Hepatorenal Syndrome Type 1: From Diagnosis Ascertainment to Goal-Oriented Pharmacotherapy

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Key Points:

Abstract:
Hepatorenal syndrome type 1 (HRS-1) is a serious form of acute kidney injury (AKI) that affects individuals with advanced cirrhosis with ascites. Prompt and accurate diagnosis is essential for effective implementation of therapeutic measures that can favorably alter its clinical course. Despite decades of investigation, HRS-1 continues to be primarily a diagnosis of exclusion. While the diagnostic criteria dictated by the International Club of Ascites (ICA) provide a useful framework to approach the diagnosis of HRS-1, they do not fully reflect the complexity of clinical scenarios that is often encountered in patients with cirrhosis and AKI. Thus, diagnostic uncertainty is often faced. In particular, the distinction between HRS-1 and acute tubular injury (ATI) is challenging with the currently available clinical tools. Because treatment of HRS-1 differs from that of ATI, distinguishing these 2 causes of AKI has direct implications in management. Therefore, the use of the ICA criteria should be enhanced with a more individualized approach and attention to the other phenotypic aspects of HRS-1 and other types of AKI. Liver transplantation is the most effective treatment for HRS-1 but it is only available to a small fraction of the affected patients worldwide. Thus, pharmacological therapy is necessary. Vasoconstrictors aimed to increase mean arterial pressure constitute the most effective approach. Administration of intravenous albumin is an established co-adjuvant therapy. However, the risk for fluid overload in patients with cirrhosis with AKI is not negligible and interventions intended to expand or remove volume should be tailored to the specific needs of the patient. Norepinephrine and terlipressin are the most effective vasoconstrictors and their use should be determined by availability, ease of administration and attention to optimal risk/benefit balance for each clinical scenario.

Disclosures: J. Velez reports the following: Consultancy Agreements: Mallinckrodt Pharmaceuticals (maker of terlipressin, and J.C.Q.V. was a site PI for the CONFIRM trial), Bayer, Travere; Honoraria: Mallinckrodt, Otsuka, Travere, Bayer; Scientific Advisor or Membership: Mallinckrodt - Advisory Board, Travere - Advisory Board; and Speakers Bureau: Otsuka Pharmaceuticals.

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Hepatorenal Syndrome Type 1: From Diagnosis Ascertainment to Goal-Oriented Pharmacological Therapy

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Abstract

Hepatorenal syndrome type 1 (HRS-1) is a serious form of acute kidney injury (AKI) that affects individuals with advanced cirrhosis with ascites. Prompt and accurate diagnosis is essential for effective implementation of therapeutic measures that can favorably alter its clinical course. Despite decades of investigation, HRS-1 continues to be primarily a diagnosis of exclusion. While the diagnostic criteria dictated by the International Club of Ascites (ICA) provide a useful framework to approach the diagnosis of HRS-1, they do not fully reflect the complexity of clinical scenarios that is often encountered in patients with cirrhosis and AKI. Thus, diagnostic uncertainty is often faced. In particular, the distinction between HRS-1 and acute tubular injury (ATI) is challenging with the currently available clinical tools. Because treatment of HRS-1 differs from that of ATI, distinguishing these 2 causes of AKI has direct implications in management. Therefore, the use if the ICA criteria should be enhanced with a more individualized approach and attention to the other phenotypic aspects of HRS-1 and other types of AKI. Liver transplantation is the most effective treatment for HRS-1 but it is only available to a small fraction of the affected patients worldwide. Thus, pharmacological therapy is necessary. Vasoconstrictors aimed to increase mean arterial pressure constitute the most effective approach. Administration of intravenous albumin is an established co-adjuvant therapy. However, the risk for fluid overload in patients with cirrhosis with AKI is not negligible and interventions intended to expand or remove volume should be tailored to the specific needs of the patient. Norepinephrine and terlipressin are the most effective vasoconstrictors and their use should be determined by availability, ease of administration and attention to optimal risk/benefit balance for each clinical scenario.
**Introduction**

The traditional approach for determining the etiology of AKI in cirrhosis is centered in the most common causes: prerenal azotemia, acute tubular injury (ATI) and hepatorenal syndrome type 1 (HRS-1). While these 3 types of AKI may indeed account for the majority of cases, the diagnostic approach should be inclusive of other etiologies, such as acute interstitial nephritis (AIN) and acute glomerulonephritis (AGN). In addition, it needs to be recognized that actual clinical scenarios tend to be cloudier than desired. Multiple elements that can potentially be causative of AKI can coexist\(^1\). Therefore, it is often difficult to ascertain whether one or more of those elements may be playing a role in the development of AKI. The deranged hemodynamics present in cirrhosis with portal hypertension that trigger HRS-1 are often referred to as hepatorenal physiology and may be the sole cause of AKI in some cases. However, it is conceivable that other pathological processes that independently impair kidney function may superimpose over an overarching state of hepatorenal physiology. Some of those processes include non-parenchymal disorders such as abdominal compartment syndrome (ACS) due to tense ascites and cardiorenal syndrome type 1 (CRS-1) due to cirrhotic cardiomyopathy, as well as renal parenchymal disorders such as various degrees of ischemic ATI and bile-acid associated toxic ATI. Thus, diagnostic overlap is plausible and can potentially influence therapeutic responses (Figure 1).

