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

Juan Carlos Q. Velez 1,2

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, euvolemic, or hypervolemic state. Blinded administration

1Department of Nephrology, Ochsner Health, New Orleans, Louisiana
2Ochsner Clinical School, University of Queensland, Brisbane, Australia

Correspondence: Dr. Juan Carlos Q. Velez, 1514 Jefferson Hwy., Clinic Tower, Room 5E328, Ochsner Medical Center, New Orleans, LA 70121. Email: juancarlos.velez@ochsner.org

KIDNEY360 3: 382–395, 2022. doi: https://doi.org/10.34067/KID.0006722021
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).

**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.

---

**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.
Table 1. Assessment of the rationale, utility, and limitations of the elements included in the current International Club of Ascites diagnostic criteria for exclusion of hepatorenal syndrome type 1, proposed adjustments to those criteria, and consideration for additional criteria

| Criterion to Exclude          | Rationale and Utility                                                                 | Limitation                                                                 | Proposed Adjustment                                                                 |
|-------------------------------|---------------------------------------------------------------------------------------|----------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| ICA criteria                  | Fixed 48-hour administration of intravenous albumin and discontinuation of diuretics | To exclude reversible prerenal azotemia                                    | Blinded to volume status, can lead to iatrogenic worsening of hypervolemic states   | Careful assessment of volume status by POCUS                                      |
|                               |                                                                                       |                                                                            | Inability to diagnose HRS-1 upon initial assessment leading to delay in initiation of vasoconstrictors | Weigh-in history and physical to determine probability of reversible prerenal azotemia |
| Nephrotoxins                  | To exclude drug-induced renal parenchymal disorders                                    | Exposure to antibiotics in this setting is extremely common; difficult to ascertain whether drug is/is not the culprit | 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 |
| Shock                         | To exclude a high probability of ischemic ATI due to organ hypoperfusion                | Unclear cutoff blood pressure level consistent with shock                   | Consider collecting additional data to confirm shock (e.g., serum lactate, invasive hemodynamics) |
| 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                         | Weigh importance of hematuria in the context of bladder catheterization              |
|                               |                                                                                       | Traumatic hematuria not uncommon due to indwelling bladder catheter insertion | Search for evidence of preexisting hematuria                                        |
|                               |                                                                                       | Chronic IgAN may be present in cirrhosis and can cause hematuria irrespective of a superimposed AKI | Assess urine RBC morphology by urinary sediment microscopy                          |
|                               |                                                                                       | Urine RBC morphology suggestive of glomerular origin not considered          |                                                                                      |
| Proteinuria >500 mg/d        | 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 | Assess both UPCR and urine dipstick and interpret with caution, taking into consideration baseline status of proteinuria (when available) |
|                               |                                                                                       | Oliguria often present, accuracy of UPCR in oliguric AKI is limited         | De novo UPCR >0.3 g/g and urine dipstick ≥1+ protein should alert consideration for renal parenchymal disorder |
|                               |                                                                                       | Preexisting proteinuria is possible                                        |                                                                                      |
| 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                |
| Criterion to Exclude Hepatorenal Syndrome Type 1 | Rationale and Utility | Limitation | Proposed Adjustment |
|-----------------------------------------------|-----------------------|------------|---------------------|
| Abnormal kidney US                            | To exclude renal parenchymal disorders that can exhibit increased cortical echogenicity or other abnormalities | Ascites produces acoustic enhancement below the fluid leading to artificial increase in cortical echogenicity of the kidney | Obtain renal US at AKI onset but consider repeating it post-large volume paracentesis when needed |
| Not included in the ICA criteria              | Leukocyturia           | Leukocyturia can be present in UTI and 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 casts) | 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 | Perform urinary sediment microscopy, including bright field illumination to identify muddy brown granular casts and phase contrast microscopy to identify acanthocytes |
| Intra-abdominal hypertension                  | To exclude abdominal compartment syndrome | Abdominal compartment syndrome may coexist with HRS-1 | Measure bladder pressure and recommend therapeutic LVP when >20 mm Hg |
| Portopulmonary hypertension and cirrhotic cardiomyopathy | To exclude cardiorenal syndrome type 1 | Cardiorenal syndrome type 1 may coexist with HRS-1 | Obtain an echocardiogram |
| Elevated urinary NGAL                         | To exclude ATI         | Overlap of ATI and HRS-1 and medium-to-low titers is still possible | Not available for clinical use |
| Triggering factor                             | To leverage a pretest probability factor | Patients often present with worsening kidney function without a clear precipitating event | 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 |

