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

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Abstract
Hepatorenal syndrome type 1 (HRS-1) is a serious form of 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. Although the diagnostic criteria dictated by the International Club of Ascites 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 is challenging with the currently available clinical tools. Because treatment of HRS-1 differs from that of acute tubular injury, distinguishing these two causes of AKI has direct implications in management. Therefore, the use of the International Club of Ascites 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, pharmacologic 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). Although these three 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. 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 pathologic processes that independently impair kidney function may superimpose over an overarching state of hepatorenal physiology. Some of those processes include nonparenchymal disorders such as abdominal compartment syndrome due to tense ascites and cardiorenal syndrome type 1 due to cirrhotic cardiomyopathy, and 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 International Club of Ascites (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 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, euvo-lemic, 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 (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 (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 (6). In 53 hospitalized patients with presumed HRS-1 and deemed clinically euvo-
lemic, 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.

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).

Figure 1. | Approach to diagnosis of AKI in cirrhosis. The conventional approach to determine the etiology of AKI in individuals with cirrhosis has been centered in the possibility of three primary causes: prerenal azotemia (Prer Az), acute tubular necrosis (renamed acute tubular injury [ATI]), and hepatorenal syndrome type 1 (HRS-1). Although those three 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], and 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 CKD should be taken into account as part of the assessment.

Change in Kidney Function

Earlier definitions of HRS-1 utilized cutoffs in absolute values of serum creatinine concentration. The updated criteria removed absolute cutoff values of serum creatinine and applied the Kidney Disease Improving Global Outcomes (KDIGO) definition of AKI instead (7). 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 (7). However, serum creatinine values carry inherent limitations (Table 1). Because sarcopenia is often present in cirrhosis, serum creatinine concentration may underestimate kidney dysfunction (8). In addition, increased tubular secretion of creatinine may occur in cirrhosis and can contribute to underestimating GFR loss (9). Furthermore, hyperbilirubinemia may cause an interference with a colorimetric assay for creatinine (10). 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 (11,12).

