Improving the Management of Hepatorenal Syndrome–Acute Kidney Injury Using an Updated Guidance and a New Treatment Paradigm

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Abstract: Cirrhosis, or advanced scarring of the liver, represents the end stage of chronic liver disease and is associated with high morbidity and mortality. Hepatorenal syndrome–acute kidney injury (HRS-AKI), a condition causing functional and progressive kidney failure, is a complication of cirrhosis that contributes to its high mortality rate. In the United States, the standard-of-care treatments for HRS-AKI have historically been suboptimal. Recently, terlipressin became the first drug approved for HRS-AKI in the United States, and the American Association for the Study of Liver Diseases updated its guidance document on HRS diagnosis and management. Clinical practice guidelines and guidance documents have a variable effect on physician behavior owing to a lack of awareness, familiarity, and education. The implementation of standardized order sets can improve guidance adherence and the quality of care delivered by encouraging data-driven treatment administration, especially for new therapies. This review seeks to facilitate improvements in the management of HRS-AKI by discussing early HRS-AKI interventions, which will streamline diagnosis and treatment in a practical way for clinical use, and how to incorporate new treatments into patient care to improve survival in this subset of patients. Finally, these recommendations are integrated into a sample order set developed by members of the Chronic Liver Disease Foundation and experts in the management of HRS-AKI.

Keywords
Cirrhosis, hepatorenal syndrome–acute kidney injury, terlipressin, diagnosis, treatment

Cirrhosis is the end stage of chronic liver disease, during which the liver has become progressively scarred or, histologically, normal liver architecture is converted into structurally abnormal nodules. In advanced or decompensated cirrhosis, this disruption in liver architecture leads to portal hypertension, with increased resistance

Table 1. Recent Trends in HRS-AKI

Study	Aim	Methods	Findings
Jamil et al[7]	To assess the temporal trend in mortality and identify the predictors of mortality among hospital admissions for HRS in the United States	A nationwide electronic health record database of hospitalized patients with HRS (n=3563) between 2009 and 2018 was retrospectively analyzed	Among the patients studied, 34% died in the hospital, 14% were discharged to hospice, and, among the remaining survivors, 38% were readmitted within 90 days of discharge. In addition, 23% of readmissions were HRS-related. Almost one-half (46.5%) of the patients did not receive vasopressors
Kaewput et al[22]	To assess the temporal trend in mortality and identify the predictors of mortality among hospital admissions for HRS in the United States	The NIS database was used to identify an unweighted sample of 4938 hospital admissions for HRS from 2005 to 2014 (weighted sample of 23,973 admissions)	The overall hospital mortality was 32%. Hospital mortality decreased from 44% in 2005 to 24% in 2014 (P<.001). The rate of liver transplant (P=.02), renal replacement therapy (P<.001), length of hospital stay (P<.001), and hospitalization cost (P<.001) significantly increased. Heightened outcomes were attributed to the optimized utilization of health care resources
Singh et al[40]	A meta-analysis to determine epidemiologic characteristics and trends for HRS hospitalizations. Additionally, inpatient mortality, mean length of stay, and mean total hospital charge were calculated using a multivariate regression trend analysis	This retrospective interrupted trend study used the NIS database for 2008, 2012, 2014, 2016, and 2018 to identify adult (≥18 years) hospitalizations with a primary diagnosis of HRS	There was an increase in the total number of HRS hospitalizations from 22,864 in 2008 to 42,985 in 2018 with a trend toward increasing hospitalizations (P-trend <.001). After a multivariate regression trend analysis, a statistically significant trend toward declining inpatient mortality was found (36.2% in 2008 to 25.7% in 2018; P-trend <.001 for HRS hospitalizations). Researchers attributed this trend in part to earlier diagnoses and the implementation of the protocolized management of HRS
Singal et al[23]	To examine recent trends, as well as the magnitude and outcomes of HRS, in a NIS database	A retrospective analysis of the NIS database on cirrhosis hospitalizations (113,454 from 2016 to 2019) owing to ALD, chronic viral hepatitis, or MASH, and complicated by AKI	Of the 113,454 hospitalizations, 18,735 (16.5%) had HRS. Based on weighted national estimates, HRS conferred a significant health care burden with 27,180 HRS hospitalizations in 2019 and requiring an estimated USD $4.2 billion for hospital care

AKI, acute kidney injury; ALD, alcoholic liver disease; HRS, hepatorenal syndrome; MASH, metabolic dysfunction-associated steatohepatitis; NIS, National Inpatient Sample; USD, US dollars.