| Criterion Consistent Hepatorenal Syndrome Type 1 | Rationale and Utility | Limitation | Proposed Adjustment |
|--------------------------------------------------|-----------------------|------------|---------------------|
| AKI definition                                   | Consistency with other AKI definitions | Creatinine based; can be affected by sarcopenia, tubular secretion, and assay interference | Consider adding oliguria factor Explore utility of cystatin C |
| Terminology: HRS-1 versus HRS-AKI                | HRS-AKI highlights the incorporation of the KDIGO AKI definition | Does not add clarity to the diagnosis Oversimplifies causes of AKI not due to HRS-1 (non-HRS-AKI is a “waste basket”) Semantically suboptimal | Maintain HRS-1 and concentrate efforts on improving diagnostics |

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 may be more informative than their quantity. Presence of urinary acanthocytes is pathognomonic of glomerular disease and inconsistent with HRS-1 (18).

Regarding proteinuria, the ICA criteria dictate exclusion of HRS-1 if its value is >500 mg/d. 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 (19). Furthermore, proteinuria should be interpreted with attention to previous results on the same patient. For instance, a patient
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 slightly 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. (48), the combination of midodrine and octreotide was more effective than a nonpressor dose of intravenous dopamine. 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 2-6:1) 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 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

---

**Figure 4.** Mechanistic rational for the use of vasoconstrictors in HRS-1. (A) Under physiologic conditions without liver disease, renal microcirculation is autoregulated to maintain perfusion within a certain range of 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 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.
Table 2. Properties of vasoconstrictors and their existing evidence of benefit for the treatment for hepatorenal syndrome type 1

| Receptor Agonism to Mediate Vasoconstriction | Number of Clinical Trials or Cohorts (Total of Subjects Studied) | Placebo Controlleda | Prospective versus Another Agent | Prospective Uncontrolled | Advantages | Adverse Effects | Logistical Pitfalls and Other Disadvantages |
|---------------------------------------------|--------------------------------------------------|---------------------|----------------------------------|------------------------|-----------|----------------|-------------------------------------------|
| Midodrine and octreotide (α-adrenergic and somatostatin) | None | 1 versus DA (n=13) (48) 2 versus NE (n=74) (52,68) 1 versus T (n=49) (51) | 1 (n=14) (75) | Oral and subcutaneous route | Urinary retention (M)Bradycardia (M,O)Glycemia ↑↓ (O) | Limited efficacy |
| Terlipressin (V1a) | 4 (n=632) (5,53,57,59) 2 (n=42) (76,77)a | 1 versus M/O (n=49) (51) 6 versus NE (n=260) (59–64) 1 versus DA (n=40) (78) | 6 (n=88) (74,79–83) | Proven efficacy No need for ICU V1a selectivity over V2 receptor Divided IV doses, no infusion | Abdominal pain Ischemia Respiratory failure | Not approved in North America |
| Vasopressin (V1a) | None | None | None | 1 (n=18) (84) | Potentially effective Bradyarrhythmia Hyponatremia Ischemia | Need for ICUb |
| Norepinephrine (α-adrenergic) | None | 6 versus T (n=260) (59–64) 2 versus M/O (n=74) (52, 68) | 2 (n=42) (60, 85) | Proven efficacy Titratable Tachyarrhythmia | Need for ICU |
| Phenylephrine (α-adrenergic) | None | None | None | Does not induce tachyarrhythmia Chest tightness Nervousness | Need for ICUb |

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 enrollment 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

**Figure 5. | Approach to medical management of HRS-1 in cirrhosis.** Top panel: The standard approach has been first to rule out prerenal azotemia as the cause of 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 ICA criteria to attempt distinguishing HRS-1 from parenchymal forms of AKI, mainly acute tubular necrosis (renamed 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) and 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 (AGN, AIN, ACS, CRS, OU). If a diagnosis of HRS-1 is reached, vasoconstrictors should be the cornerstone of therapy, aiming for a rise in MAP of $\geq 15$ mm Hg. 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.
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, coadministration 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. In parallel with their ability to raise the MAP, 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

