ baseline or sCr $\geq$ 4.0 mg/dL	UOP < .5 mL/kg/h for $\geq$ 6–12 h UOP < .5 mL/kg/h for $\geq$ 12 h UOP < .3 mL/kg/h for 24 h or anuria for $\geq$ 12 h

Abbreviations: hGFR, glomerular kidney function; RRT, renal replacement therapy; sCr, Serum creatinine; UOP, Urine output.

Box 1
International Club of Ascites stages of acute kidney injury

Stage 1
Increase in serum creatinine greater than or equal to 0.3 mg/dL (26.5 μmol/L) or increase in serum creatinine less than or equal to 1.5-fold or more to 2-fold from the baseline
Stage 1a
Creatinine less than 1.5 mg/dL
Stage 1b
Creatinine greater than or equal to 1.5 mg/dL

Stage 2
Increase in serum creatinine at least 2-fold to 3-fold from the baseline

Stage 3
Increase in serum creatinine at least threefold from baseline or serum creatinine greater than or equal to 4.0 mg/dL (353.6 μmol/L) with an acute increase of greater than or equal to 0.3 mg/dL (26.5 μmol/L) or the initiation of renal replacement therapy

cirrhosis; however, in decompensated cirrhosis, these systems are insufficient, resulting in impaired renal blood flow and consequent functional and ischemic kidney injury.

Systemic inflammation is a more recently described mechanism in the pathophysiology of HRS. Translocation of gut bacteria or bacterial products leads to increased pathogen-associated molecular patterns, such as lipopolysaccharide, flagellin, and nigericin, in the portal circulation. Similarly, hepatocellular injury leads to the release of damage-associated molecular patterns including heat shock protein, double-stranded genomic DNA, and adenosine triphosphate, among others. This proinflammatory response results in increased production of arterial vasodilators and consequent reduction in effective arterial blood volume and systemic vascular resistance leading to renal impairment.[14]

In addition, the hepato-adrenal syndrome may play a role in the development of HRS. Relative adrenal insufficiency is seen in 24% to 49% of patients with decompensated cirrhosis.[15,16] Adrenal insufficiency results in decreased arterial pressure and increased renin and norepinephrine placing these patients at higher risk for the development of HRS–AKI.[16]

Cholemic (bile cast) nephropathy[17] and intra-abdominal hypertension[18] in patients with refractory ascites have also been implicated in the development of HRS.

DIFFERENTIAL DIAGNOSIS

Besides HRS–AKI, other more common causes of renal failure are seen with cirrhosis (ie, hypovolemia, parenchymal disease, nephrotoxicity). Despite the significant overlap, distinguishing the main driver of renal failure in cirrhosis is important for prognostic and therapeutic purposes. Prerenal azotemia and ATN generally confer a better prognosis in cirrhosis, as compared with the markedly dismal prognosis in patients with HRS–AKI.[19]

Differentiating HRS–AKI from ATN remains difficult. The diagnosis of HRS–AKI requires the absence of shock, proteinuria, microhematuria, and normal renal ultrasound.[10] Patients who meet these criteria may still have tubular damage, thus ATN cannot be entirely excluded. Moreover, classical urine biomarkers such as urine sodium and fractional excretion of sodium (FeNa) used for the differential diagnosis of AKI have limitations in patients with cirrhosis. Thus, urine sodium and FeNa are no longer part of the diagnostic criteria for HRS–AKI.

Table 2
Previous and new classifications of hepatorenal syndrome

Old Classification	New Classification	Criteria
HRS type	HRS-AKI	• Increase in sCr $\geq$ 0.3 mg/dl within 48 h OR • Increase in sCr $\geq$ 1.5 times from baseline (sCr value within previous 3 mo, when available, maybe uses baseline, and value closest to presentation should be used) • No response to diuretic withdrawal and 2 d fluid challenge with 1 g/kg/d of albumin 20%–25% • Cirrhosis with ascites • Absence of shock • No current or recent use of nephrotoxic drugs (NSAIDs, contrast dye, etc.) • No signs of structural kidney injury ○ Absence of proteinuria (>500 mg/d) ○ Absence of hematuria (>50 RBCs per high-power field) ○ Normal findings on renal ultrasound
HRS type 2	HRS–NAKI HRS–AKD HRS–CKD	• eGFR < 60 mL/min per 1.73 m^2 for < 3 mo in absence of other potential causes of kidney disease • Percentage increase in sCr <50% using last available value of outpatient sCr within 3 mo as baseline value HRS-CKD • eGFR < 60 mL/min per 1.73 m^2 for $\geq$ 3 mo in absence of other potential causes of kidney disease