to portal blood flow and primary vasodilation of the systemic and splanchnic arterial circulation. In response to these vascular changes, vasoconstrictor activity in the kidney accelerates, and sodium and water retention causes plasma volume expansion. Under these conditions, the cardiac output does not increase sufficiently to sustain the needs of systemic circulation, and renal perfusion diminishes. Ultimately, patients can develop hepatorenal syndrome–acute kidney injury (HRS-AKI), a functional, progressive kidney disorder associated with cirrhosis.[1-3] If left untreated, the estimated median survival in patients with HRS-AKI is 8 to 12 weeks.[4-7] In addition, the kidneys are the most commonly affected organs in acute-on-chronic liver failure, which is characterized by acute decompensation of chronic liver disease and is associated with multiple organ failure and high short-term mortality.[8]

In the United States, HRS-AKI is associated with a high mortality rate. The prognosis of HRS-AKI can be improved with standardized and proactive medical care

resulting in early diagnosis, followed by timely treatment with approved effective medical therapy.[1] In late 2022, terlipressin (Terlivaz, Mallinckrodt), a vasopressin analogue that exerts vasoconstrictive activity via selective vasopressin 1 and 2 receptors, was approved in the United States for the treatment of HRS-AKI in combination with hyperoncotic (25%) human albumin solution.[9] In addition, the American Association for the Study of Liver Diseases (AASLD) recently published an updated guidance document focusing on the diagnosis and management of HRS-AKI.[10] Prompt universal adoption of this standard of care is key to reducing morbidity and mortality for HRS-AKI in the United States. However, in various therapeutic areas including cirrhosis,[11] clinical practice guidelines have demonstrated limited impact on physician behavior.[12] Factors negatively affecting the adoption of society guidelines include limited physician awareness of and familiarity with the guidelines[12] as well as inadequate processes to inform clinicians about the existence of these guidelines.[11] Implementation of standardized order sets in cirrhosis and its complications can limit the variability in clinical practice and improve overall timeliness and effectiveness of treatment. Prompt universal adoption of this standard of care is key to reducing morbidity and mortality for HRS-AKI in the United States.

This expert perspective review seeks to facilitate improvements in the management of HRS-AKI, and discusses early HRS-AKI interventions to streamline the diagnosis and treatment guidance in a practical way for clinical use, as well as recommends how to incorporate this guidance into clinical practice. Finally, the new treatment and updated guidance will be integrated into a sample order set developed by the authors, who are experts in the management of HRS-AKI and are members of or work closely with the Chronic Liver Disease Foundation (CLDF), a nonprofit 501(c)(3) educational organization dedicated to raising awareness of liver disease.

A Review of Hepatorenal Syndrome–Acute Kidney Injury

Previously, HRS was classified by the International Club of Ascites as either type 1 (or HRS-1, a rapid deterioration of renal function, often because of a precipitating event) or type 2 (or HRS-2, moderate and stable or slowly progressive renal dysfunction, often without an obvious precipitant), but now the International Club of Ascites delineates HRS-1 and HRS-2 according to the presence or absence of AKI, respectively. HRS-1 is now termed HRS-AKI; the new definition encourages clinicians to initiate the treatment of patients early, even when increases in serum creatinine (sCr) are small. Specifically, HRS-AKI is defined as an absolute increase in sCr of at least 0.3 mg/dL within 48 hours or an increase in sCr of at least 50% from a baseline sCr level obtained within the previous 3 months. HRS-AKI occurs in the absence of hypovolemia or significant abnormalities in kidney histology.[10] A diagnosis of HRS-AKI requires that all other causes of AKI be ruled out and that there is no current or recent treatment with nephrotoxic medication. HRS–non-AKI, or NAKI, is diagnosed in a context of subacute or chronic renal dysfunction, specifically in a patient with cirrhosis and a glomerular filtration rate less than 60 mL/min/1.73 m^2 for longer than 3 months in whom other causes have been excluded or in the context of acute kidney disease, defined as a renal dysfunction that does not meet the criteria for AKI and lasts less than 90 days.[13]

A 2015 examination of National Health and Nutrition Examination Survey data found that the prevalence of cirrhosis in the United States was 633,323 adults, or 0.3% of the population. However, this is likely an underestimate because many patients remain undiagnosed, particularly patients who have compensated disease and are asymptomatic.[14] The estimated annual incidence for HRS type 1 (now termed HRS-AKI) in the United States ranges from 9000 patients to more than 35,000 patients.[15-19] In patients with decompensated cirrhosis with ascites, the probability of developing HRS ranges between 8% and 20% per year and increases to 40% at 5 years. An estimated 35% to 40% of patients with end-stage liver disease and ascites will develop HRS.[20] HRS-AKI is potentially reversible with treatment; without treatment, the consequences of HRS-AKI include irreversible renal failure, with mortality rates approaching 100% at 3 months after diagnosis.[1,21] More recent publications have analyzed evolving trends in HRS-AKI (Table 1).[7,22-24] HRS contributes to hospitalizations of patients with cirrhosis, and these hospitalizations confer significant health care burdens.[23] High mortality rates and hospital readmissions were attributed to inconsistencies in hospital-based HRS treatment strategies and called for greater disease awareness and more effective treatment options.[7] Conversely, earlier diagnoses,[24] the implementation of the protocolized management of HRS,[24] and better utilization of health care resources[22] ameliorated outcomes.