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 spontaneous bacterial peritonitis. Those infections may indeed trigger HRS-1. However, antibiotics (e.g., fluoroquinolones, vancomycin) can be nephrotoxic and cause toxic ATI or AIN (13,14). 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.
<table>
<thead>
<tr>
<th>Criterion to Exclude</th>
<th>Hepatorenal Syndrome Type 1</th>
<th>Rationale and Utility</th>
<th>Limitation</th>
<th>Proposed Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICA criteria</td>
<td></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 and physical to determine probability of reversible prerenal azotemia</td>
</tr>
<tr>
<td>Fixed 48-hour</td>
<td></td>
<td>administration of intravenous albumin and discontinuation of diuretics</td>
<td>Inability to diagnose HRS-1 upon initial assessment leading to delay in initiation of vasoconstrictors</td>
<td>Integrate assessment of volume status by POCUS by weighing the history and physical examination</td>
</tr>
<tr>
<td>Nephrotoxins</td>
<td></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>
</tr>
<tr>
<td>Shock</td>
<td></td>
<td>To exclude a high probability of ischemic ATI due to organ hypoperfusion</td>
<td>Unclear cutoff blood pressure level consistent with shock</td>
<td>Consider collecting additional data to confirm shock (e.g., serum lactate, invasive hemodynamics)</td>
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<tr>
<td>Urine RBC &gt;50/hpf</td>
<td></td>
<td>To exclude renal parenchymal disorders that can present with hematuria (e.g., acute glomerulonephritis)</td>
<td>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</td>
<td>Weigh importance of hematuria in the context of bladder catheterization Search for evidence of preexisting hematuria Assess urine RBC morphology by urinary sediment microscopy</td>
</tr>
<tr>
<td>Proteinuria &gt;500 mg/d</td>
<td></td>
<td>To exclude renal parenchymal disorders that can present with proteinuria (e.g., glomerulopathies)</td>
<td>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</td>
<td>Assess both UPCR and urine dipstick and interpret with caution, taking into consideration baseline status of proteinuria (when available) De novo UPCR &gt;0.3 g/g and urine dipstick ≥1+ protein should alert consideration for renal parenchymal disorder</td>
</tr>
<tr>
<td>FENa &gt;0.2%</td>
<td></td>
<td>To exclude ATI</td>
<td>Cases of ATI can present with FENa ≤0.2%</td>
<td>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 &lt;10 mEq/L</td>
</tr>
<tr>
<td>Criterion to Exclude Hepatorenal Syndrome Type 1</td>
<td>Rationale and Utility</td>
<td>Limitation</td>
<td>Proposed Adjustment</td>
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<tr>
<td>Abnormal kidney US</td>
<td>To exclude renal parenchymal disorders that can exhibit increased cortical echogenicity or other abnormalities</td>
<td>Ascites produces acoustic enhancement below the fluid leading to artificial increase in cortical echogenicity of the kidney</td>
<td>Obtain renal US at AKI onset but consider repeating it post-large volume paracentesis when needed</td>
<td></td>
</tr>
<tr>
<td>Not included in the ICA criteria Leukocyturia</td>
<td>To exclude acute interstitial nephritis or acute glomerulonephritis as cause of AKI</td>
<td>Leukocyturia can be present in UTI and acute interstitial nephritis and rarely in ATI</td>
<td>Obtain urine culture and, if negative, consider acute interstitial nephritis as cause of AKI; kidney biopsy may be necessary</td>
<td></td>
</tr>
<tr>
<td>Urinary sediment microscopy findings of parenchymal cause of AKI</td>
<td>To exclude ATI (if muddy brown granular casts), acute glomerulonephritis (acanthocyturia, RBC/WBC casts)</td>
<td>Bilirubin stains sediment and creates artifactual findings. Hyaline and lightly granular casts may be incorrectly interpreted as definite evidence of ATI Renal tubular epithelial cell casts can be found in severe hyperbilirubinemia; their significance is not fully understood</td>
<td>Perform urinary sediment microscopy, including bright field illumination to identify muddy brown granular casts and phase contrast microscopy to identify acanthocytes</td>
<td></td>
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<tr>
<td>Intra-abdominal hypertension</td>
<td>To exclude abdominal compartment syndrome</td>
<td>Abdominal compartment syndrome may coexist with HRS-1</td>
<td>Measure bladder pressure and recommend therapeutic LVP when &gt;20 mm Hg</td>
<td></td>
</tr>
<tr>
<td>Portopulmonary hypertension and cirrhotic cardiomyopathy</td>
<td>To exclude cardiorenal syndrome type 1</td>
<td>Cardiorenal syndrome type 1 may coexist with HRS-1</td>
<td>Obtain an echocardiogram</td>
<td></td>
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<tr>
<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>
<td></td>
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<tr>
<td>Triggering factor</td>
<td>To leverage a pretest 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>
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<table>
<thead>
<tr>
<th>Criterion Consistent Hepatorenal Syndrome Type 1</th>
<th>Rationale and Utility</th>
<th>Limitation</th>
<th>Proposed Adjustment</th>
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</thead>
<tbody>
<tr>
<td>AKI definition 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</td>
</tr>
<tr>
<td>Terminology: HRS-1 versus HRS-AKI</td>
<td>HRS-AKI highlights the incorporation of the KDIGO AKI definition</td>
<td>Does not add clarity to the diagnosis</td>
<td>Explore utility of cystatin C</td>
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</table>

HRS-1, hepatorenal syndrome type 1; ICA, International Club of Ascites; POCUS, point-of-care ultrasound; UA, urinalysis; WBC, white blood cells; ATI, acute tubular injury; RBC, red blood cells; hpf, high power field; IgAN, IgA nephropathy; UPCR, urine protein-to-creatinine ratio; FENA, fractional excretion of urinary sodium; PPV, positive predictive value; Na, sodium; US, ultrasound; UTI, urinary tract infection; LVP, large volume paracentesis; NGAL, neutrophil gelatinase-associated lipocalin; SBP, spontaneous bacterial peritonitis; GIB, gastrointestinal bleeding; ACLF, acute-on-chronic liver failure; KDIGO, Kidney Disease Improving Global Outcomes.
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 (15).

Hematuria and Proteinuria

The current ICA criteria call for exclusion of HRS-1 when urine microscopy reveals more than 50 red blood cells (RBC) per high power field (hpf) and proteinuria of 500 mg/d 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 (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 acute glomerulonephritis with 10–50 RBC/hpf. Importantly, the morphology of urinary RBC should be interpreted with attention to previous results on the same patient. For instance, a patient

Figure 2. | Conceptual framework illustrating the rationale for a dichotomized diagnostic approach of AKI in cirrhosis. Diagnosis of 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 International Club of Ascites (ICA) criteria, additional phenotypical elements should be examined (e.g., presence of triggering infection, hyponatremia, baseline low-normal mean arterial pressure (MAP), and findings in urinary sediment microscopy). Cirrhosis portends risk factors to acquire most types of AKI. Prer Az 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). 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. ACS can occur as a result of tense ascites and is managed with large-volume paracentesis (LVP). CRS-1 can occur as a result of cirrhotic cardiomyopathy (CM) and is managed with diuretics and/or inotropes. AIN can occur from exposure to antibiotics (e.g., quinolones for spontaneous bacterial peritonitis [SBP]) and is managed with drug discontinuation and/or 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.
with cirrhosis due to nonalcoholic steatohepatitis may have metabolic syndrome and chronic albuminuria, which should not preclude the diagnosis of HRS-1.