**Establishing the diagnosis of HRS-1**

*Volume expansion as initial measure*

The ICA diagnostic criteria for HRS-1 require that as an initial step, patients with AKI and cirrhosis should receive intravenous albumin at a dose of 1 g/kg and for a minimum of 48 hours\(^2\). The spirit behind this recommendation is to resolve any reversible state of volume depletion. In addition, administration of intravenous albumin in patients with spontaneous bacterial peritonitis (SBP) is known to reduce the risk of AKI\(^3\). However, the recommendation calls for systematic administration of
intravenous albumin without explicitly taking into account whether the patient is in a hypovolemic, euvoletic or hypervolemic state. Blinded administration of volume expanders in hypervolemic patients poses a risk of iatrogenic pulmonary edema. Recently, large clinical trials have demonstrated that administration of intravenous albumin is associated with increased risk for pulmonary congestion\textsuperscript{4, 5}. Furthermore, a mandatory 48 hour trial of volume expansion may delay a diagnosis of HRS-1, thus delaying initiation of vasoconstrictors. Early implementation of vasoconstrictor therapy is associated with greater probability of reversal of HRS-1\textsuperscript{5}. Fluid administration guided by the individual volume status of the patient may circumvent this potential pitfall. Supporting this concept, a single center study demonstrated utility of point-of-care ultrasonography (POCUS)-based assessment of fluid status in individuals with suspected HRS-1\textsuperscript{6}. In 53 hospitalized patients with presumed HRS-1 and deemed clinically euvoletic, assessment of inferior vena cava diameter and collapsibility revealed that 21% of patients had findings consistent with hypervolemia and 23% exhibited hypovolemia despite presumed “adequate” volume expansion. Therefore, POCUS-based assessment of volume status may guide initial decision-making regarding administration of intravenous albumin and replace the current “all sizes fit all” approach (Table 1). There might be technical limitations for the application of POCUS in patients with cirrhosis and ascites. Therefore, optimal operator proficiency is essential to be able to extract clinically useful information from this modality. Confirmatory evidence supporting the use of this approach upon initial diagnosis of AKI in cirrhosis is still needed.

\textit{Interpretation and applicability of ICA diagnostic criteria}

The ICA criteria include elements intended to identify features suggestive of AKI secondary to parenchymal disorder or obstructive uropathy. The importance of these steps is that correct diagnosis of HRS-1 prompts initiation of a unique treatment that is not effective in other forms of parenchymal AKI (Figure 2).
Change in kidney function. Earlier definitions of HRS-1 utilized cutoffs in absolute values of serum creatinine concentration. The updated criteria removed absolute cut-off values of serum creatinine and applied the KDIGO definition of AKI instead. With the application of the KDIGO definition of AKI, HRS-1 can be diagnosed and treated early. An alternative name of HRS-AKI has been proposed. However, serum creatinine values carry inherent limitations (Table 1). Because sarcopenia is often present in cirrhosis, serum creatinine concentration may underestimate kidney dysfunction. In addition, increased tubular secretion of creatinine may occur in cirrhosis and can contribute to underestimating GFR loss. Furthermore, hyperbilirubinemia may cause an interference with a colorimetric assay for creatinine. Thus, assessment of absolute and relative changes in serum creatinine should be done with caution. Serum cystatin C may be a more accurate marker of kidney function in cirrhosis and can be utilized when readily available.

Nephrotoxins. Absence of exposure to nephrotoxins is an ICA criterion for HRS-1 diagnosis (Table 1). Patients with decompensated cirrhosis often receive antibiotic therapy to treat infections such as SBP. Those infections may indeed trigger HRS-1. However, antibiotics (e.g., fluoroquinolones, vancomycin) can be nephrotoxic and cause toxic ATI or AIN. On the other hand, discontinuation of antibiotics can result in progression of an infection to sepsis. Although clinical history and urinary abnormalities may provide diagnostic clues, they are limited in their predictability. Thus, short of performing a kidney biopsy, it may be challenging to ascertain when an antibiotic is the cause for AKI in cirrhosis.

Shock. Conventional definition of shock refers to the presence of circulatory failure leading to organ hypoperfusion. However, a low normal mean arterial pressure (MAP) may be expected in decompensated cirrhosis. As a result, the threshold for diagnosis of shock may vary. In addition, tissue hypoperfusion depends not only on MAP but also on systemic vascular resistance. Therefore, ascertainment of shock in cirrhosis may require additional parameters such as serum lactate, cardiac index and systemic vascular resistance.
Hematuria and proteinuria. The current ICA criteria call for exclusion of HRS-1 when urine microscopy reveals > 50 red blood cells (RBC) per high power field (hpf) and proteinuria of 500 mg per day because those findings suggest a glomerular cause of AKI (Table 1). This is an important consideration due to the increased susceptibility of individuals with cirrhosis to acquire certain glomerulopathies such as IgA nephropathy and hepatitis C virus-associated membranoproliferative glomerulonephritis\textsuperscript{16, 17}. Thus, without access to a prior record of a urinalysis, it may be premature to exclude HRS-1 in a patient with hematuria or proteinuria considering that HRS-1 could be superimposed over a preexisting glomerulopathy. In addition, urinary specimens are often obtained from an indwelling bladder catheter which can lead to traumatic hematuria and potentially confound a case of HRS-1. Conversely, the threshold of > 50 RBC/hpf may lead to an incorrect diagnosis of HRS-1 in a patient with AGN with 10 – 50 RBC/hpf. Importantly, the morphology of urinary RBC may be more informative than their quantity. Presence of urinary acanthocytes are pathognomonic of glomerular disease and inconsistent with HRS-1 (Figure 3)\textsuperscript{18}.

