

## Improving Outcomes in Hepatorenal Syndrome–Acute Kidney Injury With Early Diagnoses and Implementation of Approved Treatment Regimens

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## Improving Outcomes in Hepatorenal Syndrome–Acute Kidney Injury With Early Diagnoses and Implementation of Approved Treatment Regimens

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### Target Audience

This activity has been designed to meet the educational needs of nephrologists, hepatologists, gastroenterologists, hospitalists, and pharmacists caring for patients with hepatorenal syndrome–acute kidney injury (HRS-AKI).

### Goal Statement

This supplement will provide education on the latest emerging data for managing and treating HRS-AKI.

### Educational Objectives

After completing this activity, the participant should be better able to:

- Communicate a brief, updated overview of HRS-AKI.
- Discuss how to incorporate the new HRS-AKI treatment into patient care.
- Describe streamlined society guidelines on HRS-AKI diagnosis and treatment in a practical way for clinical use.

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A statement of credit will be issued only upon receipt of a completed activity evaluation form and a completed posttest with a score of 75% or better. Please visit <https://bit.ly/hrs-aki> to complete the posttest and evaluation.

### Media

Internet, print

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### Fee Information

There is no fee for this educational activity.

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## Educational Objectives

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- Discuss how to incorporate the new HRS-AKI treatment into patient care.
- Describe streamlined society guidelines on HRS-AKI diagnosis and treatment in a practical way for clinical use.

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**Abstract:** Decompensated cirrhosis, defined by the overt manifestations of liver failure and portal hypertension (eg, ascites, hepatic encephalopathy, variceal bleeding), is the inflection point associated with increased morbidity and mortality in chronic liver disease. Acute kidney injury in the setting of cirrhosis (hepatorenal syndrome–acute kidney injury [HRS-AKI]) is a severe and often fatal complication. The goals of treatment of HRS-AKI are to reverse renal failure and prolong survival in these critically ill patients or perhaps to allow the transplant team to complete the pretransplant evaluation and bridge the patient to transplant. Historically, in the United States, standard-of-care treatments for HRS-AKI were chosen by default despite lack of data, off-label use, and suboptimal results. Terlipressin represents the first drug in the United States indicated for the treatment of HRS-AKI. This review provides an up-to-date overview of HRS-AKI, discusses terlipressin and how to incorporate this new treatment into patient care and streamline society guidelines on HRS diagnosis and treatment in a practical way for clinical use, and concludes with a sample order set that highlights the recommendations discussed throughout the supplement.

## Decompensated Cirrhosis, Hepatorenal Syndrome–Acute Kidney Injury, and Associated Consequences

Cirrhosis is a consequence of numerous etiologies (eg, chronic viral infections such as hepatitis and alcohol- and nonalcohol-related liver disease) and represents the end-stage result of all chronic liver diseases. In the United

States, at least 633,000 adults have cirrhosis, which represents 0.3% of the population.<sup>1</sup> As of 2017, the global prevalence of cirrhosis was 160 million with more than 800,000 dying annually.<sup>2,3</sup> A recent study examined data on cirrhosis and other chronic liver diseases extracted from Global Burden of Diseases 2019. Investigators defined and combined 4 indicators, including mortality to incidence

ratio, prevalence to incidence ratio, disability-adjusted life-years to prevalence ratio, and years-of-life-lost to years-lived-with-disability ratio, to construct the quality-of-care index (QCI). Among underlying causes of cirrhosis, the highest QCI belonged to alcohol use, followed by hepatitis C and metabolic dysfunction-associated steatotic liver disease (formerly nonalcoholic fatty liver disease<sup>4</sup>) with QCIs

of 86.1, 85.3, and 81.1, respectively.<sup>5</sup>

Cirrhosis can be divided into 2 main types: compensated and decompensated cirrhosis. After decompensation has occurred, cirrhosis becomes a systemic disease associated with multiorgan system dysfunction.<sup>6</sup> In decompensated cirrhosis, disruption in the liver architecture leads to worsening of portal hypertension.<sup>7,8</sup> Portal hypertension reduces portal blood flow to the liver, which results in the release of vasodilators and blood pooling in the splanchnic circulation. In response to these vascular changes, intense renal vasoconstriction occurs, sodium and water are retained, and plasma volume expands. The combination of vasodilation and vasoconstriction results in increased cardiac output, but this output is not sufficient to sustain the needs of systemic circulation, and renal perfusion diminishes. Ultimately, patients can develop hepatorenal syndrome-acute kidney injury (HRS-AKI), a potentially reversible, rapidly fatal, functional, progressive kidney disorder associated with cirrhosis.<sup>9-11</sup>