The poor prognosis of cirrhotic patients with HRS-AKI and previously inadequate therapies prompted the need to develop new treatments. Liver transplantation is the gold standard for treating HRS-AKI, as it corrects the underlying liver failure. However, many patients with HRS-AKI are ineligible for a liver transplant or will expire before receiving one. Moreover, patients with significant kidney injury prior to liver transplant may demonstrate worse long-term posttransplant outcomes. Renal replacement therapy (RRT) may bridge patients to liver

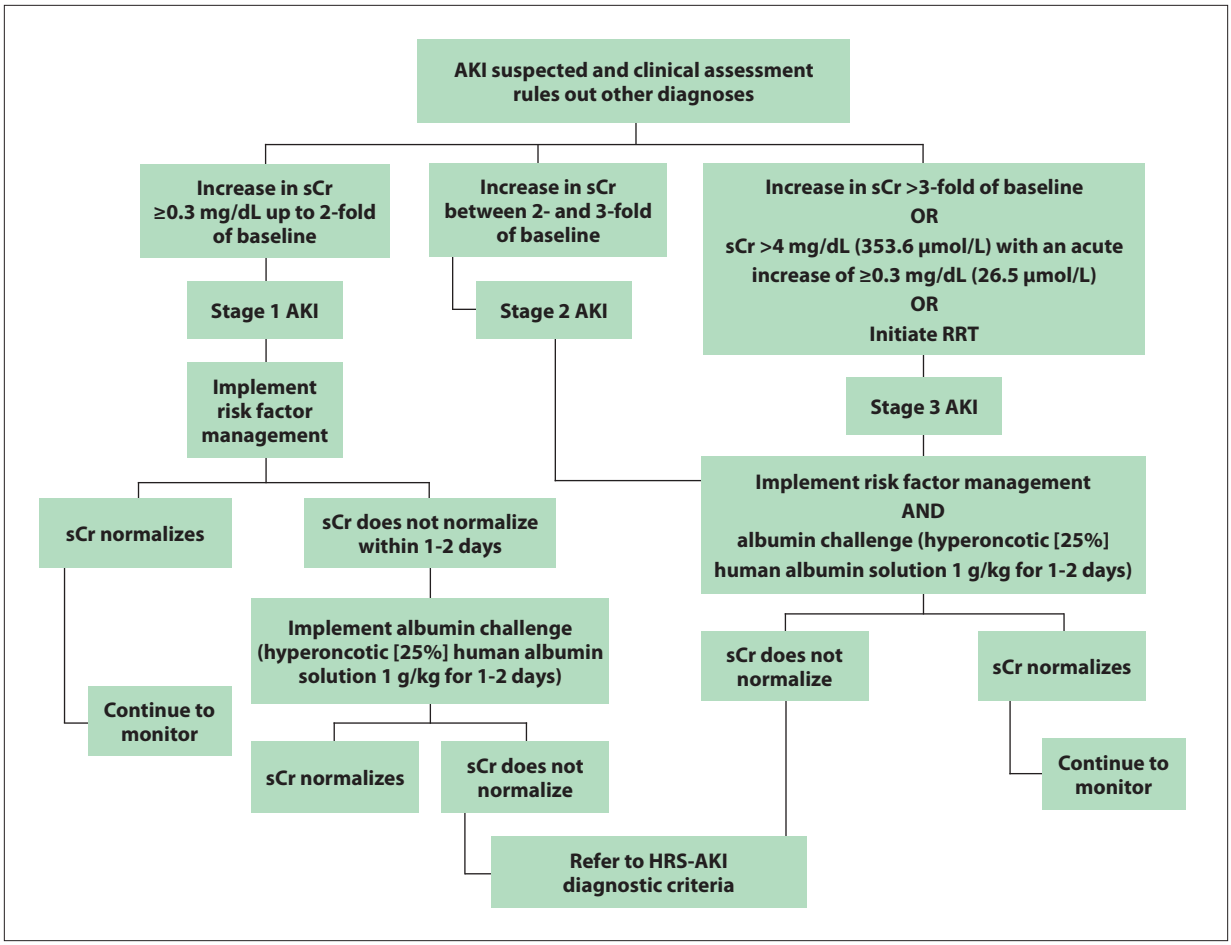

Figure. AASLD guidance recommendations to diagnose HRS-AKI.[10]