Regarding proteinuria, the ICA criteria dictate exclusion of HRS-1 if its value is > 500 mg per day. However, 24-hour urine collections are suboptimal in the hospital setting. Although dipstick proteinuria and urine protein-to-creatinine ratio are informative, they are limited in their ability to quantify proteinuria during oliguric AKI\textsuperscript{19}. Furthermore, proteinuria should be interpreted with attention to previous results on the same patient. For instance, a patient with cirrhosis due to non-alcoholic steatohepatitis (NASH) may have metabolic syndrome and chronic albuminuria which should not preclude the diagnosis of HRS-1.

Urinary sodium. Urinary sodium (UNa) concentration < 10 mEq/L was a required minor criterion in the original 1996 ICA definition of HRS-1\textsuperscript{20}. It was subsequently removed in the 2007 updated version\textsuperscript{21}. The standard cut-off value to define low UNa and low fractional excretion of UNa (FENa) are < 10-20 mEq/L and < 1%, respectively. However, based on those cut-off values, low UNa and low FENa are almost universally present in patients with cirrhosis and AKI\textsuperscript{22}. Nonetheless, studies suggest that FENa does offer utility to distinguish ATI from HRS-1 when the cutoff is lowered to < 0.1-0.2%\textsuperscript{22}. Thus, low
UNa has been re-inserted it into the ICA criteria but as FENa < 0.2%. FENa is of greater utility in the context of oliguria. Importantly, the lower limit of detection for UNa varies across hospital laboratories (<20 vs. < 10 mEq/L) which can affect the FENa. Thus, it is encouraged to request the local hospital laboratory to adjust the measurements to its lowest threshold. Fractional excretion of urea has also been proposed to distinguish ATI from HRS-1 in one report but it requires further study before it can be widely recommended.

Abnormal kidney imaging. Renal ultrasonography is the modality of choice to rule out obstructive uropathy as a cause of AKI. In addition, changes in parenchymal echogenicity indicate intrinsic kidney disease. However, ascitic fluid overlying the kidneys precludes optimal assessment of kidney parenchymal echogenicity due to the acoustic enhancement artifact.

Phenotypical aspects not included in the ICA criteria

Leukocyturia. The ICA criteria do not include absence of leukocyturia as an exclusion criterion for HRS-1. Because urinary tract infections can trigger HRS-1, it is appropriate not to exclude HRS-1 in patients who present with leukocyturia. However, if a urine culture yields no growth of bacteria, AIN should be considered and managed accordingly.

Abnormal urinary sediment microscopy. Urine sediment microscopy is not a standard component of the ICA criteria. Sheets of “muddy brown” dark granular casts are highly suggestive of ATI, and a scoring system based on the abundance of granular casts and renal tubular epithelial cells confirms the diagnosis of ATI. Although such urinary cast scores have not been validated in AKI in cirrhosis, urine sediment microscopy has proven utility in this setting. A study reported that in a cohort of 120 patients with cirrhosis and AKI, 22% were reclassified as having ATI and not HRS-1 based on urine sediment microscopy findings. However, it should be recognized that microscopic examination of the urinary sediment in severe hyperbilirubinemia may be challenging due to artifactual staining by urinary bilirubin (Figure 3). Hyaline or lightly granular casts may be misinterpreted as dark granular casts. Although renal tubular epithelial cell casts (RTECC) are often found in specimens of patients with
cirrhosis with AKI\textsuperscript{27}, they can also be identified in patients with hyperbilirubinemia without AKI\textsuperscript{28}.

RTECC can also be seen in cases of acute cholemic tubulopathy. Therefore, it remains unclear to what extent the presence of RTECC should exclude HRS-1. Leucine and bilirubin crystals can be present within casts or outside them, further increasing the complexity of the test. Thus, inspection of the urinary sediment by an experienced observer is recommended.

\textit{Intraabdominal hypertension.} Despite the increased recognition of ACS as an important cause of AKI in critically ill patients, its role in the pathogenesis of AKI in cirrhosis remains unelucidated. Historically, large-volume paracentesis (LVP) has been listed as a precipitating factor for HRS-1. However, there is insufficient evidence to support that assertion. On the other hand, a study in patients with cirrhosis and AKI in an intensive care unit reported measurements consistent with intraabdominal hypertension with a median intraabdominal pressure (IAP) of 22 mmHg and transient improvement in kidney function upon decompression\textsuperscript{29}. More recently, in a cohort of 102 hospitalized patients with cirrhosis, improvement in kidney function occurred more often (10\%) than worsening of kidney function (2\%) immediately after LVP\textsuperscript{30}. Therefore, it seems reasonable to favor LVP during AKI in cirrhosis, particularly in those with documented IAP > 20 mmHg.

\textit{Portopulmonary hypertension and cirrhotic cardiomyopathy.} Cirrhosis with portal hypertension increases the risk for pulmonary hypertension\textsuperscript{31, 32}. In addition, the state of high-output heart failure that accompanies a markedly decreased peripheral vascular resistance in advanced cirrhosis may evolve over time into a state of impaired cardiac conductance and contractility, i.e., cirrhotic cardiomyopathy\textsuperscript{33, 34}. Therefore, right and/or left ventricular failure may complicate a case of AKI and cirrhosis by aggravating peripheral edema, venous congestion, and potentially exacerbating hydrothorax and/or pulmonary edema. In cohort of 76 patients with cirrhosis, invasive measurements of central venous pressure (CVP) revealed that 29\% of patients had a CVP > 12 cm H2O, i.e., consistent with venous congestion\textsuperscript{35}. One could expect the percentage to be even higher when AKI is present. Thus, an
echocardiogram obtained at the time of AKI should provide useful information to optimize volume-related therapeutic maneuvers.