ROLE OF BIOMARKERS

Several novel urinary biomarkers of tubular damage have been investigated to differentiate ATN from HRS–AKI. Tubular proteins released during cell damage (neutrophil gelatinase-associated lipocalin [NGAL]), kidney injury molecule-1, and liver-type fatty acid-binding protein and markers of inflammation (interleukin-18 [IL-18]) are a few of the biomarkers studied for this purpose. Among these, NGAL and IL-18 are the most widely studied and demonstrate the most promising results.

NGAL is a protein expressed by injured kidney tubular epithelia and rises exponentially early during tubular damage.[20] Several studies have demonstrated that urine NGAL has high accuracy in differentiating ATN from HRS–AKI and hypovolemia-induced AKI.[20–22] Urinary NGAL performs best after the 2 days of plasma expansion with albumin that is recommended in the management of AKI. In this setting, the urinary NGAL cut-off value of greater than 220 μg/g of creatinine had the highest diagnostic accuracy for ATN.[21] Studies have also shown that urinary NGAL is an independent predictor of short-term mortality.[20,21] A limitation of NGAL is that levels are also increased in patients with urinary tract infections due to its expression by leukocytes.[23]

IL-18 is a proinflammatory cytokine expressed in the proximal tubule, which is released during tubular injury.[24] Significantly higher IL-18 levels have been observed in patients with cirrhosis and ATN compared with other causes of renal injury. As with NGAL, data also suggest a correlation between IL-18 levels and short-term mortality.[25,26]

RISK FACTORS AND PREVENTION

Predictors of HRS–AKI include hyponatremia, high plasma renin activity, liver size,[13] and severity of ascites.[27,28] The prevalence of HRS–AKI in the absence of identifiable precipitating events is only 1.8%.[28] The most common precipitant of HRS–AKI is large volume paracentesis without albumin administration. Albumin supplementation (6–8 g/L of ascitic fluid removed) post-large volume paracentesis ($\geq$4–5 L) significantly reduces the risk of HRS–AKI and short-term mortality.[29,30] This protective effect is unique to albumin compared with other volume expanders, which may be explained by its antioxidant, anti-inflammatory, endothelial-stabilizing, and endotoxin-inactivation properties.[30–33]

The acute hemodynamic changes associated with infection are another major risk factor for HRS–AKI. Roughly 30% of patients with spontaneous bacterial peritonitis (SBP) developed HRS–AKI.[34] Albumin administration (at a recommended dose of 1.5 g/kg on day 1 and 1 g/kg on day 3) in addition to antibiotic treatment reduces the incidence of SBP-associated HRS–AKI and improves overall survival.[35]

In addition, patients with low ascitic protein fluid (<1.5 mg/dL) associated with liver or kidney dysfunction (Child-Turcotte-Pugh score $\geq$9 with bilirubin $\geq$ 3 mg/dL, or serum creatinine $\geq$1.2 mg/dL, serum sodium $\leq$ 130 mEq/L or blood urea nitrogen $\geq$25) are at increased risk for SBP. Antibiotic prophylaxis prevents the development of SBP and reduces the risk of HRS–AKI and mortality.[35,36]

MANAGEMENT

Early recognition and treatment of renal dysfunction in patients with cirrhosis is important and may improve outcomes. Once AKI has been diagnosed, management should start immediately (**Fig. 1**). Nephrotoxic agents (eg, nonsteroidal anti-inflammatory drugs, contrast agents), vasodilators, and beta-blockers should be discontinued, and diuretic therapy should be withdrawn. Infection should be investigated and treated. AKI stage 1A (serum creatinine < 1.5 g/dL) is most often secondary to volume depletion and greater than 90% of cases resolve with risk factor management. This contrasts with only approximately 50% resolution seen in patients with AKI stage 1B.[3,37,38] Patients who present with or progress to AKI stage 1B or greater, should in addition to withdrawal of diuretics and nephrotoxic agents, and treatment of infection, receive fluid challenge of 20% to 25% intravenous albumin at 1 g/kg/d for 2 d. This step is important to rule out prerenal azotemia and is required before a diagnosis of HRS–AKI can be made. If the renal function does not improve and patients meet the additional diagnostic criteria of HRS–AKI, vasoconstrictors in combination with albumin should be initiated.