AASLD, American Association for the Study of Liver Diseases; AKI, acute kidney injury; HRS-AKI, hepatorenal syndrome–acute kidney injury; RRT, renal replacement therapy; sCr, serum creatinine.

transplant, although outcomes are poor,[1] and acute renal failure patients must meet specific criteria to qualify for simultaneous liver–kidney transplant. Therefore, pharmacologic interventions to optimize renal outcomes are clearly needed. Current treatments involve volume expansion and vasoconstriction. Hyperoncotic (25%) human albumin solution is considered a crucial volume expander to treat HRS-AKI when used with vasoconstrictors. The additive effects of vasoconstrictors and albumin infusion improve outcomes compared with either agent alone.[1,25] Historically, the vasoconstrictive component included the administration of midodrine and octreotide (an α–adrenergic agonist combined with a selective splanchnic vasoconstrictor) or norepinephrine (an α-adrenergic agonist). These medications are not approved in the United States for HRS-AKI but are used off-label based on results from small, nonrandomized studies. Norepinephrine is generally administered in the intensive care unit (ICU) and frequently requires a central line for administration, especially with prolonged use.[1] Thus, midodrine and octreotide became the default unapproved regimen of choice in the United States owing to a lack of better options. In Europe, terlipressin has been approved for longer than a decade.[26] Moreover, the European Association for the Study of the Liver Clinical Practice Guidelines recommended terlipressin as the first-line agent in HRS-AKI management.[27] The US Food and Drug Administration's recent approval of terlipressin makes it the first approved drug in the United States for the treatment of HRS-AKI.

Applying Guidance Recommendations to Clinical Practice

The Diagnosis, Evaluation, and Management of Ascites, Spontaneous Bacterial Peritonitis, and Hepatorenal Syndrome: 2021 Practice Guidance by the AASLD offers comprehensive guidance on the diagnosis, evaluation, and management of the aforementioned complications

Table 2. Stages of AKI[10]

AKI stage	Description
1	Increase in sCr ≥0.3 mg/dL up to 2-fold of baseline
2	Increase in sCr between 2-fold and 3-fold of baseline
3	Increase in sCr >3-fold of baseline or sCr >4 mg/dL (353.6 µmol/L) with an acute increase of ≥0.3 mg/dL (26.5 µmol/L) or the initiation of RRT

AKI, acute kidney injury; RRT, renal replacement therapy; sCr, serum creatinine.

Table 3. Criteria to Diagnose HRS-AKI[10]

Cirrhosis with ascites
AKI according to the ICA-AKI criteria (increase in sCr ≥0.3 mg/dL from the baseline within 48 hours or an increase in sCr of ≥50%, which is known or presumed to have occurred within the preceding 7 days)
No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with hyperoncotic (25%) human albumin solution infusion (1 g/kg of body weight per day)
Absence of shock
No current or recent use of nephrotoxic drugs (NSAIDs, aminoglycosides, or iodinated contrast media)
No signs of structural kidney injury, as indicated by proteinuria (>500 mg per day), microhematuria (>50 red blood cells per high-power field), and/or abnormal renal ultrasonography

The patient must meet all these criteria to confirm the diagnosis of HRS-AKI.

AKI, acute kidney injury; HRS, hepatorenal syndrome; ICA, International Club of Ascites; NSAIDs, nonsteroidal anti-inflammatory drugs; sCr, serum creatinine.

of cirrhosis. It replaces prior AASLD guidance on the same topics published in 2012.[10] The management of HRS-AKI depends on the appropriate risk factor management. To facilitate the use of this guidance statement in clinical practice, the algorithm in the Figure and the section that follows provide a streamlined version of the HRS-AKI recommendations set forth in the 2021 guidance document.