J. Velez reports consultancy agreements with Bayer, Mallinckrodt Pharmaceuticals (maker of terlipressin, and J.C.Q.V. was a site PI for the CONFIRM trial), and Traver; honoraria from Bayer, Mallinckrodt, Otsuka, and Traver; and is on the advisory boards of Mallinckrodt and Traver and participates in a speakers’ bureau for Otsuka Pharmaceuticals.

Funding

None.

Acknowledgment

Thanks to Serenella A. Velez for her contribution drafting some of the illustrations.

Author Contributions

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

References

1. Velez JCQ, Therapondos G, Juncos LA: Reappraising the spectrum of AKI and hepatorenal syndrome in patients with cirrhosis [published correction appears in Nat Rev Nephrol 16: 186, 2020 10.1038/s41581-020-0255-z]. Nat Rev Nephrol 16: 137–155, 2020 https://doi.org/10.1038/s41581-019-0218-4
2. Angeli P, Ginès P, Wong F, Bernardi M, Boyer TD, Gerbes A, Moreau R, Jalal R, Sarin SK, Plano S, Moore K, Lee SS, Durand F, Salerno F, Caraceni P, Kim WR, Arroyo V, Garcia-Tsao G: Diagnosis and management of acute kidney injury in patients with cirrhosis: Revised consensus recommendations of the International Club of Ascites [published corrections appears in J Hepatol 63: 290, 2015 10.1016/j.jhep.2015.04.001]. J Hepatol 62: 968–974, 2015 https://doi.org/10.1016/j.jhep.2014.12.029
3. Sort P, Navasa M, Arroyo V, Aldeguer X, Planas R, Ruiz-del-Arbol L, Castells L, Vargas V, Soriano G, Guevara M, Ginès P, Rodés J: Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. N Engl J Med 341: 403–409, 1999 https://doi.org/10.1056/NEJM199908053410306
4. China L, Freemantle N, Forrest E, Kallis Y, Ryder SD, Wright G, Portal AJ, Becares Salles N, Gilroy DW, O’Brien A; ATTIRE Trial Investigators: A randomized trial of albumin infusions in hospitalized patients with cirrhosis. N Engl J Med 384: 808–817, 2021 https://doi.org/10.1056/NEJMoa2022166
5. Wong F, Pappas SC, Curry MP, Reddy KR, Rubin RA, Porayko MK, Gonzalez SA, Mumtaz K, Lim N, Simonetto DA, Sharma P, Sanyal AJ, Mayo MJ, Frederick RT, Escalante S, Jamil K; CONFIRM Study Investigators: Terlipressin plus albumin for the treatment of type 1 hepatorenal syndrome. N Engl J Med 384: 818–828, 2021 https://doi.org/10.1056/NEJMoa2008290
6. Velez JCQ, Petkovich B, Karakala N, Huggins JT: Point-of-care echocardiography unveils misclassification of acute kidney injury as hepatorenal syndrome. Am J Nephrol 50: 204–211, 2019 https://doi.org/10.1159/000501299
7. Wong F, Angeli P: New diagnostic criteria and management of acute kidney injury. J Hepatol 66: 860–861, 2017 https://doi.org/10.1016/j.jhep.2016.10.024
8. Montano-Loza AJ, Duarte-Rojo A, Meza-Junco J, Baracos VE, Sawyer MB, Pang JX, Beaumont C, Esfandiari N, Myers RP: Inclusion of sarcopenia within MELD (MELD-sarcopenia) and the prediction of mortality in patients with cirrhosis. Clin