VASOCONSTRICTORS

Splanchnic vasoconstriction results in decreased portal flow, consequently portal pressure, and increased effective systemic arterial blood volume and renal blood flow. The increase in mean arterial pressure promoted by vasoconstrictors is associated with higher rates of HRS reversal.[39]

The vasoconstrictors used in the treatment of HRS-AKI include terlipressin, norepinephrine, and the combination of octreotide and midodrine (**Table 3**).

Terlipressin, a synthetic vasopressin analog, is used to treat HRS-AKI in many European and Asian countries. As a predominant vasopressin 1a agonist, terlipressin acts mainly as a splanchnic vasoconstrictor.[40] It also demonstrates mild activation of vasopressin 1b receptors, leading to the release of adrenocorticotrophic hormone and cortisol. This counteracts the relative adrenal insufficiency seen in cirrhosis.[41] Terlipressin also acts as a modest vasopressin receptor 2 agonist.

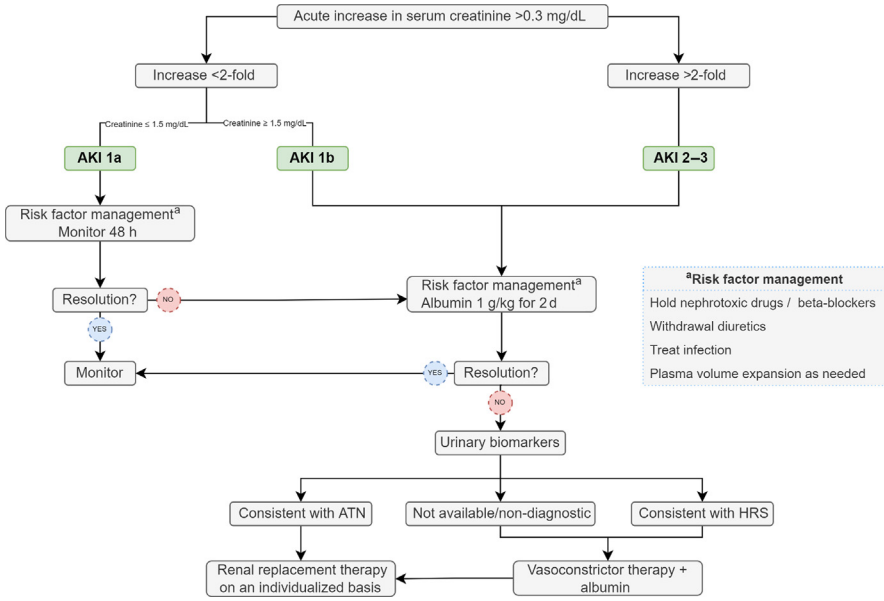

Fig. 1. Algorithm for management of acute kidney injury with cirrhosis. (*Adapted from* Simonetto DA, Gines P, Kamath PS. Hepatorenal syndrome: pathophysiology, diagnosis, and management. BMJ. 2020;370:m2687.)

Terlipressin may be administered as intravenous boluses (0.5 mg to 1 mg every 4–6 hours up to 2 mg every 4 hours) or as a continuous infusion (1 mg/d–12 mg/d). Terlipressin dose should be increased in a stepwise manner based on the response of serum creatinine for a maximum of 14 days.[38] Complete response (final serum creatinine within 0.3 mg/dL of baseline or less than 1.5 mg/dL) or partial response (improvement of AKI but final serum creatinine is $\geq$ 0.3 mg/dL of baseline) is achieved in 40% to 50% of patients. The recurrence rate of HRS–AKI is less than 20%, and in the event of recurrence, most patients respond to retreatment.[42,43]

Terlipressin is not currently Food and Drug Administration-approved in the United States, probably in part due to the rate of adverse respiratory events in patients on terlipressin.[44] The CONFIRM trial reported respiratory adverse events (including acute respiratory failure, hypoxia, pleural effusions, and pulmonary edema) in 39.5% of patients on terlipressin versus 25.3% of placebo.[45] The risk of pulmonary events may be mitigated by avoiding its use in patients with acute liver failure grade 3 or creatinine greater than or equal to 5 mg/dL, because of a lower response rate and higher risk of respiratory failure seen in these patients on sub-group analysis.[44] Further, albumin should be used with careful clinical monitoring of volume status and treatment modification or discontinuation if side effects occur. Finally, terlipressin given by continuous infusion has been associated with fewer adverse events compared with boluses administration.[46]