Previously, HRS was classified by the International Club of Ascites as either Type 1 (HRS-1) or Type 2 (HRS-2). This discussion will focus on HRS as it relates to AKI (HRS-AKI), formerly HRS-1, in the setting of cirrhosis. HRS without AKI, or HRS-non-AKI (NAKI, formerly HRS-2), is a diagnosis in the setting of chronic kidney disease and is beyond the scope of this supplement. The original definition of HRS-1 required that the diagnosis be established at an advanced stage of AKI, with a final serum creatinine (sCr) cutoff value of greater than 2.5 mg/dL. The new term for HRS-1, HRS-AKI, is now 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 obtained within the previous 3 months, without hypovolemia or significant abnormalities in kidney histology (as histologic abnormalities might occur as the disease progresses<sup>12</sup>).<sup>13</sup> A recent study found that applying these criteria is

estimated to result in earlier diagnosis and treatment of HRS-AKI patients by approximately 2 to 4 days,<sup>14</sup> which is likely to improve outcomes.

The estimated annual incidence for HRS-1 (the term previously used for HRS-AKI) in the United States ranges from 9000 to more than 35,000 patients.<sup>15-19</sup> Although these rates technically classify HRS-AKI as rare, the literature regards it as a “relatively frequent problem.” 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.<sup>20,21</sup> If left untreated, the estimated median survival in patients with HRS-AKI is 8 to 12 weeks,<sup>22-25</sup> with mortality rates approaching 100% 3 months after diagnosis.<sup>9,26</sup> Aside from the risk of death, HRS-AKI is associated with intensive care hospital admissions and high readmission rates.<sup>27,28</sup> Standardized and proactive medical care for HRS-AKI includes early diagnosis and timely treatment with effective medical therapy,<sup>29,30</sup> but this is not consistently achieved. A recent study by Jamil and colleagues retrospectively analyzed a nationwide electronic health record database of hospitalized HRS patients (n=3563) between 2009 and 2018. Almost one-half of these HRS-AKI patients did not receive recommended treatment with vasopressors.<sup>25</sup> This expert perspective review seeks to facilitate improvements in the diagnosis and management of HRS-AKI.

### Methods for Treating Hepatorenal Syndrome-Acute Kidney Injury

#### *Liver Transplantation*

Liver transplantation corrects the underlying liver failure and is therefore the gold standard for treating HRS-AKI, but many patients die while awaiting a transplant and others do not meet eligibility criteria. This is because a prolonged wait for liver

transplantation (ie, >4 weeks) results in irreversible kidney damage and transplanting the liver will no longer correct HRS-AKI. Moreover, patients with significant kidney injury prior to liver transplant may demonstrate worse long-term posttransplant outcomes.<sup>9,30</sup>

#### *Renal Replacement Therapy*

Renal replacement therapy (RRT) is a temporary option in HRS-AKI patients and is mainly used to bridge patients to liver transplantation. Survival with RRT in patients with end-stage liver disease presenting with HRS-AKI is short, with a 59% mortality rate observed in liver transplant candidates requiring more than 7 days of in-hospital continuous RRT.<sup>31</sup> RRT patients are also at risk for general acute complications (eg, intradialytic hypotension, increased risk of cardiac events, complications related to venous access).<sup>22</sup> Patients with decompensated cirrhosis demonstrate further challenges with RRT use, as portal hypertension and splanchnic vasodilation result in decreased effective circulating volume and low mean arterial pressure, which impact volume management.<sup>32,33</sup> Continuous RRT typically involves intensive care unit (ICU) care or specialized dialysis unit placement, immobilization, and anticoagulation and subsequent bleeding risks. Intermittent RRT is complicated by hemodynamic instability owing to rapid fluid and solute shifts,<sup>34</sup> resulting in intradialytic hypotension and cerebral edema. Although HRS-AKI is considered to be reversible with liver transplantation, post-liver transplantation renal function may be adversely affected in patients who require dialysis pretransplant. According to the United Network for Organ Sharing criteria, if patients require dialysis for 6 or more weeks prior to liver transplant, they are candidates for simultaneous liver-kidney transplant because of the risk of renal nonrecovery.<sup>9,35</sup>