**Urinary biomarkers.** Because of the abovementioned limitations of the available diagnostic tools, there has been interest in developing urinary biomarkers for adequate discrimination between ATI and HRS-1. Neutrophil gelatinase-associated lipocalin (NGAL) has been extensively studied and shows promise. Although the NGAL titer tends to be significantly higher in ATI compared to HRS-1, there is still overlap in the distribution of values. A recent USA-based study reported an AUC of 0.76 for diagnosis of ATI using a cutoff value of 244 μg/g. A combination of NGAL with other biomarkers (L-type fatty acid binding protein, interleukin 18, albumin) has been proposed as a way to enhance the tool. The AUC for urine albumin, which is available for clinical use, approximates to that of NGAL. A single center study reported optimal performance of the urinary micro RNA molecule miR-21 that showed an AUC of 0.97 for distinguishing ATI from HRS-1. To date, NGAL is not available for clinical use in the USA. An important caveat of studies assessing the performance of biomarkers is that they are tested against a clinical diagnosis as the gold standard, not tissue diagnosis. Alternatively, a retrospective diagnosis of HRS-1 can be made based on successful therapeutic response to a vasoconstrictor. A study showed acceptable performance of serum adrenomedullin and urinary thromboxane B₂ for classification of HRS-1 vs. ATI, but they failed to predict response to therapy. Therefore, an optimal urinary biomarker to confirm HRS-1 diagnosis is still lacking.

**Management**

**Choice of vasoconstrictor therapy and its proper use**

Although an in-depth narrative of the pathogenesis of HRS-1 is beyond the scope of this review, it should be emphasized that the use of vasoconstrictors is substantiated by the notion that portal hypertension triggers splanchnic vasodilation, baroreceptor-mediated activation of the sympathetic
nervous system (SNS), upregulation of the renin-angiotensin system (RAS), loss of renal autoregulation, stimulation of a hepatorenal reflex and ultimately a fall in renal blood flow (RBF)\(^1,45,46\). Vasoconstrictors raise the MAP, counteract splanchnic vasodilation, reset the SNS and RAS activation and restore RBF (Figure 4). Non-selective beta-blockers lower the MAP and increase the risk for HRS-1 and should be avoided in this setting\(^47\). Various vasoconstrictors have been tested in clinical trials (Table 2).

The combination of midodrine and octreotide is the most commonly utilized vasoconstrictor therapy in the United States of America (USA). However, evidence supporting its use is modest at best. In a seminal non-parallel controlled study by Angeli et al, the combination of midodrine and octreotide was more effective than a non-pressor dose of intravenous dopamine\(^48\). Subsequently, only uncontrolled retrospective cohorts reported benefit of midodrine and octreotide in the treatment of HRS-1\(^49,50\). Small randomized controlled trials have found the combination of midodrine and octreotide to be inferior to both terlipressin\(^51\) and norepinephrine\(^52\), although no mortality benefit was observed in those studies. Furthermore, studies have reported efficacy of terlipressin or norepinephrine in patients who previously failed to benefit from midodrine and octreotide\(^5,53,54\). Thus, midodrine and octreotide should not be first-line therapy for HRS-1 in the ICU setting in North America nor in general wards in countries where terlipressin is available.

Terlipressin and norepinephrine are the vasoconstrictors that have consistently demonstrated therapeutic efficacy in the treatment of HRS-1. Terlipressin, a vasopressin analog with greater affinity for the vasopressin V2 receptor (V2R:V1R \(\sim 6:1\)) compared to vasopressin\(^55,56\), is the most commonly utilized vasoconstrictor in Europe, Asia, and parts of Latin America. However, it is not approved by the Food and Drug Administration (FDA) in North America. A placebo-controlled randomized controlled trial conducted in India and published in 2003 reported that terlipressin led to reversal of HRS-1, i.e., return to serum creatinine to < 1.5 mg/dL, in 42% compared to 0% with placebo\(^57\). The first placebo-controlled randomized controlled trial testing the efficacy and safety of terlipressin in USA, the OT-0401 study,
was published in 2008\textsuperscript{53}. At the time of publication, the primary endpoint was not reached. However, outcomes analyzed based on the primary endpoint utilized in the more recent CONFIRM trial revealed that terlipressin was more efficacious than placebo (34\% vs. 13\%, \( p = 0.008 \))\textsuperscript{58}. The second trial in the USA, REVERSE, also showed a signal for therapeutic efficacy but failed to reach significance\textsuperscript{59}. The third and largest North American trial (CONFIRM) enrolling 300 patients was published in 2020. The primary endpoint was reached, with reversal of HRS-1 occurring in 29\% of terlipressin-treated subjects compared to 16\% for the placebo arm. However, from the safety perspective, terlipressin-treated subjects had a greater incidence of respiratory failure events. Overzealous use of intravenous albumin prior to enrollment may have played a role in the increased incidence of respiratory failure and fluid overload. The manufacturer of terlipressin and the FDA are currently reviewing the evidence and proposed mitigation strategies to determine if approval in North America will be granted.