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
Transl Gastroenterol 6: e102, 2015 https://doi.org/10.1038/tg.2015.31
9. Sanssoe G, Ferrari A, Castellana CN, Bonardi L, Villa E, Manenti F: Cimetidine administration and tubular creatinine secretion in patients with compensated cirrhosis. *Clin Sci (Lond)* 102: 91–98, 2002 https://doi.org/10.1042/CS20010122
10. Daugherty NA, Hammonds KB, Osberg JM: Bilirubin interference with the kinetic Jaffé method for serum creatinine. *Clin Chem* 24: 392–393, 1978 https://doi.org/10.1093/clinchem/24.2.392
11. Gomaa SH, Shamsyaa MM, Madkour MA: Clinical utility of urinary neutrophil gelatinase-associated lipocalin and serum cystatin C in a cohort of liver cirrhosis patients with renal dysfunction: A challenge in the diagnosis of hepaticorenal syndrome. *Eu J Gastroenterol Hepatol* 31: 692–702, 2019 https://doi.org/10.1097/MEG.0000000000001347
12. Woitas RP, Stoefel-Wagner B, Flommersfeld S, Poege U, Schiedermaier P, Klehr HU, Spengler U, Bidlingmaier F, Sauerbruch T: Correlation of serum concentrations of cystatin C and creatinine to inulin clearance in liver cirrhosis. *Clin Chem* 46: 712–715, 2000 https://doi.org/10.1093/clinchem/46.5.712
13. Haji M, Jobali H, Mad A, Bieł V, Brahmi N, Kheder R, Beji S, Fatma LB, Smaoui W, Kriss M, Hmida FB, Rais L, Zouaghi MK: Nephrotoxicity of ciprofloxacin: Five cases and a review of the literature. *Drug Saf Case Rep* 5: 17, 2018 https://doi.org/10.1007/s40800-018-0073-4
14. Velez JCQ, Obadan NO, Kaushal A, Alzubaidi M, Bhasin B, Velez CR, Ohler H, Wandel E, Brunck B: Acanthocyturia – Another piece in the puzzle. *Clin Case Rep* 4: 139:1-142, 2018 https://doi.org/10.1002/ccr3.10487149
15. Rhee C, Klompas M: New sepis and septic shock definitions: Clinical implications and controversies. *Int Dis Clin North Am* 31: 397–413, 2017 https://doi.org/10.1016/j.idcn.2017.05.001
16. Waeedi HM, Geiger XJ, Cortese C, Mai ML, Kramer DJ, Rossor BG, Keaveny AP, Willingham DL, Ahsan N, Gonwa TA: Kidney allocation to liver transplant candidates with renal failure of undetermined etiology: Role of percutaneous renal biopsy. *Am J Transplant* 8: 2618–2626, 2008 https://doi.org/10.1111/j.1600-6143.2008.02426.x
17. Pichler RH, Huskey J, Kowalewska J, Moiz A, Perkins J, Davis CL, Lea N: Kidney biopsies may help predict renal function after liver transplantation. *Transplantation* 100: 2122–2128, 2016 https://doi.org/10.1097/TP.0000000000001334
18. Köhler H, Wandel E, Bunchk A: Acanthocyturia – A characteristic marker for glomerular bleeding. *Kidney Int* 40: 115–120, 1991 https://doi.org/10.1046/j.1523-1755.1991.f1.1008260608
19. Nguyen MT, Maynard SE, Kimmel PL: Misapplications of com-