#### *Human Serum Albumin Solution*

Based on the limitations associated with liver transplantation and RRT,



**Table 1.** Frequently Asked Questions Surrounding HSA Administration

Frequently asked question <sup>44</sup>	Recommendation
What are the target serum albumin levels during HSA treatment?	Correcting albumin based on fluid status is more important than achieving goal serum albumin levels. HSA use should be guided by functional (volume status, treatment response) rather than quantitative laboratory value endpoints <sup>43,44</sup>
What are the most common AEs?	<ul style="list-style-type: none"> <li>• Because it is difficult to identify the optimum HSA dose, the most common AEs of HSA administration are pulmonary edema and fluid overload</li> <li>• Pulmonary edema is precipitated by HSA-induced increases in plasma volume, especially when infused rapidly<sup>44</sup></li> </ul>
How are AEs managed?	<ul style="list-style-type: none"> <li>• The HSA dose and rate of infusion should be adjusted according to the patient's volume status,<sup>39,40</sup> which requires evaluation after each HSA dose<sup>44</sup></li> <li>• Evaluation should include signs of cardiopulmonary dysfunction and fluid status after each dose of HSA: blood pressure, pulse, oxygenation, escalating oxygen requirements, respiratory rate, development of peripheral edema, and renal function<sup>44</sup></li> <li>• Volume overload can also be determined via chest radiograph or bedside echocardiography</li> <li>• Upon the first clinical sign(s) of cardiovascular overload (headache, dyspnea, jugular venous distention, increased blood pressure), the infusion must be slowed or stopped immediately<sup>40</sup> and diuretics can be considered for volume management<sup>44</sup></li> <li>• Clinicians should also be mindful of the sodium content in HSA preparations, which is included for isotonicity. As a result, hyponatremia occurs in patients administered HSA over several days, and this may contribute to the development of pulmonary edema<sup>44</sup></li> </ul>
Which patients are at increased risk of AEs?	<ul style="list-style-type: none"> <li>• HSA must be used with caution in conditions where hypervolemia and its consequences could represent a special risk to the patient, such as pulmonary hypertension with right heart failure, congestive heart failure, pulmonary edema, renal insufficiency, and chronic kidney disease<sup>44,61</sup></li> <li>• In patients with HRS-AKI, the additive effects provided by vasoconstrictors and HSA infusion provide benefits, but this may further complicate the AE profile. These patients should be closely monitored for the possible development of side effects of vasoconstrictors and HSA, including ischemic complications and pulmonary edema<sup>13,44</sup></li> <li>• Assessing intravascular volume status by measuring the inferior vena cava diameter and percent collapsibility with inspiration using conventional ultrasound machines or at bedside using point-of-care ultrasound could be a useful tool in guiding HSA infusion<sup>44</sup></li> </ul>

AE, adverse event; HRS-AKI, hepatorenal syndrome–acute kidney injury; HSA, human serum albumin.

pharmacologic interventions to optimize renal outcomes are essential. Current treatments involve volume expansion and vasoconstriction. Human serum albumin (HSA) solution is considered a crucial volume expander to treat HRS-AKI. The additive effects of vasoconstrictors (ie, terlipressin, midodrine/octreotide, and norepinephrine) with HSA infusion are proven to improve outcomes compared with either intervention alone.<sup>9,36</sup>

Albumin is an abundant and important plasma protein in the human body.<sup>5</sup> As liver disease progresses to decompensated cirrhosis, quantitative, qualitative, and functional changes to albumin occur, and supplementation with HSA is benefi-

cial.<sup>37,38</sup> Medicinal HSA is a parenteral colloid derived from human plasma and is available in 2 concentrations: HSA 5% and 25%. HSA 5% is more commonly used in rapid resuscitation situations that necessitate rapid, large volume replacement to restore hemodynamics and volume loss. HSA 25% is the therapeutic choice either when fluid is restricted or in cases of oncotic deficiencies,<sup>39</sup> which is common in patients with cirrhosis who are prone to developing edema with a large intravenous volume infusion. Therefore, HSA 25% is the formulation that should be used in most circumstances for patients with cirrhosis. Exogenously administered HSA 25% increases the oncotic pressure of the intravascular system, increases fluid

mobilization from the interstitial space, helps to restore systemic circulation, increases renal blood flow, and restores the glomerular filtration rate.<sup>40,41</sup> The most current and well-established indications for the use of HSA in cirrhosis pertain to conditions characterized by an acute worsening of effective hypovolemia,<sup>42</sup> such as ascites, postparacentesis circulatory dysfunction, spontaneous bacterial peritonitis, and HRS-AKI.<sup>13</sup>

Current literature indicates that high cost and periodic shortages have made the appropriate use of HSA a long-standing subject of debate.<sup>43</sup> In order to standardize the use of HSA for cirrhosis across clinical practitioners, real-world recommendations, as detailed in Table 1,<sup>44</sup> have been