1. Once acute kidney injury is established, perform a differential diagnostic workup

Clinical histories are critically important in determining the cause of AKI. Per the definition of AKI, an increase in sCr of at least 0.3 mg/dL within 48 hours or a 50% or greater increase in sCr that is known or presumed to have occurred within the preceding 7 days should lead to the suspicion of AKI and be followed by a clinical assessment. Serum tests can indicate abnormalities in sCr, which should be compared with the patient's baseline sCr, if available, hemoglobin/hematocrit, total protein/albumin, calcium bicarbonate, and uric acid. Moreover, urine should be tested for decreased urine volume (<500 mL/day), urine specific gravity (>1.105), urine sodium (<20 mEq/L), fractional excretion of sodium (<1%), fractional excretion of urea (<35%), or fractional excretion of uric acid (<10%). Although sodium excretion is impacted by diuretics, neither the fractional excretion of urea nor uric acid is affected by diuretic use. These tests can provide a differential diagnosis, such as acute tubular necrosis, acute interstitial nephritis, urinary tract infection, or urinary tract obstruction, that warrants different treatment recommendations than those for HRS-AKI.[10]

2. Determine the stage of acute kidney injury

After other diagnoses are ruled out, the patient is considered to have AKI, and the next step is to determine if the patient has stage 1, 2, or 3 (Table 2) AKI.[10]

3. Next steps in patients with stage 1 acute kidney injury

AKI cannot be reversed by any specific therapy, but some of the underlying causes may be treatable. If AKI is diagnosed, risk factor management should be implemented, which may include the withdrawal of nephrotoxic drugs, the reduction or withdrawal of diuretics, the reduction or withdrawal of β-blockers or other antihypertensive medications, an evaluation for and treatment of infections, and volume replacement (if severely volume depleted). If sCr normalizes with risk factor management, the situation should continue to be monitored. If sCr does not normalize within 1 to 2 days despite risk factor management, the albumin challenge should be implemented. This consists of hyperoncotic (25%) human albumin solution 1 g/kg/day (maximum dose 100 g/day; maximum rate 1-2 mL/min) until an adequate volume is achieved (as indicated by better hemodynamic parameters and renal function) or a maximum of 2 days. An absolute sCr of greater than 1.5 mg/dL should expedite the use of vasoconstrictors. If there is no resolution following the albumin challenge, refer to the criteria used to diagnose HRS-AKI (Table 3).[10]

4. Next steps in patients with stage 2 or 3 acute kidney injury

In patients with stage 2 or 3 AKI, the described risk factor management should be implemented during the albumin challenge: hyperoncotic (25%) human albumin solution

Table 4. Terlipressin US Prescribing Information Recommendations[9]

Indications	To improve kidney function in adults with hepatorenal syndrome with rapid reduction in kidney function
Boxed warning	**Warning: serious or fatal respiratory failure** Terlipressin may cause serious or fatal respiratory failure. Patients with volume overload or with ACLF Grade 3[a] are at increased risk. Assess oxygenation saturation (eg, SpO_2) before initiating terlipressin. Do not initiate terlipressin in patients experiencing hypoxia (eg, SpO_2 <90%) until oxygenation levels improve. Monitor patients for hypoxia using continuous pulse oximetry during treatment and discontinue terlipressin if SpO_2 decreases below 90%
Contraindications	In patients experiencing hypoxia or worsening respiratory symptoms, and in patients with ongoing coronary, peripheral, or mesenteric ischemia
Warnings and precautions	**Serious or fatal respiratory failure:** Monitor patients for changes in respiratory status using pulse oximetry and regular clinical assessments. Actively manage intravascular volume overload and adjust terlipressin therapy as appropriate **Ineligibility for liver transplant:** Terlipressin-related adverse reactions may make a patient ineligible for liver transplant, if listed **Ischemic events:** Terlipressin is a vasoconstrictor and can cause ischemic events (cardiac, peripheral, or mesenteric) that may require dose interruption or discontinuation **Embryo–fetal toxicity:** Terlipressin may cause fetal harm when used during pregnancy. Advise females of reproductive potential of the potential hazard to the fetus
Adverse reactions	The most common adverse reactions (≥10%) include abdominal pain, nausea, respiratory failure, diarrhea, and dyspnea

ACLF, acute-on-chronic liver failure; SpO_2, oxygen saturation.

[a]For more information on ACLF and access to an online calculator, visit https://www.mdcalc.com/calc/10240/clif-c-aclf-acute-chronic-liver-failure.

1 g/kg for 2 days. If sCr normalizes, the physician should continue to monitor the patient. If there is no resolution, the physician should refer to the criteria used to diagnose HRS-AKI (Table 3).[10]

5. Managing the patient with acute kidney injury meeting hepatorenal syndrome–acute kidney injury criteria

Notably, the hospitalist plays a pivotal role in recognizing HRS-AKI. However, once diagnosed, the involvement of specialists (eg, hepatologist, gastroenterologist, nephrologist, critical care physician, transplant surgeon[10]) is essential. All patients with HRS-AKI are in the advanced stages of liver disease, and there are likely many additional comorbidities to address. After the multidisciplinary team is established, treatment decisions can be made collaboratively.