Norepinephrine is an intravenous systemic vasoconstrictor that works by the activation of α-1 adrenergic receptors on vascular smooth muscle cells. Norepinephrine is used as a continuous infusion (starting at 0.5 mg/h and titrated up to obtain a 10 mm Hg increase in the mean arterial blood pressure) and should be administered via a central line in an intensive care unit (ICU) setting. It has similar efficacy to terlipressin with a reversal rate of HRS–AKI ranging between 40% and 70%.[47–49]

Table 3
Vasoconstrictor therapy in the management of hepatorenal syndrome

Treatment	Route	Dose	Frequency
Terlipressin	Intravenous	1 mg; titrate if no improvement (decrease in serum creatinine by 25% by day 3) up to maximum 12 mg/d	Every 4–6 h or continuous infusion
Norepinephrine	Intravenous	0.5–3 mg/h; titrate to achieve 10 mm Hg increase in mean arterial pressure	Continuous infusion
Midodrine	Oral	5–15 mg	3 times daily
Octreotide	Subcutaneous or intravenous	100–200 μg (subcutaneous) or 50 μg/h (infusion)	3 times daily or continuous infusion

Midodrine is an oral α-1 receptor agonist. Octreotide is a somatostatin analog that inhibits glucagon (a splanchnic vasodilator) secretion and acts as a direct mesenteric vasoconstrictor. When used alone its benefit in HRS is limited.[50] However, a combination of octreotide and midodrine has a potential benefit and is the only available treatment of HRS–AKI in the United States outside the ICU.[51,52] Midodrine is dosed between 5 and 15mg three times per day and titrated based on MAP with the goal being to raise MAP by about 10 mm Hg. Octreotide may be administered either subcutaneously (100–200 mcg three times per day) or as a continuous infusion (50 mcg/h). To date, there has only been one study comparing the effect of terlipressin with midodrine and octreotide. The complete response rate in the midodrine and octreotide group was 4.8% compared with 55% with terlipressin. The overall response rate was 28.6% for midodrine and octreotide and 70.4% with terlipressin.[53] Thus, the potential benefit of midodrine and octreotide in HRS–AKI remains in question.

The role of vasoconstrictor therapy in the management of HRS–NAKI is unclear and needs to be explored in future studies.

ALBUMIN

Albumin infusion is central to the effective management of HRS–AKI and should be used in combination with vasoconstrictor therapy. Albumin acts as a volume expander and has positive cardiac ionotropic effects.[54] Studies also provide supportive evidence for its antioxidant and immunomodulatory properties.[32,55,56] Albumin may be dosed at 20 to 40 g/d based on volume and respiratory status. Excessive albumin use may result in pulmonary edema and worse outcomes, particularly when used in combination with vasoconstrictors.

TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT

Portal hypertension may be treated with a transjugular intrahepatic portosystemic shunt (TIPS). TIPS is beneficial in patients with cirrhosis who cannot tolerate diuretics or have diuretic-refractory ascites and as salvage, rescue, or preemptive therapy in gastroesophageal variceal hemorrhage. However, the use of TIPS in HRS–AKI remains investigational. Improvement in renal function and reduction in the activity of renin–angiotensin and sympathetic nervous system after TIPS insertion for HRS–AKI was demonstrated in one small nonrandomized study.[57] Likewise, a meta-analysis of 128 patients who underwent TIPS insertion in the setting of HRS–AKI showed

improvement in serum creatinine, serum sodium, and urine output.[58] However, patients with markedly elevated bilirubin, active infection, and hepatic encephalopathy were excluded from the study. The findings may be limited to a select group of patients. TIPS is not currently recommended solely for the treatment of HRS–AKI.