**Table 2.** Terlipressin US Prescribing Information Recommendations<sup>47</sup>

<b>Indications</b>	To improve kidney function in adults with hepatorenal syndrome with rapid reduction in kidney function
<b>Boxed warning</b>	<b>Warning: serious or fatal respiratory failure</b> Terlipressin may cause serious or fatal respiratory failure. Patients with volume overload or with ACLF Grade 3 <sup>a</sup> are at increased risk. Assess oxygenation saturation (eg, SpO <sub>2</sub> ) before initiating terlipressin. Do not initiate terlipressin in patients experiencing hypoxia (eg, SpO <sub>2</sub> <90%) until oxygenation levels improve. Monitor patients for hypoxia using continuous pulse oximetry during treatment and discontinue terlipressin if SpO <sub>2</sub> decreases below 90%
<b>Contraindications</b>	In patients experiencing hypoxia or worsening respiratory symptoms, and in patients with ongoing coronary, peripheral, or mesenteric ischemia
<b>Warnings and precautions</b>	<b>Serious or fatal respiratory failure:</b> 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 <b>Ineligibility for liver transplant:</b> Terlipressin-related adverse reactions may make a patient ineligible for liver transplant, if listed <b>Ischemic events:</b> Terlipressin is a vasoconstrictor and can cause ischemic events (cardiac, peripheral, or mesenteric) that may require dose interruption or discontinuation <b>Embryo–fetal toxicity:</b> Terlipressin may cause fetal harm when used during pregnancy. Advise females of reproductive potential of the potential hazard to the fetus
<b>Adverse reactions</b>	The most common adverse reactions (≥10%) include abdominal pain, nausea, respiratory failure, diarrhea, and dyspnea

ACLF, acute-on-chronic liver failure; SpO<sub>2</sub>, oxygen saturation.

<sup>a</sup>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>.

formulated based on frequently asked questions. Streamlined, practical recommendations set forth in guidance from the American Association for the Study of Liver Diseases (AASLD) provide direction on HSA administration in HRS-AKI and will be discussed later in this supplement.

### Terlipressin

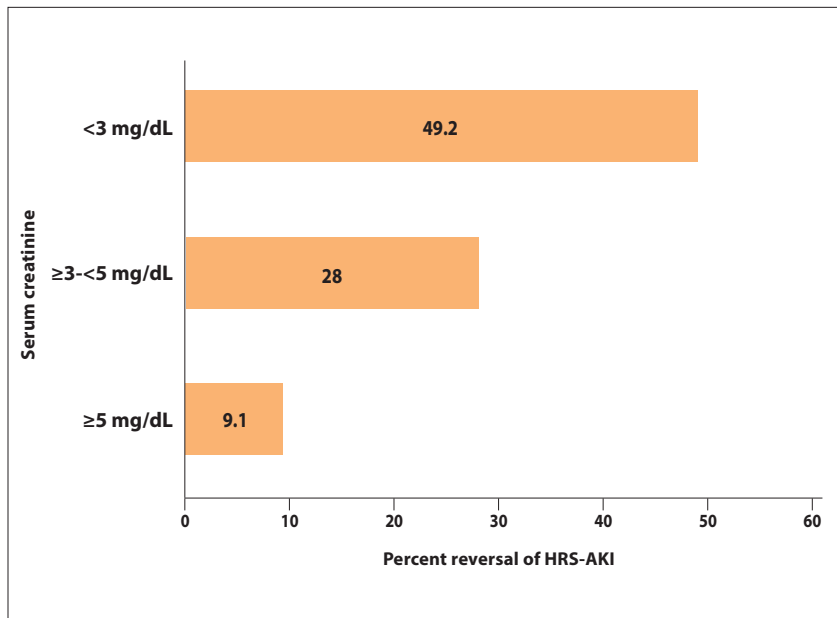
In 2022, the US Food and Drug Administration approved terlipressin for the treatment of HRS-AKI, making it the first drug in the United States with this indication. Terlipressin is a partial agonist at V1 and a full agonist at V2 receptors of vascular smooth muscle cells. Terlipressin works by causing vasoconstriction, mainly of the splanchnic circulation. It also reduces portal blood flow and portal pressure, increases effective blood volume, and leads to renal vasodilation.<sup>45,46</sup>

Table 2 details the terlipressin US prescribing information recommendations.<sup>47</sup> The pivotal terlipressin study was the phase 3 CONFIRM study, which observed 300 patients

with cirrhosis and HRS-1 (the preferred terminology when the study was conducted). Patients received 1 mg of terlipressin acetate (0.85 mg terlipressin) combined with HSA 25% (n=199) or a placebo combined with HSA 25% (n=101) in a blinded manner. The primary endpoint was verified HRS reversal, defined as 2 consecutive sCr measurements of 1.5 mg/dL or less at least 2 hours apart up to day 14 and survival without RRT for at least an additional 10 days. A total of 32% of terlipressin-treated patients and 17% of placebo-treated patients ( $P=.006$ ) met this primary endpoint. More adverse events (AEs), including abdominal pain, nausea, diarrhea, and respiratory failure, occurred with terlipressin than with placebo, with death within 90 days because of respiratory disorders occurring in 11% of terlipressin-treated patients compared with 2% of placebo-treated patients.<sup>29</sup> With regard to AEs, patients with cirrhosis may develop volume overload owing to extravasation of albumin from increased capillary permeability.<sup>48</sup> In

patients treated with terlipressin and albumin, it is difficult to determine whether the volume overload is secondary to this pathophysiology or is a direct adverse effect from both or one of the treatments.<sup>49</sup> Regardless, 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,<sup>50</sup> as recommended in the AASLD guidance.<sup>13</sup> In CONFIRM, among patients who received terlipressin, 84.4% were treated on a standard medical floor, thereby avoiding ICU admission.<sup>51</sup>