The AASLD recommends vasoconstrictors, in combination with albumin, to improve kidney function in patients with HRS-AKI. The AASLD guidance document designates terlipressin as the vasoconstrictor of choice for HRS-AKI and recommends alternatives in settings where terlipressin is unavailable. The second choice is norepinephrine, which necessitates an ICU setting for infusion and preferably a central line for administration. If neither can be administered, a trial of oral midodrine with octreotide may be considered; however, the guidance notes that efficacy of this regimen is low.[10] Treatment administration, including dosing and monitoring recommendations, is covered later in this review. Terlipressin administration recommendations are based on US prescribing information and expert panel feedback.

Terlipressin US Prescribing Information and Data Update

The approval of terlipressin was based on results from the phase 3 CONFIRM study, which observed 300 patients with cirrhosis and HRS-1 (the preferred terminology when the study was conducted). Patients received terlipressin (n=199) or placebo (n=101) in a blinded manner, with 1 mg of terlipressin acetate (0.85 mg terlipressin) or placebo administered intravenously over 2 minutes every 5.5 to 6.5 hours. Concomitant hyperoncotic (25%) human albumin solution was administered at a recommended dose of 1 g/kg of body weight to a maximum of 100 g on day 1 and 20 g to 40 g per day thereafter. Patients were eligible for terlipressin or placebo dose adjustments following the sCr results on day 4. The primary endpoint of verified HRS reversal was defined as 2 consecutive

sCr measurements of less than or equal to 1.5 mg/dL at least 2 hours apart up to day 14 and survival without RRT for at least an additional 10 days of HRS. This was reported in 32% of terlipressin-treated patients and 17% of placebo-treated patients (*P*=.006). More adverse events, including abdominal pain, nausea, diarrhea, and respiratory failure, occurred with terlipressin than with placebo, with death within 90 days owing to respiratory disorders occurring in 11% of terlipressin-treated patients compared with 2% of placebo-treated patients.[28] Finally, of the patients who received terlipressin, 84.4% were treated on the floor, thereby avoiding ICU admission.[29] Table 4 shows the terlipressin US prescribing information recommendations.[9]

An updated meta-analysis of randomized controlled trials with terlipressin in HRS-AKI, including CONFIRM, was recently published. Eight randomized controlled trials with 974 patients and a median follow-up of 100 days were included in the analysis. Compared with the placebo, terlipressin was associated with a significantly higher likelihood of HRS reversal (relative risk [RR], 2.08; 95% CI, 1.51-2.86; *P*<.001), significantly lower sCr (mean differences, -0.64; 95% CI, -1.02 to -0.27; *P*<.001), and a trend toward fewer RRT requirements (RR, 0.61; 95% CI, 0.36-1.02; *P*=.06). There was no difference in survival at 90 days between groups (RR, 1.09; 95% CI, 0.84-1.43; *P*=.52), which the authors attributed to the high risk of other fatal complications unrelated to HRS. Although terlipressin is effective in improving renal function, it does not reverse cirrhosis. Patients in this analysis had a mean Model for End-Stage Liver Disease score of 33 ± 6, which indicates advanced liver decompensation and high acute mortality. The major adverse effects associated with terlipressin align with those found in CONFIRM and include abdominal pain and respiratory distress.[30] The risk of ischemic side effects related to terlipressin may be reduced by administering the drug in a continuous intravenous infusion with a recommended starting dose of 2 mg/day increased every 24 to 48 hours, up to 12 mg/day, until sCr decreases,[31] as recommended in the AASLD guidance.[10]

Prior studies, like those described, have demonstrated that terlipressin is effective in treating HRS-AKI, but liver transplantation remains the ultimate solution. A recently published study evaluated the impact of responses to treatment with terlipressin and albumin on posttransplant outcomes in patients with HRS-AKI. The study's population consisted of patients who developed HRS-AKI before their transplant and were treated with terlipressin and albumin (n=82). After their liver transplants, patients were followed up until discharge, every month for the first 3 months and every 3 months thereafter. Of the patients treated with terlipressin and albumin, 52% (n=43) responded. Compared with nonresponders, patients who responded demonstrated better 30-day transplant-free survival (60% vs 33%; *P*=.006), longer transplant waiting list time (37 vs 17 days; *P*=.041), and lower Model for End-Stage Liver Disease score at transplant (23 vs 29; *P*=.007). Among patients with HRS-AKI undergoing transplants, nonresponders required RRT more frequently than responders (20% vs 0%; *P*=.024) and demonstrated a significantly higher incidence of chronic kidney disease at 1 year after transplant than responders (65% vs 31%; *P*=.019). This study demonstrates that terlipressin improves liver transplant outcomes in patients with HRS-AKI.[32]

A Sample Hepatorenal Syndrome–Acute Kidney Injury Order Set

The authors of this review have collaborated to create a sample order set (Tables 5A and 5B), which incorporates all the recommendations discussed throughout this review, including guidance-specific recommendations[10] and expert panel clinical experience and expertise. This can be used to help guide clinical decision-support tool development for managing hospitalized patients with HRS-AKI or can serve as a reference for developing an institution-specific order set. For example, a hospital-specific information technology department or electronic medical records specialist could use this blueprint to customize an electronic finished product.