Norepinephrine was first found to be effective as treatment for HRS-1 in a small pilot study\textsuperscript{60}. Subsequently, 6 head-to-head small scale trials have consistently demonstrated comparable efficacy of intravenous infusion of norepinephrine versus scheduled intravenous doses of terlipressin, along with comparable safety\textsuperscript{61-66}. One study reported fewer adverse events with norepinephrine\textsuperscript{66}. Another study specifically enrolling patients with acute-on-chronic liver failure (ACLF) and HRS-1 suggested superiority of terlipressin infusion over norepinephrine infusion\textsuperscript{67}. However, due to the unexpectedly low efficacy of norepinephrine in that trial, more evidence is needed before drawing clear conclusions about continuous infusion of terlipressin. Although norepinephrine was reported to be comparable to midodrine and octreotide in one study\textsuperscript{68}, a more recent randomized controlled trial demonstrated greater efficacy for the treatment of HRS-1, with 58\% of norepinephrine-treated subjects achieving full response compared to 20\% of midodrine and octreotide-treated subjects\textsuperscript{52}. Therefore, norepinephrine constitutes a reasonable first-line treatment for HRS-1. The main limitation for using norepinephrine in HRS-1 is the requirement of an intensive care unit (ICU) and the risk of tachyarrhythmias. A recent report shared a successful single-center experience of a norepinephrine-based HRS-1 protocol.
executed outside of the ICU. However, the protocol required 3:1 nursing and was associated with 25% incidence of cardiac arrhythmias\textsuperscript{69}. Therefore, widespread implementation of such approach may require additional studies.

\textit{Targeting a rise in MAP}

Multiple lines of evidence demonstrate that the benefit of vasoconstrictor therapy in HRS-1 is strongly associated to the degree of increase in MAP induced by the vasoconstrictor\textsuperscript{54, 70, 71}. The question remains as to what the ideal target of MAP is. Some studies suggest that a rise > 10 mmHg may suffice whereas other studies suggest > 15 mmHg may be necessary for optimal response\textsuperscript{54, 69, 72}. In clinical grounds, ICU nursing personnel and practitioners are familiar with a MAP target of 65 mmHg for shock. Thus, a barrier for adequate implementation of MAP goals in HRS-1 relates to lack of uniform education of healthcare providers. In addition, selection of a single absolute value of MAP (e.g., 85 mmHg) leads to rapid down-titration of the vasoconstrictor as soon as the MAP exceeds the target, which in turns causes the MAP to fall down to pre-treatment values. Thus, perhaps a sounder approach is to target a MAP rise ≥ 15 mmHg from baseline but to provide an acceptable goal range to the nursing personnel to minimize the risk of overzealous down-titration and unwanted MAP fluctuations. However, prospective controlled studies are still required to determine the MAP rise target with the most optimal balance of safety and efficacy. Stabilization and/or improvement in serum creatinine may take up to 48-72 hours, which is considered a reasonable duration for a therapeutic trial. For responders, treatment should be continued for 5-14 days depending on the clinical scenario. Patients who responded to a vasopressor may be re-treated if HRS-1 recurs.

\textit{Concomitant administration of albumin with a vasoconstrictor}
The standard approach for implementing vasoconstrictor therapy in HRS-1 is to do so along with concomitant administration of intravenous albumin. Most, if not all, clinical trials testing a vasoconstrictor in HRS-1 have included co-administration of albumin. The rationale for this approach is that the albumin is considered to enhanced the efficacy of a vasoconstrictor. The best evidence supporting this notion comes from a study by Ortega et al\textsuperscript{73}. In a small study of 16 subjects with HRS-1, reversal was achieved more often for those treated with terlipressin and albumin compared to those treated with terlipressin alone. In most randomized controlled trials for HRS-1 published to date, coadministration of albumin was part of the treatment protocol\textsuperscript{1,53,57}. The combination of preload increase by albumin and afterload increase by terlipressin may have precipitated pulmonary edema in CONFIRM. Therefore, volume status should be carefully evaluated when deciding if concomitant administration of albumin is warranted. Dyspnea, oxygenation, radiological evidence of fluid overload and prior administration of albumin should be assessed. Notably, many clinical trials of vasoconstrictors in HRS-1 included in their study design specific parameters, such as CVP, to guide the investigators in titration of albumin or even administration of diuretics\textsuperscript{60,62,74}.

**Conclusions**

The diagnosis of HRS-1 continues to be a challenging task for clinicians involved in the care of patients with advanced cirrhosis and AKI. The ICA constitute a solid foundation to assemble an approach to diagnosis. However, utilization of traditional and modern tools can enhance our ability to establish the diagnosis more rapidly and with more certainty. Norepinephrine and terlipressin constitute the most efficacious vasoconstrictors and their therapeutic benefit go in parallel with their ability to raise the MAP.
Disclosure

J. Velez reports the following: Consultancy Agreements: Mallinckrodt Pharmaceuticals (maker of terlipressin, and J.C.Q.V. was a site PI for the CONFIRM trial), Bayer, Travere; Honoraria: Mallinckrodt, Otsuka, Travere, Bayer; Scientific Advisor or Membership: Mallinckrodt - Advisory Board, Travere - Advisory Board; and Speakers Bureau: Otsuka Pharmaceuticals.

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Author Contributions

Juan Carlos Velez: Conceptualization; Data curation; Investigation; Methodology; Writing - original draft; Writing - review and editing.


**TABLES**

**Table 1.** Assessment of the rationale, utility and limitations of the elements included in the current ICA diagnostic criteria for exclusion of HRS-1. Proposed adjustments to those criteria as well as consideration for additional criteria are also listed.