A post hoc analysis was performed based on pooled data from CONFIRM and 2 other North America-based, phase 3, placebo-controlled clinical studies (OT-0401 and REVERSE). Data were examined across 3 sCr subgroups (<3, ≥3-<5, and ≥5 mg/dL) to further delineate their correlation with HRS reversal, RRT-free survival, and overall survival. The study concluded



**Figure 1.** Lower serum creatinine, combined with terlipressin treatment, resulted in higher HRS-AKI reversal.<sup>52</sup>

HRS-AKI, hepatorenal syndrome-acute kidney injury.

that patients with HRS-AKI (formerly HRS-1) and lower sCr levels who were treated with terlipressin had higher HRS reversal and survival outcomes. Specifically, sCr was significantly associated with HRS reversal in univariate and multivariate logistic regression analyses ( $P<.001$ ). The incidence of HRS reversal inversely correlated with sCr subgroup (<3 mg/dL, 49.2%; ≥3-<5 mg/dL, 28.0%; ≥5 mg/dL, 9.1%; Figure 1). At day 30 follow-up, RRT-free survival was significantly higher for patients with HRS-1 in the lower sCr subgroups than in the higher subgroup (<5 vs >5 mg/dL;  $P=.01$ ). Terlipressin-treated patients with HRS-1, with a lower baseline sCr level, had a higher overall survival ( $P<.001$ ) and higher transplant-free survival at day 90 ( $P=.04$ ). These data reinforce the importance of early identification and treatment of HRS-AKI patients, as this is when sCr levels are typically lower and a greater response to terlipressin will be achieved.<sup>52</sup> It is also important to note that, in this study, a sCr of 2.25 mg/dL was required for inclusion. With the new diagnostic criteria, these patients may be identified

and potentially experience benefits of treatment even earlier.

Another post hoc analysis of CONFIRM included a 12-month follow-up of liver transplant recipients from this study. Of the 300 patients in CONFIRM (terlipressin, n=199; placebo, n=101), 70 patients (23%) underwent liver transplant alone (terlipressin, n=43; placebo, n=27), and 5 patients had simultaneous liver-kidney transplant (terlipressin, n=3; placebo, n=2). Compared with placebo, patients

**Table 3.** Stages of AKI<sup>13</sup>

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.

receiving terlipressin demonstrated a significantly higher rate of HRS reversal (37%, n=16 vs 15%, n=4;  $P=.033$ ), significantly lower pretransplant need for RRT ( $P=.007$ ), and significantly higher overall survival ( $P=.009$ ).<sup>53</sup> A separate, recently published study evaluated the impact of responses to treatment with terlipressin and albumin on posttransplant outcomes in patients with HRS-AKI. The study population consisted of patients who developed HRS-AKI before transplant and were treated with terlipressin and HSA (n=82). This study found that, in patients with HRS-AKI, response to terlipressin and HSA reduced the need for RRT after liver transplant and reduced the risk of chronic kidney disease at 1 year after liver transplant.<sup>54</sup>

An open-label study of continuous terlipressin infusion in patients with HRS-AKI and cirrhosis, known as INFUSE, is currently ongoing.

**Table 4.** Criteria to Diagnose HRS-AKI<sup>13</sup>

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.

An interim analysis was performed following at least 50% enrollment (n=32; Model for End-Stage Liver Disease score ≤35; sCr ≤5 mg/dL; acute-on-chronic liver failure grade 0-2). Following a 0.5 mg bolus, terlipressin was administered as a continuous infusion at 2 mg/day up to a maximum of 8 mg/day based on sCr response and tolerability. A high complete response rate of 53% was observed with continuous terlipressin infusion. There were no unexpected drug-related serious AEs. Further enrollment and long-term follow-up for survival, transplant, and kidney-related outcomes is ongoing.<sup>55</sup>

**Other Vasoconstrictors**

Prior to the availability of terlipressin in the United States, the vasoconstrictive component of the HRS-AKI treatment regimen included the administration of midodrine/octreotide or norepinephrine. Alpha-adrenergic receptor agonists, including norepinephrine and midodrine, act by binding to alpha-1-adrenergic receptors on vascular smooth muscle cells, leading to vasoconstriction. The somatostatin analog octreotide inhibits the release of glucagon and other vasodilator peptides, leading to vasoconstriction in splanchnic, portal, and systemic circulations.<sup>56</sup> In the United States, these medications are used off-label based on results from small, nonrandomized studies.