Regarding HRS-AKI treatment (Table 5B), the terlipressin US prescribing information recommends 0.85 mg as an intravenous push every 6 hours on days 1 through 3, with sCr reassessments on day 4, followed by dose adjustments accordingly.[9] The terlipressin dosing recommendations in the AASLD guidance differ slightly from the current prescribing information and were developed before the US Food and Drug Administration's approval of terlipressin. These recommendations are based on long-term experience in Europe, and this panel adheres to these guidance recommendations in practice. Institutions are encouraged to review both dosing options and choose which delivery system, or both, to place on their formulary. If further data become available and the individual hospital has a champion of this cause, order sets can be updated.

The AASLD recommends vasoconstrictors, with albumin, for enhancing kidney functioning in patients with HRS-AKI.[10] Albumin is available in 2 formulations: 5% and 25%. Hyperoncotic (25%) human albumin solution is the therapeutic choice when fluid is restricted or in cases of oncotic deficiencies,[33] which is common in patients with cirrhosis who are prone to developing edema with a large intravenous volume infusion. The optimum

albumin dose is difficult to determine. Therefore, patients are at risk of pulmonary edema and fluid overload secondary to albumin-induced increases in plasma volume. The hyperoncotic (25%) human albumin solution dose and rate of infusion should be adjusted according to the patient's volume status,[33,34] which requires evaluation after each hyperoncotic (25%) human albumin solution dose and includes signs of cardiopulmonary dysfunction and fluid status (eg, blood pressure, pulse, oxygenation, escalating oxygen requirements, respiratory rate, development of peripheral edema, daily weights, inputs, and outputs). In patients with HRS-AKI, the additive effects provided by vasoconstrictors and hyperoncotic (25%) human albumin solution infusion are thought to improve outcomes when compared with either agent alone,[1,25] although this may further complicate the adverse event profile. Close monitoring for these side effects is recommended,[10] and the 48-hour albumin stopping rule is included in the sample order set as a checkpoint for a committed benefit. Upon the first clinical sign of cardiovascular overload (headache, dyspnea, jugular venous distention, and increased blood pressure), the infusion must be slowed or stopped immediately,[35] and furosemide can be considered for volume management.

Data indicate that a rise in mean arterial pressure (MAP) during vasoconstrictor or albumin therapy in HRS is associated with better kidney function.[36] The achievement of a prespecified target of MAP increases might improve renal outcomes in HRS-AKI.[37] However, as Velez and colleagues concluded, the minimum required MAP elevation to achieve a beneficial effect for kidney functioning remains speculative and would require a prospective study for confirmation.[37]

Importantly, all patients with HRS-AKI, including those who respond to vasoconstrictors, should be considered for urgent liver transplant evaluation, given the high short-term mortality in this patient population. In candidates for transplant, the use of RRT is indicated in cases of worsening renal function, electrolyte disturbances, or increasing volume overload unresponsive to vasoconstrictor therapy. HRS-AKI requiring RRT in severe liver failure may be a marker of the likelihood of further deterioration or other organ dysfunction that may not necessarily be improved by the provision of RRT.[38] Therefore, in those patients who are not transplant candidates, determining whether to initiate RRT involves defining the goals of care with the patients and their families,[10] with the understanding that without liver transplant and without a meaningful chance of renal recovery, continuous RRT is considered futile owing to the high mortality rate and low rate of renal recovery, high risk of complications (eg, bleeding), and more prolonged hospitalizations.[39] Consequently, the decision to start RRT in these patients is

Table 5. A Sample HRS Order Set
A. HRS-AKI Diagnosis

Test		Priority and frequency
Serum blood tests	CMP	On admission
	Uric acid	On admission
	sCr	On admission and daily
	Hemoglobin/hematocrit	On admission and daily
	Total protein/albumin	On admission and daily
Urine	Urine analysis	On admission
	Urine specific gravity	On admission
	Urine sodium	On admission
	Urine uric acid	On admission
	Fractional excretion of sodium	On admission
	Fractional excretion of urea	On admission
Microbiology	Urine culture	On admission
	Blood culture	On admission
Diagnostic paracentesis		On admission
Imaging	Ultrasound of kidney/bladder	On admission
	Chest radiograph	On admission
		If volume overload is suspected
Risk factor management[10]	Withdraw nephrotoxic drugs (NSAIDs)	On admission
	Reduce or withdraw diuretics and β-blockers	On admission
	Volume replacement if severely depleted	On admission
Albumin challenge[10]	Administer hyperoncotic (25%) human albumin solution 1 g/kg/day (maximum dose 100 g/day; maximum rate 1-2 mL/min) until adequate volume is achieved (as indicated by improvement in hemodynamic parameters and renal function) or a maximum of 2 days	Following risk factor management, if sCr does not normalize