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<tr>
<th>ICA criteria</th>
<th>Criterion to exclude HRS-1</th>
<th>Rationale and Utility</th>
<th>Limitation</th>
<th>Proposed Adjustment</th>
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<tr>
<td><strong>Fixed 48 hr administration of intravenous albumin and discontinuation of diuretics</strong></td>
<td>To exclude reversible prerenal azotemia</td>
<td>Blinded to volume status, can lead to iatrogenic worsening of hypervolemic states</td>
<td>Careful assessment of volume status by POCUS Weigh in history &amp; physical to determine probability of reversible prerenal azotemia</td>
<td></td>
</tr>
<tr>
<td><strong>Nephrotoxins</strong></td>
<td>To exclude drug-induced renal parenchymal disorders</td>
<td>Exposure to antibiotics in this setting is extremely common, difficult to ascertain whether drug is/ is not the culprit</td>
<td>Integrate timing of drug administration and findings in UA (e.g., WBC) and urinary sediment microscopy (e.g., casts) to determine if drug-induced AKI should be considered Lower threshold for kidney biopsy</td>
<td></td>
</tr>
<tr>
<td><strong>Shock</strong></td>
<td>To exclude a high probability of ischemic ATI due to organ hypoperfusion</td>
<td>Unclear cut-off blood pressure level consistent with shock</td>
<td>Consider collecting additional data to confirm shock (e.g., serum lactate, invasive hemodynamics)</td>
<td></td>
</tr>
</tbody>
</table>
| **Urine RBC > 50/hpf** | To exclude renal parenchymal disorders that can present with hematuria (e.g., acute glomerulonephritis) | Arbitrary cutoff, not linkable to specific etiology
Traumatic hematuria not uncommon due to indwelling bladder catheter insertion
Chronic IgAN may be present in cirrhosis and can cause hematuria irrespective of a superimposed AKI
Urine RBC morphology suggestive of glomerular origin not considered | Weigh importance of hematuria in the context of bladder catheterization
Search for evidence of preexisting hematuria
Assess urine RBC morphology by urinary sediment microscopy |
| **Proteinuria > 500 mg/day** | To exclude renal parenchymal disorders that can present with proteinuria (e.g., glomerulopathies) | 24-hour urine collection cumbersome and rarely done in an inpatient setting
Oliguria often present, accuracy of UPCR in oliguric AKI is limited
Preexisting proteinuria is possible | Assess both UPCR and urine dipstick and interpret with caution taking in consideration baseline status of proteinuria (when available)
De novo UPCR > 0.3 g/g and urine dipstick ≥ 1+ protein should alert consideration for renal parenchymal disorder |
| **FENa > 0.2%** | To exclude ATI | Cases of ATI can present with FENa ≤ 0.2% | Consider FENa as a test with reasonable PPV to detect ATI if value is ≥ 1%
(or if urine Na ≥ 30 mEq/L) but do not rule out ATI if FENa ≤ 0.2%
Contact hospital laboratory to lower the detection limit to < 10 mEq/L |
| **Abnormal kidney US** | To exclude renal parenchymal disorders that can exhibit increased cortical echogenicity or other abnormalities
To exclude obstructive uropathy that can present with hydronephrosis | Ascites produces acoustic enhancement below the fluid leading to artificial increase in cortical echogenicity of the kidney
Preexisting abnormalities may not be known | Obtain renal US at AKI onset but consider repeating it post-large volume paracentesis when needed
Search for baseline renal US |

**Not included in the ICA criteria**

| **Leukocyturia** | To exclude acute interstitial nephritis or acute glomerulonephritis as cause of AKI | Leukocyturia can be present in UTI, acute interstitial nephritis and rarely in ATI | Obtain urine culture and if negative, consider acute interstitial nephritis as cause of AKI. Kidney biopsy may be necessary |
| **Urinary sediment microscopy findings of parenchymal cause of AKI** | To exclude ATI (if muddy brown granular casts), acute glomerulonephritis (acanthocyturia, RBC/WBC) | Bilirubin stains sediment and creates artifactual findings. Hyaline and lightly granular casts may be incorrectly | Perform urinary sediment microscopy including bright field illumination to identify muddy brown granular casts |
Renal tubular epithelial cell casts can be found in severe hyperbilirubinemia. Their significance is not fully understood and phase contrast microscopy to identify acanthocytes

<table>
<thead>
<tr>
<th>Intraabdominal hypertension</th>
<th>To exclude abdominal compartment syndrome</th>
<th>Abdominal compartment syndrome may coexist with HRS-1</th>
<th>Measure bladder pressure and recommend therapeutic LVP when &gt; 20 mmHg</th>
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<td>Obtain an echocardiogram</td>
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<td>Elevated urinary NGAL</td>
<td>To exclude ATI</td>
<td>Overlap of ATI and HRS-1 and medium-to-low titers is still possible</td>
<td>Not available for clinical use</td>
</tr>
<tr>
<td>Triggering factor</td>
<td>To leverage a pre-test probability factor</td>
<td>Patients often present with worsening kidney function without a clear precipitating event</td>
<td>Presence of SBP or other infections should increase suspicion for HRS-1 Consider GIB and ACLF also as potential triggers Remove LVP as triggering factor</td>
</tr>
</tbody>
</table>

### AKI Definition

<table>
<thead>
<tr>
<th>Criterion consistent HRS-1</th>
<th>Rationale and Utility</th>
<th>Limitation</th>
<th>Proposed Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>KDIGO AKI</td>
<td>Consistency with other AKI definitions</td>
<td>Creatinine-based, can be affected by sarcopenia, tubular secretion and assay interference</td>
<td>Consider adding oliguria factor Explore utility of cystatin C</td>
</tr>
<tr>
<td>Terminology: HRS-1 vs HRS-AKI</td>
<td>HRS-AKI highlights the incorporation of the KDIGO AKI definition</td>
<td>Does not add clarity to the diagnosis Oversimplifies causes of AKI not due to HRS-1 (non-HRS-AKI is a &quot;waste basket&quot;) Semantically suboptimal</td>
<td>Maintain HRS-1 and concentrate efforts on improving diagnostics</td>
</tr>
</tbody>
</table>

Table 2. Properties of vasoconstrictors and their existing evidence of benefit for the treatment for HRS-1.