In the past, the use of midodrine and octreotide, as well as norepinephrine, in HRS-AKI was widespread. The first meta-analysis of HRS-1 (the accepted nomenclature at the time for HRS-AKI) included 13 randomized controlled trials that enrolled 739 adults with HRS-1. All the studies compared the efficacy of vasoactive drugs, in combination with HSA, to placebo. The primary outcome was reduction in short-term mortality. Secondary outcomes included reversal of HRS, relapse of HRS after initial reversal, and AEs. Terlipressin studies were included in this meta-analysis, although terlipressin was only available

**Table 5.** A Sample HRS Order Set<sup>30</sup>  
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 <sup>13</sup>	Withdraw nephrotoxic drugs (NSAIDs)	On admission
	Reduce or withdraw diuretics and β-blockers	On admission
	Volume replacement if severely depleted	On admission
Albumin challenge <sup>13</sup>	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)

outside the United States at the time. The authors found that terlipressin with albumin might reduce short-term mortality compared with placebo in patients with HRS-AKI. Terlipressin with albumin and noradrenaline with albumin were both superior to midodrine plus octreotide with albumin for the reversal of HRS-AKI.<sup>57</sup>

Norepinephrine is often associ-

ated with reversible cardiac and digital ischemia,<sup>58</sup> and infusion therefore requires intensive hemodynamic monitoring in the ICU setting.<sup>9,59</sup> Although norepinephrine has proven benefits, ICU administration is impractical, and therefore its use is uncommon.<sup>9</sup> The AASLD guidance document and the European Association for the Study of the Liver and



**Table 5.** A Sample HRS Order Set<sup>30</sup> (Continued)

**B.** HRS-AKI Treatment

Is terlipressin available at your institution?		<input type="checkbox"/> <b>Yes: Proceed to first-choice recommendation</b> <input type="checkbox"/> <b>No: Proceed to second-choice recommendation</b>
Treatment preference <sup>13</sup>	Medications <sup>13</sup>	Treatment dosage(s) and administration
First choice	Terlipressin + 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 <sup>47</sup> OR Start via continuous IV infusion at 2 mg/day; increase every 24-48 hours up to 12 mg/day until sCr decreases <sup>13</sup> 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 <sup>13</sup> or 25 g every 6-8 hours. Stop albumin after 48 hours and reassess Initiate continuous pulse oximetry monitoring, and discontinue terlipressin if SpO <sub>2</sub> <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 <sup>13</sup> Coadminister albumin to maintain a central venous pressure between 4 and 10 mm Hg <sup>13</sup> Stop albumin after 48 hours and reassess
Third choice <sup>a</sup>	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 <sup>13</sup> 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 <sup>13</sup> Coadminister 25 g albumin BID for 4 doses, with daily reevaluation and decision-making according to patient status <sup>13</sup>

AASLD, American Association for the Study of Liver Diseases; AKI, acute kidney injury; BID, twice daily; HRS, hepatorenal syndrome; IV, intravenous; MAP, mean arterial pressure; SC, subcutaneous; sCr, serum creatinine; SpO<sub>2</sub>, oxygen saturation.

<sup>a</sup>The AASLD warns that the efficacy of this treatment regimen is low.

American College of Gastroenterology guidelines all designate terlipressin as the vasoconstrictor of choice for HRS-AKI.<sup>6,13,30,60</sup> In cases where terlipressin is not available, norepinephrine is the second choice, followed by midodrine/octreotide.<sup>13</sup> This is discussed in step 5 (*Managing the acute kidney injury patient meeting hepatorenal syndrome-acute kidney injury criteria*) of the following section.

**Applying American Association for the Study of Liver Diseases Guidance Recommendations to Clinical Practice**

In 2021, the AASLD published a comprehensive guidance on the diagnosis, evaluation, and management of HRS-AKI.<sup>13</sup> To facilitate the use of this guidance in clinical practice, the algorithm in Figure 2 and the section that follows

provide a streamlined version of the HRS-AKI recommendations set forth in the 2021 guidance document.<sup>30</sup>