AKI, acute kidney injury; CMP, comprehensive metabolic panel; HRS, hepatorenal syndrome; NSAIDs, nonsteroidal anti-inflammatory drugs; sCr, serum creatinine.

(Continues on next page)

Table 5. A Sample HRS Order Set *(Continued)*
B. HRS-AKI Treatment

Is terlipressin available at your institution?		**☐ Yes: Proceed to first-choice recommendation** **☐ No: Proceed to second-choice recommendation**
Treatment preference[10]	**Medications[10]**	**Treatment dosage(s) and administration**
First choice	Terlipressin[a] + hyperoncotic (25%) human albumin solution	Terlipressin 0.85 mg IV push over 2 minutes (5 mL) every 6 hours × 72 hours (3 days), with sCr reassessments on day 4, followed by dose adjustments accordingly[9] OR Start via continuous IV infusion at 2 mg/day; increase every 24-48 hours up to 12 mg/day until sCr decreases[10] Response to terlipressin is defined by sCr decreases to <1.5 mg/dL or return to within 0.3 mg/dL of the baseline over a maximum of 14 days. In patients whose sCr remains at or above the pretreatment level over 4 days with the maximum tolerated doses of the vasoconstrictor, therapy may be discontinued Coadminister albumin 1 g/kg (max 100 g) on day 1 of therapy followed by 40-50 g/day for the duration of therapy[10] or 25 g every 6-8 hours. Stop albumin after 48 hours and reassess Initiate continuous pulse oximetry monitoring, and discontinue terlipressin if SpO_2 <90%. Contact the provider
Second choice	Norepinephrine + hyperoncotic (25%) human albumin solution	Start norepinephrine via continuous IV infusion, 0.05 µg/kg/hr titrated by 0.01 µg/kg/hr every 5 minutes, to achieve a MAP goal (as listed) or urine output goal (as listed) Response to norepinephrine is defined by sCr decreases to <1.5 mg/dL or a return to within 0.3 mg/dL of the baseline over a maximum of 14 days. In patients whose sCr remains at or above the pretreatment level over 4 days with the maximum tolerated doses of the vasoconstrictor, therapy may be discontinued[10] Coadminister albumin to maintain a central venous pressure between 4 and 10 mm Hg[10] Stop albumin after 48 hours and reassess
Third choice[b]	Midodrine/ octreotide + hyperoncotic (25%) human albumin solution	Administer 5-15 mg oral midodrine every 8 hours in combination with 100-200 µg SC octreotide every 8 hours or 50 µg/hour intravenously[10] Maintain midodrine/octreotide until sCr returns to baseline (up to 14 days), which may be extended in certain cases. In patients whose sCr remains at or above the pretreatment level over 4 days with the maximum tolerated doses of midodrine/octreotide, therapy may be discontinued[10] Coadminister 25 g albumin BID for 4 doses, with daily reevaluation and decision-making according to patient status[10]

AASLD, American Association for the Study of Liver Diseases; AKI, acute kidney injury; BID, twice daily; FDA, US Food and Drug Administration; HRS, hepatorenal syndrome; IV, intravenous; MAP, mean arterial pressure; SC, subcutaneous; sCr, serum creatinine; SpO_2, oxygen saturation.

[a]The AASLD guidance was published before FDA approval of terlipressin. For the purposes of this article, the recommended terlipressin dose and administration is based on FDA-approved prescribing information.
[b]The AASLD warns that the efficacy of this treatment regimen is low.

difficult and should be individualized, considering that young patients and those with alcoholic hepatitis who stopped consuming alcohol might have a better chance at renal recovery.

Conclusion

HRS-AKI frequently occurs in patients with advanced cirrhosis and is associated with significant morbidity and mortality. Although the ultimate treatment of HRS-AKI is liver transplantation, early recognition of this condition, leading to timely intervention, can yield significant clinical improvements. This article provides an overview of the diagnosis and management of HRS-AKI, which the authors believe will guide health care providers, regardless of specialty, to recognize and treat this condition. The article also includes a sample order set for the diagnosis and management of HRS-AKI that can be modified by hospitals and health systems for use to standardize care of this condition.

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