<table>
<thead>
<tr>
<th>Receptor agonism to mediate vasoconstriction</th>
<th>Number of clinical trials or cohorts (total of subjects studied)</th>
<th>Advantages</th>
<th>Adverse effects</th>
<th>Logistical pitfalls and other disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo controlled[^]{^a}</td>
<td>Prospective vs another agent</td>
<td>Prospective uncontrolled</td>
<td></td>
</tr>
<tr>
<td>Midodrine and Octreotide (M/O)</td>
<td>α-adrenergic and somatostatin</td>
<td>none</td>
<td>1 vs DA (n=13)[48] 2 vs NE (n=74)[52, 68] 1 vs T (n=49)[51]</td>
<td>1 (n=14)[75]</td>
</tr>
<tr>
<td>Terlipressin (T)</td>
<td>V1a</td>
<td>4 (n=632)[5, 53, 57, 59] ^2 (n=42)[76, 77]</td>
<td>1 vs M/O (n=49)[51] 6 vs NE (n=260)[59-64] 1 vs DA (n=40)[78]</td>
<td>6 (n=88)[74, 79-83]</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>V1a</td>
<td>none</td>
<td>none</td>
<td>1 (n=18)[84]</td>
</tr>
<tr>
<td>Norepinephrine (NE)</td>
<td>α-adrenergic</td>
<td>none</td>
<td>6 vs T (n=260)[59-64] 2 vs M/O (n=74)[52, 68]</td>
<td>2 (n=42)[60, 85]</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>α-adrenergic</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
</tbody>
</table>

DA: dopamine, ICU: intensive care unit, IV: intravenous. ^ vs. albumin alone (no actual placebo). * Only recommended as monotherapy in patients who experience limiting adverse reactions to NE or T.
Figure 1 | Approach to diagnosis of acute kidney injury (AKI) in cirrhosis. The conventional approach to determine the etiology of acute kidney injury (AKI) in individuals with cirrhosis has been centered in the possibility of 3 primary causes: prerenal azotemia (Prer Az), acute tubular necrosis (renamed acute tubular injury, ATI) and hepatorenal syndrome type 1 (HRS-1). Although those 3 etiologies may account for the majority of cases of AKI in this patient population, other causes are possible and not as rare as previously assumed [abdominal compartment syndrome (ACS), cardiorenal syndrome type 1 (CRS-1), acute glomerulonephritis (AGN), acute interstitial nephritis (AIN), obstructive uropathy (OU)]. In addition, it is conceivable and mechanistically plausible that, in some instances, etiologies of AKI may not be entirely mutually exclusive. Thus, coexistence of more than one cause of acute kidney dysfunction may occur. Furthermore, presence of preexisting chronic kidney disease (CKD) should be taken into account as part of the assessment.

Figure 2 | Conceptual framework illustrating the rationale for a dichotomized diagnostic approach of acute kidney injury (AKI) in cirrhosis. Diagnosis of hepatorenal syndrome type 1 (HRS-1) prompts consideration to a treatment modality that is unique to HRS-1 and not effective in any other form of AKI. In addition to the ICA criteria, additional phenotypical elements should be examined (e.g., presence of triggering infection, hyponatremia, baseline low-normal mean arterial pressure, findings in urinary sediment microscopy). Cirrhosis portends risk factors to acquire most types of AKI. Prerenal azotemia (PrerAz) can occur as a result of gastrointestinal (GI) losses (e.g., from laxatives used for hepatic encephalopathy) and is managed with intravenous albumin and intravenous fluids (IVF). Acute tubular injury (ATI) can occur as a result of ischemia (e.g., from GI bleeding (GIB)) or toxic injury (e.g., bile acids) and is managed with supportive care. Abdominal compartment syndrome (ACS) can occur as a result of tense ascites and is managed with large-volume paracentesis (LVP). Cardiorenal syndrome type 1 (CRS-1) can occur as a result of cirrhotic cardiomyopathy (CM) and is managed with diuretics +/- inotropes. Acute interstitial nephritis (AIN) can occur from exposure to antibiotics [e.g.,
quinolones for spontaneous bacterial peritonitis (SBP) and is managed with drug discontinuation +/- corticosteroids (CS)). Acute glomerulonephritis can occur in cirrhosis (e.g., IgA nephropathy (IgAN), hepatitis C-associated membranoproliferative GN (HCV-MPGN) and can be managed with immunosuppressive therapy (IST). Cirrhosis does not increase the risk for obstructive uropathy.