**1. Once acute kidney injury is established, perform a differential diagnostic workup<sup>13</sup>**

- 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

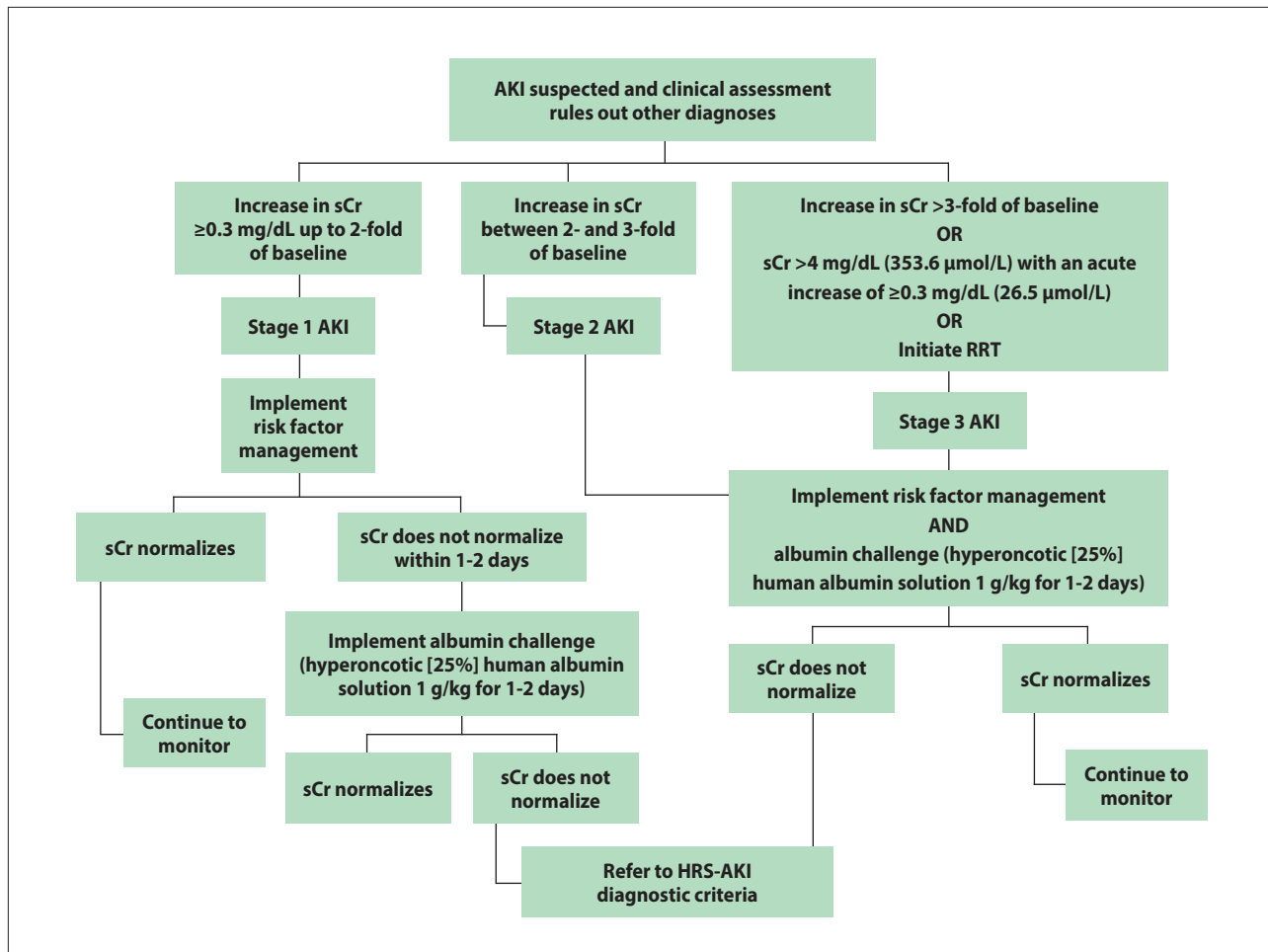


Figure 2. AASLD guidance recommendations to diagnose HRS-AKI.<sup>13</sup>

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.

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 should be tested.
- 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, which warrant different treatment recommendations than those for HRS-AKI.

**2. Determine the stage of acute kidney injury<sup>13</sup>**

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 AKI (Table 3<sup>13</sup>).

**3. Next steps in the Stage 1 acute kidney injury patient<sup>13</sup>**

- AKI cannot be reversed by any specific therapy, but some of the underlying causes may be treatable. Therefore, if AKI is diagnosed, risk factor management should be implemented, which may include:
  - Withdrawal of nephrotoxic drugs
  - Reduction or withdrawal of diuretics
  - Reduction or withdrawal of beta-blockers or other antihypertensive medications
  - An evaluation for and treatment of infections
  - Volume replacement (if severely volume depleted)