20. Arroyo V, Gines P, Gerbes AL, Dudley FL, Gentilini P, Lafiti G, Reynolds TB, Ring-Larsen H, Schölmerich J: Definition and diagnostic criteria of refractory ascites and hepaticorenal syndrome in cirrhosis. *International Ascites Club*. *Hepatology* 23: 164–176, 1996 https://doi.org/10.1002/hep.1800230122
21. Salerno F, Gerbes A, Gines P, Wong F, Arroyo V: Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. *Cir* 56: 110–116, 2007
22. Alsaid AA, Waeedi HM: Fractional excretion of sodium in hepato-
ternal syndrome: Clinical and pathological correlation. *World J Hepatol* 8: 1497–1501, 2016 https://doi.org/10.4254/wjh.v8.i3.1497
23. Patidar KR, Kang L, Bajaj JS, Carl D, Sanyal AJ: Fractional excretion of urea: A simple tool for the differential diagnosis of acute kidney injury in cirrhosis. *Hepatology* 68: 224–233, 2018 https://doi.org/10.1002/hep.29772
24. Chawla LS, Dommu A, Berger A, Shih S, Patel SS: Urinary sedi-
ment cast scoring index for acute kidney injury: A pilot study. *Nephron Clin Pract* 110: c145–c150, 2008 https://doi.org/10.1159/0001166005
25. Perazella MA, Coca SG, Khanbay M, Brewer UC, Parikh CR: Diagnostic value of urine microscopy for differential diagnosis of acute kidney injury in hospitalized patients. *Clin J Am Soc Nephrol* 3: 1615–1619, 2008 https://doi.org/10.2215/CN.08266008
26. Allegretti AS, Ortiz G, Wenger J, Deferio JJ, Wibecan J, Kalim S, Tamez H, Chung RT, Kamurchi SA, Thadhani RI: Progno-
sis of acute kidney injury and hepatorenal syndrome in patients with cirrhosis: A prospective cohort study. *Int J Nephrol* 2015: 108139, 2015 https://doi.org/10.1155/2015/108139
27. Eknayan G: Letter: Renal disorders in hepatic dysfunction. *BMJ* 2: 670, 1974 https://doi.org/10.1136/bmj.2.5920.670-b
28. Poloni JAT, Perazella MA, Keitel E, Marroni CA, Leite SB, Rotta LN: Utility of a urine sediment score in hyperbilirubinemia/ hyperbilirubinuria. *Clin Nephrol* 92: 141–150, 2019 https://doi.

29. Shahvaran SA, Menyhért I, Cseh J, Ettori F, Cohen-Solal A, Mal H, Bernuau J, Marty J, Lebrec D, Valla D, Durand F: Diagnosis of portopulmonary hypertension in candidates for liver transplantation: A prospective study. *Hepatology* 37: 401–409, 2003 https://doi.org/10.1002/hep.20060
30. Krag A, Glud LL: Cross-talk between the liver, heart and kidney—Another piece in the puzzle. *J Gastroenterol Liver Dis* 23: 119–121, 2014 https://doi.org/10.15403/jgld.2014.1121.a1
31. Shahvaran SA, Menyhért I, Cseh J, Ettori F, Cohen-Solal A, Mal H, Bernuau J, Marty J, Lebrec D, Valla D, Durand F: Diagnosis and prevalence of cirrhotic cardiomyopathy: A systematic review and meta-analysis. *Curr Probl Cardiol* 46: 100821, 2021 https://doi.org/10.1016/j.cpcardiol.2021.100821
32. Premkumar M, Rangegowda D, Kajal K, Khumuckham JS: Non-invasive estimation of intravascular volume status in cirrhosis by dynamic size and collapsibility indices of the inferior vena cava using bedside echocardiography. *IJCH Open* 3: 322–328, 2019 https://doi.org/10.31703/jgld.2014.1121.ak1
33. Huelin P, Solé E, Elia C, Solé C, Risso A, Moreira R, Carol M, Fabrellas N, Bassegoda O, Juanola A, de Prada G, Albertos S, Plano S, Graupelone I, Ariza X, Napolitan E, Péladeau S, Moraes-Ruiz M, Kess F, Fernandez J, Jimenez W, Poch M, Torres F, Gines P: Neutrophil gelatinase-associated lipocalin for assessment of acute kidney injury in cirrhosis: A prospective study. *Hepatology* 70: 319–333, 2019 https://doi.org/10.1002/hep.30592
34. Puthuman J, Ariza X, Belcher JM, Graupela I, Ginés P, Parikh CR: Urine interleukin 18 and lipocalin 2 are biomarkers of acute tubular necrosis in patients with cirrhosis: A systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 15: 1003–1013.e3, 2017 https://doi.org/10.1016/j.chj.2016.11.035
35. Fagundes C, Pépin MN, Guevara M, Barreto R, Casals G, Soló E, Pereira C, Rodríguez E, García E, Prado V, Poch E, Jiménez W, Fernández J, Arroyo V, Ginés P: Urinary neutrophil gelatinase-associated lipocalin as biomarker in the differential diagnosis of impairment of kidney function in cirrhosis. *J Hepatol* 57: 267–273, 2012 https://doi.org/10.1016/j.jhep.2012.03.015
36. Hamdy HS, El-Ray A, Salaheldin M, Lasheen M, Aboul-Ezz M, Abdel-Moaty AS, Abdel-Rahim A: Urinary neutrophil gelatinase-associated lipocalin predicts mortality and identifies acute kidney injury in cirrhosis. *Dig Dis Sci* 57: 2362–2370, 2012 https://doi.org/10.1007/s10620-012-2180-x
69. Kwong A, Kim WR, Kwo PY, Wang U, Cheng X: Feasibility and effectiveness of norepinephrine outside the intensive care setting for treatment of hepatorenal syndrome. Liver Transpl 27: 1095–1105, 2021 https://doi.org/10.1002/hep.26065

