Hyponatremia and Hepatorenal Syndrome

Arpan Mohanty, MD, and Guadalupe Garcia-Tsao, MD

Dr Mohanty is a clinical fellow in the Section of Digestive Diseases at Yale University School of Medicine in New Haven, Connecticut and is affiliated with the Section of Digestive Diseases at the Veterans Administration–Connecticut Health Care System in West Haven, Connecticut. Dr Garcia-Tsao is a professor of medicine in the Section of Digestive Diseases at Yale University School of Medicine and is the chief of the Section of Digestive Diseases at the Veterans Administration–Connecticut Health Care System.

Address correspondence to:
Dr Guadalupe Garcia-Tsao
Section of Digestive Diseases
Yale University School of Medicine
One Gilbert Street, TAC, #S241-B
New Haven, CT 06510
Tel: 203-737-6063
Fax: 203-785-7273
E-mail: guadalupe.garcia-tsao@yale.edu

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Abstract: Hyponatremia and hepatorenal syndrome are severe complications in patients with cirrhosis and ascites resulting from circulatory abnormalities (splanchnic and systemic vasodilatation) that develop with portal hypertension. Both conditions are associated with an increased risk of death. Hyponatremia and renal failure may develop in patients with cirrhosis due to causes other than portal hypertension. Making an accurate differential diagnosis is important both therapeutically and prognostically. In this article, we discuss the pathophysiology, diagnosis, differential diagnosis, and management of hyponatremia and hepatorenal syndrome in patients with cirrhosis.

Hyponatremia and hepatorenal syndrome (HRS) are severe complications that occur in patients with cirrhosis and ascites and are associated with lower survival than in patients with decompensated cirrhosis (eg, those who have uncomplicated ascites, variceal hemorrhage, or encephalopathy).[1,2] Therefore, the development of these 2 complications represents a stage of further decompensation of cirrhosis.

Dilutional hyponatremia and HRS (a type of renal failure unique to patients with cirrhosis) represent manifestations of a continuum of pathophysiologic events stemming from portal hypertension and the resultant vasodilatation, which are the main mechanisms responsible for the development of ascites.[3] In a prospective inception cohort study of patients with cirrhosis and new-onset ascites who were followed for a mean of 41 months, hyponatremia developed in 28% of the patients, 11% developed refractory ascites, and 8% developed HRS, suggesting a sequential process (from ascites to hyponatremia to refractory ascites to HRS).[4] Each of these processes was associated with increasing severity of liver disease, worsening vasodilatation evidenced by decreasing mean arterial pressure (MAP), and more avid sodium retention.[3]

However, it is important to recognize that hyponatremia and renal failure in the patient with cirrhosis may result from conditions that occur in noncirrhotic patients and that result from pathophysiologic mechanisms different from worsening portal hypertension/

vasodilatation. Making an accurate differential diagnosis is important both prognostically and therapeutically. We therefore review the pathophysiology, diagnosis, differential diagnosis, and management of hyponatremia and HRS in patients with cirrhosis.

Pathophysiology of Hyponatremia and Hepatorenal Syndrome

Vasodilatation of both the splanchnic and systemic circulations is one of the main factors contributing to the development of hyponatremia and HRS in cirrhosis (Figure 1). Vasodilatation occurs after portal hypertension has led to the formation of portosystemic collaterals when factors that have not been well elucidated (vascular endothelial growth factor being one of them) trigger the production of nitric oxide and other vasodilators.[5,6] This vasodilatation leads to decreased effective arterial volume and activation of various vasoconstrictor and antinatriuretic neurohumoral systems (the renin-angiotensin-aldosterone system and sympathetic nervous system), leading to renal sodium and water retention and an increase in intravascular volume, which in turn leads to a hyperdynamic circulatory state.