**Urinary Sodium**

A urinary sodium (UNa) concentration <10 mEq/L was a required minor criterion in the original 1996 ICA definition of HRS-1 (20). It was subsequently removed in the 2007 updated version (21). The standard cutoff value to define low UNa and low fractional excretion of UNa (FENa) are <10–20 mEq/L and <1%, respectively. However, on the basis of those cutoff values, low UNa and low FENa are almost universally present in patients with cirrhosis and AKI (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% (22). Thus, low UNa has been reinserted 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 versus <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 (23).

**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 (1).

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 (24,25). 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 on the basis of urine sediment microscopy findings (26). 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 (27), they can also be identified in patients with hyperbilirubinemia without AKI (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.

Intraabdominal Hypertension

Despite the increased recognition of abdominal compartment syndrome 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 (ICU) reported measurements consistent with intra-abdominal hypertension with a median intra-abdominal pressure of 22 mm Hg and transient improvement in kidney function upon decompression (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 (3%) immediately after LVP (30). Therefore, it seems reasonable to favor LVP during AKI in cirrhosis, particularly in those with a documented intra-abdominal pressure >20 mm Hg.

Portopulmonary Hypertension and Cirrhotic Cardiomyopathy

Cirrhosis with portal hypertension increases the risk for pulmonary hypertension (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 (33,34). Therefore, right and/or left ventricular failure may complicate a case of AKI and cirrhosis by aggravating peripheral edema and 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 (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 (36–38). Although the NGAL titer tends to be significantly higher in ATI compared with HRS-1, there is still overlap in the distribution of values (36,37,39,40). A recent US-based study reported an area under the curve (AUC) of 0.76 for diagnosis of ATI using a cutoff value of 244 μg/g (41). A combination of NGAL with other biomarkers (L-type fatty acid binding protein, IL-18, albumin) has been proposed as a way to enhance the tool (42). The AUC for urine albumin, which is available for clinical use, approximates to that of NGAL (42). A single-center study reported optimal performance of the urinary microRNA molecule miR-21 that showed an AUC of 0.97 for distinguishing ATI from HRS-1 (43). To date, NGAL is not available for clinical use in the United States. 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 on the basis of successful therapeutic response to a vasoconstrictor. A study showed acceptable performance of serum adrenomedullin and urinary thromboxane B2 for classification of HRS-1 versus ATI, but they failed to predict response to therapy (44). 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, upregulation of the renin-angiotensin system, loss of renal autoregulation, stimulation of a hepatoportal reflex, and ultimately a fall in renal blood flow (1,45,46). Vasoconstrictors raise the MAP, counteract
splanchnic vasodilation, reset the sympathetic nervous system and renin-angiotensin system activation, and restore renal blood flow (Figure 4). Nonselective 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. However, evidence supporting its use is modest at best. In a seminal nonparallel controlled study by Angeli et al., the combination of midodrine and octreotide was more effective than a nonpressor 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 (53,54). Thus, midodrine and octreotide should not be first-line therapy for HRS-1 in the ICU setting in North America or 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 V1 receptor (V1R:V2R 2:1) 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 randomized placebo-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 with 0% with placebo (57). The first randomized placebo-controlled trial testing the efficacy and safety of terlipressin in the United States, the OT-0401 study, was published in 2008 (53). At the time of publication, the primary end point was not reached. However, outcomes analyzed on the basis of the primary end point utilized in the more recent CONFIRM trial revealed that terlipressin was more efficacious than placebo (34% versus 13%, P=0.008) (58). The second trial in the United States, REVERSE, also showed a signal for therapeutic efficacy but failed to reach significance (59). The third and largest North American trial (CONFIRM) enrolling 300 patients was published in 2020. The primary end point was reached, with reversal of HRS-1 occurring in 29% of terlipressin-treated subjects compared with 16% for the placebo arm. However, from a safety perspective, terlipressin-treated subjects had a greater incidence of respiratory failure events. Overzealous use of intravenous albumin before enrollment may have played a role in the increased incidence of respiratory failure and fluid overload. The manufacturer of terlipressin...
Table 2. Properties of vasoconstrictors and their existing evidence of benefit for the treatment for hepatorenal syndrome type 1