70. Velez JC, Nietert PJ: Therapeutic response to vasoconstrictors in hepatorenal syndrome parallels increase in mean arterial pressure: A pooled analysis of clinical trials. Am J Kidney Dis 58: 928–938, 2011 https://doi.org/10.1053/j.ajkd.2011.07.017

71. Maddukuri G, Cai CX, Munigala S, Mohammadi F, Zhang Z: Targeting an early and substantial increase in mean arterial pressure is critical in the management of type I hepatorenal syndrome: A combined retrospective and pilot study. Dig Dis Sci 59: 471–481, 2014 https://doi.org/10.1007/s10620-013-2899-7

72. Cai CX, Maddukuri G, Jiaipaul N, Zhang Z: A treat-to-target concept to guide the medical management of hepatorenal syndrome. Dig Dis Sci 60: 1474–1481, 2015 https://doi.org/10.1007/s10620-014-3483-x

73. Ortega R, Gines P, Uriz J, Cardenas A, Calahorra B, De Las Heras D, Guevara M, Bataller R, Jimenez W, Arroyo V, Rodes J: Terlipressin therapy with and without albumin for patients with hepatorenal syndrome: Results of a prospective, non-randomized study. Hepatology 36: 941–948, 2002 https://doi.org/10.1053/hep.2002.35819

74. Nazar A, Pereira GH, Guevara M, Martin-Llaih M, Pepin MN, Marinelli M, Solà E, Baccaro ME, Terra C, Arroyo V, Gines P: Predictors of response to therapy with terlipressin and albumin in patients with cirrhosis and type 1 hepatorenal syndrome. Hepatology 51: 219–226, 2010 https://doi.org/10.1002/hep.23283

75. Wong F, Pantea L, Sniderman K: Midodrine, octreotide, albumin, and TIPS in selected patients with cirrhosis and type 1 hepatorenal syndrome. Hepatology 40: 55–64, 2004 https://doi.org/10.1002/hep.20262

76. Martin-Llaih M, Pepin MN, Guevara M, Diaz F, Torre A, Monescillo A, Soriano G, Terra C, Fabrega E, Arroyo V, Rodes J, Gines P; TAHRS Investigators: Terlipressin and albumin vs albumin in patients with cirrhosis and hepatorenal syndrome: A randomized study. Gastroenterology 134: 1352–1359, 2008 https://doi.org/10.1053/j.gastro.2008.02.024

77. Neri S, Pulvirenti D, Malaguarnera M, Cosimo BM, Bertino G, Ignaccio L, Siringo S, Castellino P: Terlipressin and albumin in patients with cirrhosis and type I hepatorenal syndrome. Dig Dis Sci 53: 830–835, 2008 https://doi.org/10.1007/s10620-007-9919-9

78. Srivastava S, Shalimar, Vishnubhatla S, Prakash S, Sharma H, Thakur B, Acharya SK: Randomized controlled trial comparing the efficacy of terlipressin and albumin with a combination of concurrent dopamine, furosemide, and albumin in hepatorenal syndrome. J Clin Exp Hepatol 5: 276–285, 2015 https://doi.org/10.1016/j.jceh.2015.08.003

79. Uriz J, Gines P, Cardenas A, Sor P, Jimenez W, Salmeron JM, Bataller R, Mas A, Navasa M, Arroyo V, Rodes J: Terlipressin plus albumin infusion: An effective and safe therapy of hepatorenal syndrome. J Hepatol 33: 43–48, 2000 https://doi.org/10.1016/S0168-8278(00)80158-0