**Table 6.** Frequently Asked Questions on the Sample HRS-AKI Order Set<sup>30</sup>

Frequently asked question	Recommendation
Why are 2 terlipressin dosing regimens recommended?	<p>The terlipressin PI recommends 0.85 mg as an IV push every 6 hours on days 1-3, with sCr reassessments on day 4, followed by dose adjustments accordingly.<sup>47</sup></p> <p>The terlipressin dosing recommendations set forth in the AASLD guidance differ slightly from the PI and were developed before the FDA approval of terlipressin. These recommendations are based on long-term terlipressin experience in Europe.</p> <p>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.</p>
Why are the recommended HSA doses nonspecific?	<p>The optimum HSA dose is difficult to determine. Therefore, patients are at risk of pulmonary edema and fluid overload secondary to HSA-induced increases in plasma volume. The HSA dose and rate of infusion should be adjusted according to the patient's volume status.<sup>39,40</sup></p> <p>Close monitoring for these side effects is recommended,<sup>13</sup> and the 48-hour albumin stopping rule is included in the sample order set as a checkpoint for a committed benefit.</p> <p>Upon the first clinical sign(s) of cardiovascular overload (headache, dyspnea, jugular venous distention, increased blood pressure), the infusion must be slowed or stopped immediately,<sup>61</sup> and furosemide can be considered for volume management.</p>
What are the MAP goals during vasoconstrictor/HSA treatment?	<p>Data indicate that a rise in MAP during vasoconstrictor/albumin therapy in HRS is associated with better kidney function.<sup>62</sup></p> <p>The achievement of a prespecified target of MAP increases might improve renal outcomes in HRS-AKI.<sup>63</sup></p> <p>However, as Velez et al concluded, the minimum required MAP elevation to achieve a beneficial effect for kidney functioning remains speculative and would require a prospective study for confirmation.<sup>63</sup></p> <p>Hence, MAP goals in treated patients per kidney function remain speculative.</p>
When should RRT be considered?	<p>In patients deemed candidates for liver transplantation, the use of RRT is indicated in cases of worsening renal function, electrolyte disturbances, or increasing volume overload unresponsive to vasoconstrictor therapy.</p> <p>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.<sup>64</sup></p> <p>Therefore, in patients who are not transplant candidates, determining whether to initiate RRT involves defining the goals of care with the patients and their families,<sup>13</sup> with the understanding that without liver transplantation 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 hospitalization.<sup>33</sup></p> <p>Consequently, the decision to start RRT in these patients is difficult and should be individualized, considering that young patients and those with alcoholic hepatitis who stopped consuming alcohol might have better chance at renal recovery.</p>

AASLD, American Association for the Study of Liver Diseases; FDA, US Food and Drug Administration; HRS-AKI, hepatorenal syndrome-acute kidney injury; HSA, human serum albumin; IV, intravenous; MAP, mean arterial pressure; PI, prescribing information; RRT, renal replacement therapy; sCr, serum creatinine.

- If sCr normalizes with risk factor management, one should continue to monitor the situation.
- If sCr does not normalize within 1 to 2 days despite risk factor management, the albumin challenge should be implemented. It consists of hyperoncotic (25%) HSA 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 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 4).<sup>13</sup>

**4. Next steps in Stage 2 or 3 acute kidney injury patients<sup>13</sup>**

- In Stage 2 or 3 AKI patients, risk factor management (described previously) should be implemented during the albumin challenge:

hyperoncotic (25%) HSA 1 g/kg for 2 days, as described in step 3.

- 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 4).<sup>13</sup>

### 5. Managing the acute kidney injury patient meeting hepatorenal syndrome-acute kidney injury criteria<sup>13</sup>

- All HRS-AKI patients are in the advanced stages of liver disease, and there are likely many additional comorbidities to address. Therefore, at this point, establishing a multidisciplinary team of specialists is essential (eg, hospitalist, hepatologist, gastroenterologist, nephrologist, critical care physician, transplant surgeon,<sup>13</sup> pharmacist).
- As previously discussed, the AASLD recommends vasoconstrictors, in combination with HSA, 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 and an arterial line for monitoring. If neither can be administered, a trial of oral midodrine with octreotide may be considered; however, the guidance notes that efficacy is low.<sup>13</sup>

### A Sample Hepatorenal Syndrome-Acute Kidney Injury Order Set

A sample order set is provided in Tables 5A and 5B<sup>30</sup> and incorporates all the recommendations discussed throughout this supplement, including guidance-specific recommendations<sup>13</sup> and those based on clinical experience. 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. Some frequently asked questions regarding the order set are answered in Table 6.<sup>30</sup>

### Conclusion

The prevalence of HRS-AKI is expected to increase in the United States as the number of patients with advanced liver disease increases. HRS-AKI is rapidly fatal under any circumstances without effective interventions. Fortunately, outcomes improve with early recognition and timely interventions with effective treatment regimens. This supplement can be used to guide clinicians on the most efficient and effective ways to recognize and treat this critical condition.

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