<table>
<thead>
<tr>
<th>Vasoconstrictor</th>
<th>Receptor Agonism to Mediate Vasoconstriction</th>
<th>Number of Clinical Trials or Cohorts (Total of Subjects Studied)</th>
<th>Placebo Controlled</th>
<th>Prospective versus Another Agent</th>
<th>Prospective Uncontrolled</th>
<th>Advantages</th>
<th>Adverse Effects</th>
<th>Logistical Pitfalls and Other Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midodrine and octreotide</td>
<td>α-adrenergic and somatostatin</td>
<td>None</td>
<td>1 versus DA (n=13) (48)</td>
<td>1 (n=14) (75)</td>
<td>Oral and subcutaneous route</td>
<td>Urinary retention (M)Bradycardia (M,O)Glycemia ↑↓ (O)</td>
<td>Abdominal pain Ischemia Respiratory failure</td>
<td>Limited efficacy</td>
</tr>
<tr>
<td>Terlipressin</td>
<td>V1a</td>
<td>4 (n=632) (5,53,57,59) 2 (n=42) (76,77)</td>
<td>1 versus M/O (n=49) (51) 6 versus NE (n=260) (59–64) 1 versus DA (n=40) (78)</td>
<td>6 (n=88) (74,79–83)</td>
<td>Proven efficacy No need for ICU V1a selectivity over V2 receptor Divided IV doses, no infusion</td>
<td>Proven efficacy Titratable Does not induce tachyarrhythmia</td>
<td>Need for ICU</td>
<td>Not approved in North America</td>
</tr>
</tbody>
</table>
| Vasopressin | V1a | None | None | 1 (n=18) (84) | Potentially effective Bradyarrhythmia Hyponatremia Ischemia | Need for ICU | M/O, midocrine and octreotide; T, terlipressin; NE, norepinephrine; HRS-1, hepatorenal syndrome type 1; DA, dopamine; ICU, intensive care unit; IV, intravenous. 

aCompared to albumin alone (no actual placebo).
bOnly recommended as monotherapy in patients who experience limiting adverse reactions to NE or T.
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 (60). Subsequently, six 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 (61–66). One study reported fewer adverse events with norepinephrine (66). Another study specifically enrolling patients with acute-on-chronic liver failure and HRS-1 suggested superiority of terlipressin infusion over norepinephrine infusion (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 with midodrine and octreotide in one study (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 with 20% of midodrine- and octreotide-treated subjects (52). Therefore, norepinephrine constitutes a reasonable first-line treatment for HRS-1. The main limitations for using norepinephrine in HRS-1 are the requirement of an 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 (69). Therefore, widespread implementation of such approach may require additional studies.

**Targeting a Rise in MAP**

Multiple lines of evidence demonstrate that the benefit of vasoconstrictor therapy in HRS-1 is strongly associated...
with the degree of increase in MAP induced by the vasoconstrictor (54,70,71). The question remains as to what the ideal target of MAP is. Some studies suggest that a rise >10 mm Hg may suffice, whereas other studies suggest >15 mm Hg may be necessary for optimal response (54,69,72). In clinical grounds, ICU nursing personnel and practitioners are familiar with a MAP target of 65 mm Hg for shock. Thus, a barrier for adequate implementation of MAP goals in HRS-1 relates to lack of uniform education of health care providers. In addition, selection of a single absolute value of MAP (e.g., 85 mm Hg) leads to rapid down-titration of the vasoconstrictor as soon as the MAP exceeds the target, which in turns causes the MAP to drop to pretreatment values. Thus, perhaps a sounder approach is to target a MAP rise ≥15 mm Hg 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.

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 enhance the efficacy of a vasoconstrictor. The best evidence supporting this notion comes from a study by Ortega et al. (73). In a small study of 16 subjects with HRS-1, reversal was achieved more often for those treated with terlipressin and albumin compared with those treated with terlipressin alone. In most randomized controlled trials for HRS-1 published to date, co-administration of albumin was part of the treatment protocol (1,53,57). The combination of preload increases 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, radiologic 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 (60,62,74) (Figure 5).

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.

Disclosures

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Author Contributions

J. Carlos Velez conceptualized the study, curated the data curation, conducted the investigation and methodology, wrote the original draft of the manuscript, and reviewed and edited the manuscript.

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