80. Mulayk JP, Louis H, Doncker V, Bourgeois N, Adler M, Deviere J, Le Moine O: Long-term terlipressin administration improves renal function in cirrhotic patients with type 1 hepatorenal syndrome: A pilot study. Acta Gastroenterol Belg 64: 15–19, 2001

81. Saner F, Kavuk I, Lang H, Biglarnia R, Frühaufer NR, Schäfers RF, Malago M, Broelsch CE: Terlipressin and gelafundin: Safe therapy of hepatorenal syndrome. Eur J Med Res 9: 78–82, 2004

82. Muñoz LE, Alcalá EG, Cordero P, Martínez MA, Vázquez NY, Galindo S, Mendoza E, Segura JJ: Reversal of hepatorenal syndrome in cirrhotic patients with terlipressin plus albumin. First experience in Mexico. Ann Hepatol 8: 207–211, 2009 https://doi.org/10.1016/S1665-2681(19)31767-3

83. Narahara Y, Kanazawa H, Sakamoto C, Maruyama H, Yokosuka O, Mochida S, Uemura M, Fukui H, Sumino Y, Matsuzyaki Y, Masaki N, Kobuku S, Okita K: The efficacy and safety of terlipressin and albumin in patients with type 1 hepatorenal syndrome: A multicenter, open-label, explorative study. J Gastroenterol 47: 313–320, 2012 https://doi.org/10.1007/s00535-011-0485-8

84. Eisenman A, Armali Z, Etat R, Bankir L, Baruch Y: Low-dose vasopressin restores diuresis both in patients with hepatorenal syndrome and in anuric patients with end-stage heart failure. J Intern Med 246: 183–190, 1999 https://doi.org/10.1046/j.1365-2796.1999.0055.x

85. Gupta K, Rani P, Rohatgi A, Verma M, Handa S, Dalal K, Jain A: Noradrenaline for reverting hepatorenal syndrome. Acta Gastroenterol Belg 64: 15–19, 2001

86. Mulkay JP, Louis H, Doncker V, Bourgeois N, Adler M, Deviere J, Le Moine O: Long-term terlipressin administration improves renal function in cirrhotic patients with type 1 hepatorenal syndrome: A pilot study. Acta Gastroenterol Belg 64: 15–19, 2001

87. Saner F, Kavuk I, Lang H, Biglarnia R, Frühaufer NR, Schäfers RF, Malago M, Broelsch CE: Terlipressin and gelafundin: Safe therapy of hepatorenal syndrome. Eur J Med Res 9: 78–82, 2004

88. Muñoz LE, Alcalá EG, Cordero P, Martínez MA, Vázquez NY, Galindo S, Mendoza E, Segura JJ: Reversal of hepatorenal syndrome in cirrhotic patients with terlipressin plus albumin. First experience in Mexico. Ann Hepatol 8: 207–211, 2009 https://doi.org/10.1016/S1665-2681(19)31767-3

89. Narahara Y, Kanazawa H, Sakamoto C, Maruyama H, Yokosuka O, Mochida S, Uemura M, Fukui H, Sumino Y, Matsuzyaki Y, Masaki N, Kobuku S, Okita K: The efficacy and safety of terlipressin and albumin in patients with type 1 hepatorenal syndrome: A multicenter, open-label, explorative study. J Gastroenterol 47: 313–320, 2012 https://doi.org/10.1007/s00535-011-0485-8

90. Eisenman A, Armali Z, Etat R, Bankir L, Baruch Y: Low-dose vasopressin restores diuresis both in patients with hepatorenal syndrome and in anuric patients with end-stage heart failure. J Intern Med 246: 183–190, 1999 https://doi.org/10.1046/j.1365-2796.1999.0055.x

91. Gupta K, Rani P, Rohatgi A, Verma M, Handa S, Dalal K, Jain A: Noradrenaline for reverting hepatorenal syndrome: A prospective, observational, single-center study. Clin Exp Gastroenterol 11: 317–324, 2018 https://doi.org/10.2147/CEG.S153858

Received: October 18, 2021 Accepted: December 2, 2021