RENAL REPLACEMENT THERAPY

The decision to initiate renal replacement therapy in patients with cirrhosis and AKI is based on the etiology of the AKI and the patient's transplant candidacy (**Fig. 2**). RRT has no role in the management of HRS–AKI as a stand-alone therapy.[59] However, it may be indicated in patients with treatment-refractory HRS–AKI as a bridge to liver transplantation or when the precipitating event is reversible as in selected patients with alcohol-associated hepatitis.[60,61]

LIVER TRANSPLANTATION

Liver transplantation is the definitive treatment for patients with HRS-AKI in cirrhosis. The kidney function is expected to recover after successful liver transplantation, owing to the functional nature of HRS–AKI.[62,63] However, recovery of renal function after liver transplantation is not universal and depends on multiple factors including age, comorbid conditions, and the duration of kidney injury.[64] Simultaneous liver–kidney transplantation may be indicated in these cases. In the United States, a listing policy based on consensus recommendations for a simultaneous liver–kidney transplant requires sustained AKI defined as a need for dialysis or a GFR of less than or equal to 25 mL/min for a minimum of 6 consecutive weeks.[65]

EMERGING TREATMENTS

The development of novel and effective treatment options for HRS–AKI are needed. Serelaxin is a recombinant form of the human peptide hormone relaxin-2. It increases renal perfusion by reducing renal vascular resistance and reverses endothelial dysfunction.[66] In animal models of cirrhosis, serelaxin has been shown to reduce intrahepatic vascular resistance and thus improve portal hypertension.[67] A randomized phase II study showed 65% improvement in renal perfusion from baseline in compensated cirrhotic patients treated with serelaxin.[68] Further studies are needed to elucidate the role of serelaxin in patients with HRS.

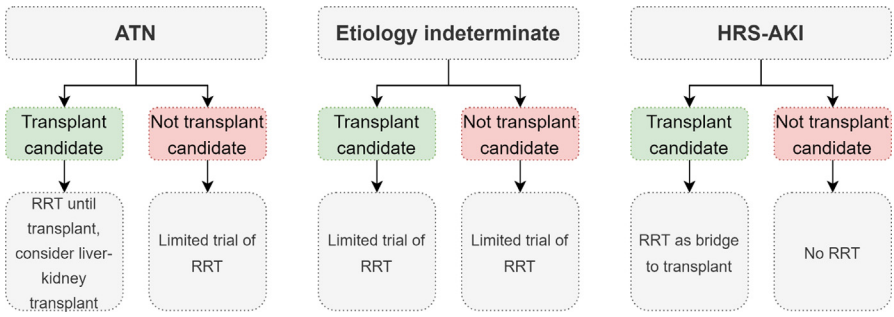

Fig. 2. Renal replacement therapy in the management of acute kidney injury in cirrhosis. Selected patients with HRS–AKI may be considered for RRT if the precipitating event is reversible, as with alcohol-associated hepatitis.

Several other drugs are currently being investigated and demonstrate promise for the treatment of HRS. These include ifetroban (a thromboxane A2/prostaglandin H2 receptor antagonist) that has successfully completed a phase II clinical trial (NCT01436500) and OCE-205 (a peptide therapeutic with a mechanism of action designed to selectively target complications of portal hypertension) that has an upcoming phase II trial (NCT05309200).

SUMMARY

Renal failure is a common and severe complication in patients with decompensated cirrhosis. HRS–AKI is a functional form of AKI in cirrhosis that confers a poor prognosis. Recently, the criteria for renal failure and HRS have been modified based on AKIN criteria with prognostic significance for cirrhosis. Our understanding of the pathophysiology of HRS–AKI has also evolved beyond circulatory dysfunction with systemic inflammation being recognized as a major factor in its development. Emphasis should remain on preventive measures for patients at risk of HRS, including appropriate use of antibiotics and albumin when indicated. Novel biomarkers such as NGAL may be useful to help determine the etiology of AKI in cirrhosis. First-line treatment of HRS–AKI is vasoconstrictor therapy and intravenous albumin. A liver transplant remains the optimal treatment and timely evaluation is critical.

CLINICS CARE POINTS

- The diagnosis of hepatorenal syndrome (HRS) is one of exclusion, and therefore should only be entertained after other possible causes of kidney injury have been ruled out.
- Classic urinary biomarkers such as urine sodium and fractional excretion of sodium, as well as the presence of renal epithelial cells and granular casts on urine microscopy, have limited accuracy in distinguishing ATN from HRS–AKI in cirrhosis. Thus, the diagnosis of ATN in patients with cirrhosis who do not respond to a fluid challenge is based on the medical history.

DISCLOSURE

The authors have no conflict of interest or funding sources to disclose.