**Figure 3 | Urinary sediment microscopy in patients with cirrhosis, hyperbilirubinemia and acute kidney injury.** *Top row:* A) bilirubin-stained hyaline cast (bright field illumination); B) hyaline casts with surrounding bilirubin-stained particles (phase contrast); C) bilirubin-stained finely granular cast (bright field illumination); D) bilirubin-stained waxy cast (bright field illumination). *Second row:* E) bilirubin-stained finely granular and coarse granular casts (bright field illumination); F) “muddy brown” granular casts (bright field illumination); G) “muddy brown” granular cast (dark field illumination); H) acanthocytes (inset pointed by white arrow) indicative of glomerular hematuria within a field filled with occasional nucleated cells and bilirubin-stained amorphous, crystalline and granular structures (phase contrast). *Third row:* I) bilirubin-stained renal tubular epithelial cell (RTEC) cast (bright field illumination); J) same bilirubin-stained RTEC cast under polarized light; K) bilirubin-stained RTEC cast (phase contrast); L) bilirubin-stained RTEC cast (dark field illumination). *Fourth row:* M) leucine crystals (bright field); N) same leucine crystals under polarized light; O) bilirubin-stained finely granular cast containing leucine crystals (bright field illumination); P) bilirubin crystals (bright field illumination). All images captured at 400X magnification. Only “muddy brown” granular casts are deemed conclusively indicative of acute tubular injury (ATI) and inconsistent with HRS-1. Waxy casts also denote tubular injury, but they could be of acute (ATI) or chronic (CKD) origin. RTEC casts may suggest ongoing ATI. The remainder of the findings can be present in a urine specimen of a patient with HRS-1 despite the primary functional nature of HRS-1.

**Figure 4 | Mechanistic rational for the use of vasoconstrictors in HRS-1.** A) Under physiological conditions without liver disease, renal microcirculation is autoregulated to maintain perfusion within a certain range of mean arterial pressure (MAP); B) cirrhosis and portal hypertension (HTN) lead to
splanchnic vasodilation, fall in MAP, stimulation of baroreceptors, activation of the sympathetic nervous system (SNS) and the renin-angiotensin system (RAS), activation of the hepatorenal reflex and ultimately renal vasoconstriction and fall in glomerular filtration rate (GFR); C) vasoconstrictors restore the MAP, counteract the splanchnic vasodilation, reset the trigger for SNS and RAS activation, restore renal blood flow (RBF) and improve GFR.

**Figure 5 | Approach to medical management of hepatorenal syndrome type 1 (HRS-1) in cirrhosis. Top panel:** The standard approach has been to first rule out prerenal azotemia as the cause of acute kidney injury (AKI) by systematically proceeding with volume resuscitation with intravenous albumin for up to 48 hours (1) before entertaining the diagnosis of hepatorenal syndrome type 1 (HRS-1). Subsequently, it has been advised to apply to International Club of Ascites (ICA) criteria to attempt distinguishing HRS-1 from parenchymal forms of AKI, mainly acute tubular necrosis (renamed acute tubular injury, ATI) (2). Then, for those diagnosed as HRS-1, the combination of intravenous albumin and vasoconstrictor therapy is advised. **Bottom panel:** A more analytical approach is proposed. First, obviate blinded systematic administration of intravenous albumin. Instead, careful assessment of volume and respiratory status (with tools such as physical examination, ultrasonography, x-ray-based imaging) as well as assessment of evidence of renal parenchymal injury (microscopic examination of the urinary sediment) and kidney health (urinary sodium concentration) is recommended to guide decisions (1). Then, administration of intravenous albumin or other fluids could be appropriate, but diuretics and/or paracentesis may also be considered depending on the case (2). At this stage, application of the ICA criteria should be done in conjunction with a more comprehensive consideration of other causes of AKI [acute glomerulonephritis (AGN), acute interstitial nephritis (AIN), abdominal compartment syndrome (ACS), cardiorenal syndrome (CRS), obstructive uropathy (OU)]. If the diagnosis of HRS-1 is reached, vasoconstrictors should be the cornerstone of therapy, aiming for a rise in mean arterial pressure (MAP) of ≥ 15 mmHg. Need for co-administration of intravenous albumin or diuretics should be weighed judiciously and dynamically (3). Renal replacement therapy can be initiated
at any stage of the process if clinically indicated, provided that the risk: benefit ratio and life expectancy factors are adequately assessed. Ultimately, liver transplantation should be pursued in eligible individuals as definite treatment for HRS-1.
Figure 1
Unique Treatment: Vasoconstrictor Therapy

Diagnostic Approach in AKI in Cirrhosis

- ICA Criteria
- Additional Phenotypical Aspects of HRS-1

ICA Criteria:
- PrerAz: eg, GI (laxative) losses
- ATI: eg, ischemia (GIB), toxic (bile)
- ACS: eg, tense ascites
- CRS-1: eg, cirrhotic CM
- AIN: eg, quinolone in SBP
- AGN: eg, IgAN, HCV-MPGN

HRS-1 Not Main AKI Driver

Supportive Care:
- Albumin +/- IVF
- LVP
- Diuretics +/- Inotropes
- Stop Drug +/- CS
- IST

Unique Treatment: Vasoconstrictor Therapy
**Figure 5**

- **Standard Approach**
  1. ESLD + AKI
  2. Volume resuscitation for 48 hrs.
  3. Prerenal
     - HRS-1
     - No HRS-1
  4. If Dx: HRS-1

- **Analytical Approach**
  1. ESLD + AKI
  2. Volemia
     - Kidney parenchyma
     - ICA criteria
     - Phenotype
  3. Prerenal
     - HRS-1 or HRS-1/ATI
  4. If Dx: HRS-1
     - Vasoconstrictor
     - MAP goal: ↑ 15 mmHg

- **Vasoconstrictor**
  - ATI
  - AGN
  - AIN
  - ACS
  - CRS
  - OU

- **Standard Approach**
  - If Dx: HRS-1

- **Analytical Approach**
  - If Dx: HRS-1

- **MAP goal**
  - ↑ 15 mmHg