REFERENCES

1. Garcia-Tsao G, Parikh CR, Viola A. Acute kidney injury in cirrhosis. Hepatology 2008;48(6):2064–77.
2. Fagundes C, Barreto R, Guevara M, et al. A modified acute kidney injury classification for diagnosis and risk stratification of impairment of kidney function in cirrhosis. J Hepatol 2013;59(3):474–81.
3. Piano S, Rosi S, Maresio G, et al. Evaluation of the Acute Kidney Injury Network criteria in hospitalized patients with cirrhosis and ascites. J Hepatol 2013;59(3):482–9.
4. Arroyo V, Ginès P, Gerbes AL, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. International Ascites Club. Hepatology 1996;23(1):164–76.
5. Sherman DS, Fish DN, Teitelbaum I. Assessing renal function in cirrhotic patients: Problems and pitfalls. Am J Kidney Dis 2003;41(2):269–78.
6. Bellomo R, Ronco C, Kellum JA, et al. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the

Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004;8(4):R204–12.
7. Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007;11(2):R31.
8. Summary of recommendation Statements. Kidney Int Suppl 2012;2(1):8–12.
9. Angeli P, Gines P, Wong F, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. Gut 2015;64(4):531–7.
10. Angeli P, Garcia-Tsao G, Nadim MK, et al. News in pathophysiology, definition and classification of hepatorenal syndrome: a step beyond the International Club of Ascites (ICA) consensus document. J Hepatol 2019;71(4):811–22.
11. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002;39(2 Suppl 1):S1–266.
12. Wong F. The evolving concept of acute kidney injury in patients with cirrhosis. Nat Rev Gastroenterol Hepatol 2015;12(12):711–9.
13. Schrier RW, Arroyo V, Bernardi M, et al. Peripheral arterial vasodilation hypothesis: a proposal for the initiation of renal sodium and water retention in cirrhosis. Hepatology 1988;8(5):1151–7.
14. Simonetto DA, Gines P, Kamath PS. Hepatorenal syndrome: pathophysiology, diagnosis, and management. BMJ 2020;370:m2687.
15. Jang JY, Kim TY, Sohn JH, et al. Relative adrenal insufficiency in chronic liver disease: its prevalence and effects on long-term mortality. Aliment Pharmacol Ther 2014;40(7):819–26.
16. Piano S, Favaretto E, Tonon M, et al. Including relative adrenal insufficiency in definition and classification of acute-on-chronic liver failure. Clin Gastroenterol Hepatol 2020;18(5):1188–96.e3.
17. Bräsen JH, Mederacke YS, Schmitz J, et al. Cholemic nephropathy causes acute kidney injury and is Accompanied by loss of Aquaporin 2 in Collecting Ducts. Hepatology 2019;69(5):2107–19.
18. Umgelter A, Reindl W, Wagner KS, et al. Effects of plasma expansion with albumin and paracentesis on haemodynamics and kidney function in critically ill cirrhotic patients with tense ascites and hepatorenal syndrome: a prospective uncontrolled trial. Crit Care 2008;12(1):R4.
19. Martín-Llahí M, Guevara M, Torre A, et al. Prognostic importance of the cause of renal failure in patients with cirrhosis. Gastroenterology 2011;140(2):488–96.e4.
20. Verna EC, Brown RS, Farrand E, et al. Urinary neutrophil gelatinase-associated lipocalin predicts mortality and identifies acute kidney injury in cirrhosis. Dig Dis Sci 2012;57(9):2362–70.
21. Huelin P, Solà E, Elia C, et al. Neutrophil gelatinase-associated lipocalin for assessment of acute kidney injury in cirrhosis: a prospective study. Hepatology 2019;70(1):319–33.
22. Fagundes C, Pépin MN, Guevara M, et al. Urinary neutrophil gelatinase-associated lipocalin as biomarker in the differential diagnosis of impairment of kidney function in cirrhosis. J Hepatol 2012;57(2):267–73.
23. Decavele AS, Dhondt L, De Buyzere ML, et al. Increased urinary neutrophil gelatinase associated lipocalin in urinary tract infections and leukocyturia. Clin Chem Lab Med 2011;49(6):999–1003.
24. Liu Y, Guo W, Zhang J, et al. Urinary interleukin 18 for Detection of acute kidney injury: a meta-analysis. Am J Kidney Dis 2013;62(6):1058–67.
25. Ariza X, Solà E, Elia C, et al. Analysis of a urinary biomarker panel for clinical outcomes assessment in cirrhosis. PLoS One 2015;10(6):e0128145.

26. Puthumana J, Ariza X, Belcher JM, et al. Urine interleukin 18 and lipocalin 2 are biomarkers of acute tubular necrosis in patients with cirrhosis: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2017;15(7):1003–13.e3.
27. Ginès A, Escorsell A, Ginès P, et al. Incidence, predictive factors, and prognosis of the hepatorenal syndrome in cirrhosis with ascites. Gastroenterology 1993; 105(1):229–36.
28. Wong F, Jepsen P, Watson H, et al. Un-precipitated acute kidney injury is uncommon among stable patients with cirrhosis and ascites. Liver Int 2018;38(10): 1785–92.
29. Ginès P, Titó L, Arroyo V, et al. Randomized comparative study of therapeutic paracentesis with and without intravenous albumin in cirrhosis. Gastroenterology 1988;94(6):1493–502.
30. Bernardi M, Caraceni P, Navickis RJ, et al. Albumin infusion in patients undergoing large-volume paracentesis: a meta-analysis of randomized trials. Hepatology 2012;55(4):1172–81.
31. Fernández J, Monteagudo J, Bargallo X, et al. A randomized unblinded pilot study comparing albumin versus hydroxyethyl starch in spontaneous bacterial peritonitis. Hepatology 2005;42(3):627–34.
32. Zhang W-J, Frei B. Albumin selectively inhibits TNFα-induced expression of vascular cell adhesion molecule-1 in human aortic endothelial cells. Cardiovasc Res 2002;55(4):820–9.
33. Chen T-A, Tsao Y-C, Chen A, et al. Effect of intravenous albumin on endotoxin removal, cytokines, and nitric oxide production in patients with cirrhosis and spontaneous bacterial peritonitis. Scand J Gastroenterol 2009;44(5):619–25.
34. Follo A, Llovet JM, Navasa M, et al. Renal impairment after spontaneous bacterial peritonitis in cirrhosis: incidence, clinical course, predictive factors and prognosis. Hepatology 1994;20(6):1495–501.
35. Fernández J, Navasa M, Planas R, et al. Primary prophylaxis of spontaneous bacterial peritonitis Delays hepatorenal syndrome and improves survival in cirrhosis. Gastroenterology 2007;133(3):818–24.
36. Kamal F, Khan MA, Khan Z, et al. Rifaximin for the prevention of spontaneous bacterial peritonitis and hepatorenal syndrome in cirrhosis: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol 2017;29(10):1109–17.
37. Huelin P, Piano S, Solà E, et al. Validation of a staging system for acute kidney injury in patients with cirrhosis and association with acute-on-chronic liver failure. Clin Gastroenterol Hepatol 2017;15(3):438–45.e5.
38. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol 2018;69(2):406–60.
39. Velez JC, Nietert PJ. Therapeutic response to vasoconstrictors in hepatorenal syndrome parallels increase in mean arterial pressure: a pooled analysis of clinical trials. Am J Kidney Dis 2011;58(6):928–38.
40. Jamil K, Pappas SC, Devarakonda KR. In vitro binding and receptor-mediated activity of terlipressin at vasopressin receptors V(1) and V(2). J Exp Pharmacol 2017;10:1–7.
41. Tanoue A, Ito S, Honda K, et al. The vasopressin V1b receptor critically regulates hypothalamic-pituitary-adrenal axis activity under both stress and resting conditions. J Clin Invest 2004;113(2):302–9.
42. Boyer TD, Medicis JJ, Pappas SC, et al. A randomized, placebo-controlled, double-blind study to confirm the reversal of hepatorenal syndrome type 1 with terlipressin: the REVERSE trial design. Open Access J Clin Trials 2012;4:39–49.

43. Martín-Llahí M, Pépin MN, Guevara M, et al. Terlipressin and albumin vs albumin in patients with cirrhosis and hepatorenal syndrome: a randomized study. Gastroenterology 2008;134(5):1352–9.
44. Belcher JM, Parada XV, Simonetto DA, et al. Terlipressin and the treatment of hepatorenal syndrome: How the CONFIRM trial Moves the story Forward. Am J Kidney Dis 2022;79(5):737–45.
45. Wong F, Pappas SC, Curry MP, et al. Terlipressin plus albumin for the treatment of type 1 hepatorenal syndrome. New Engl J Med 2021;384(9):818–28.
46. Cavallin M, Piano S, Romano A, et al. Terlipressin given by continuous intravenous infusion versus intravenous boluses in the treatment of hepatorenal syndrome: a randomized controlled study. Hepatology 2016;63(3):983–92.
47. Alessandria C, Ottobrelli A, Debernardi-Venon W, et al. Noradrenalin vs terlipressin in patients with hepatorenal syndrome: a prospective, randomized, unblinded, pilot study. J Hepatol 2007;47(4):499–505.
48. Sharma P, Kumar A, Shrama BC, et al. An open label, pilot, randomized controlled trial of noradrenaline versus terlipressin in the treatment of type 1 hepatorenal syndrome and predictors of response. Am J Gastroenterol 2008;103(7):1689–97.
49. Singh V, Ghosh S, Singh B, et al. Noradrenaline vs. terlipressin in the treatment of hepatorenal syndrome: a randomized study. J Hepatol 2012;56(6):1293–8.
50. Angeli P, Volpin R, Piovan D, et al. Acute effects of the oral administration of midodrine, an α-adrenergic agonist, on renal hemodynamics and renal function in cirrhotic patients with ascites. Hepatology 1998;28(4):937–43.
51. Angeli P, Volpin R, Gerunda G, et al. Reversal of type 1 hepatorenal syndrome with the administration of midodrine and octreotide. Hepatology 1999;29(6):1690–7.
52. Wong F, Pantea L, Sniderman K. Midodrine, octreotide, albumin, and TIPS in selected patients with cirrhosis and type 1 hepatorenal syndrome. Hepatology 2004;40(1):55–64.
53. Cavallin M, Kamath PS, Merli M, et al. Terlipressin plus albumin versus midodrine and octreotide plus albumin in the treatment of hepatorenal syndrome: a randomized trial. Hepatology 2015;62(2):567–74.
54. Bortoluzzi A, Ceolotto G, Gola E, et al. Positive cardiac inotropic effect of albumin infusion in rodents with cirrhosis and ascites: molecular mechanisms. Hepatology 2013;57(1):266–76.
55. Stocker R, Glazer AN, Ames BN. Antioxidant activity of albumin-bound bilirubin. Proc Natl Acad Sci 1987;84(16):5918–22.
56. Cantin AM, Paquette B, Richter M, et al. Albumin-mediated regulation of cellular glutathione and nuclear factor kappa B activation. Am J Respir Crit Care Med 2000;162(4 Pt 1):1539–46.
57. Guevara M, Ginès P, Bandi JC, et al. Transjugular intrahepatic portosystemic shunt in hepatorenal syndrome: effects on renal function and vasoactive systems. Hepatology 1998;28(2):416–22.
58. Song T, Rössle M, He F, et al. Transjugular intrahepatic portosystemic shunt for hepatorenal syndrome: a systematic review and meta-analysis. Dig Liver Dis 2018;50(4):323–30.
59. Zhang Z, Maddukuri G, Jaipaul N, et al. Role of renal replacement therapy in patients with type 1 hepatorenal syndrome receiving combination treatment of vasoconstrictor plus albumin. J Crit Care 2015;30(5):969–74.

60. Lenhart A, Hussain S, Salgia R. Chances of renal recovery or liver transplantation after Hospitalization for alcoholic liver disease requiring dialysis. Dig Dis Sci 2018;63(10):2800–9.
61. Jones BE, Allegretti AS, Pose E, et al. Renal replacement therapy for acute kidney injury in severe alcohol-associated hepatitis as a bridge to transplant or recovery. Dig Dis Sci 2022;67(2):697–707.
62. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. J Hepatol 2010; 53(3):397–417.
63. Runyon BA. Management of adult patients with ascites due to cirrhosis: an update. Hepatology 2009;49(6):2087–107.
64. Israni AK, Xiong H, Liu J, et al. Predicting end-stage renal disease after liver transplant. Am J Transpl 2013;13(7):1782–92.
65. Organ Procurement and Transplantation Network. Policies. 2022. Available at: https://optn.transplant.hrsa.gov/media/eavh5bf3/optn_policies.pdf
66. Conrad KP. Unveiling the vasodilatory actions and mechanisms of relaxin. Hypertension 2010;56(1):2–9.
67. Snowdon VK, Lachlan NJ, Hoy AM, et al. Serelaxin as a potential treatment for renal dysfunction in cirrhosis: Preclinical evaluation and results of a randomized phase 2 trial. Plos Med 2017;14(2):e1002248.
68. Stine JG, Wang J, Cornella SL, et al. Treatment of type-1 hepatorenal syndrome with Pentoxifylline: a randomized placebo controlled clinical trial. Ann Hepatol 2018;17(2):300–6.