In advanced stages of cirrhosis, progressive vasodilatation leads not only to avid sodium retention (with formation of ascites that is now refractory to diuretics) but also to the nonosmotic release of antidiuretic hormone or arginine vasopressin (AVP). The biological effects of AVP in increasing water reabsorption are mediated through G protein–coupled receptors, specifically vasopressin 2 (V2) receptors located on the basolateral membrane of principal cells of the collecting ducts. When activated by AVP, V2 receptors enable translocation of selective water channels called aquaporins from the cytosol to the luminal plasma membrane of the collecting ducts, increasing water permeability. This increase in water reabsorption exceeds that of sodium retention and leads to dilutional hyponatremia. V2 receptor antagonism has therefore been a potential target for drugs used in the treatment of this dilutional hyponatremia.

Progressive vasodilatation also leads to further activation of vasoconstrictive systems (mainly renin and angiotensin), resulting in renal vasoconstriction and decreased renal blood flow. In addition, a relative decrease in cardiac output in this high-output cardiac failure state (or cirrhotic cardiomyopathy) may further contribute to decreased renal blood flow.[5,7,8] This decrease in renal blood flow leads to a decreased glomerular filtration rate and a prerenal type of kidney injury (ie, HRS).

Hepatorenal physiology as described above may be present in many patients with advanced cirrhosis who may develop HRS without an obvious precipitating event. However, more often than not, HRS is precipitated by factors that cause either a decrease in effective arterial blood volume, such as rapid fluid loss (eg, excessive diuresis and gastrointestinal bleeding), or worsening vasodilatation induced by drugs (eg, nitrates, carvedilol, and angiotensin-converting enzyme inhibitors) or by a systemic inflammatory response (eg, infection).

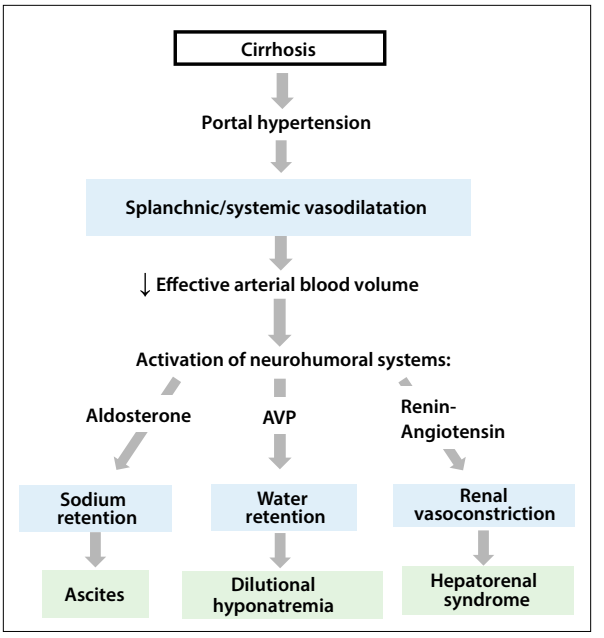

Figure 1. The pathophysiology of hyponatremia and hepatorenal syndrome (HRS) in cirrhosis. Cirrhosis and portal hypertension lead to the development of splanchnic and systemic vasodilatation that causes a decrease in effective circulatory volume, which in turn leads to the activation of various vasoconstrictor and antinatriuretic neurohumoral systems (renin-angiotensin-aldosterone system, sympathetic nervous system, and nonosmotic release of antidiuretic hormone). This initially leads to water and salt retention increasing intravascular volume and allowing for the continuous formation of ascites. However, with worsening cirrhosis (or with precipitant factors), splanchnic/systemic vasodilatation worsens, leading to a significant increase in antidiuretic hormone release and water retention (in excess of sodium retention) and, thereby, to dilutional hyponatremia. Maximal vasodilatation and activation of vasoconstrictive systems (renin-angiotensin) lead to renal vasoconstriction and the development of HRS.

AVP, arginine vasopressin.

Hyponatremia in Cirrhosis

Hyponatremia in cirrhosis has been arbitrarily defined as a serum sodium level of less than 130 mEq/L and is present in approximately one-fifth of patients with decompensated cirrhosis.[9] It is important to note that, although not meeting this definition, a serum sodium level of less

than 135 mEq/L in patients listed for liver transplantation has been associated with increased mortality, independent of Model for End-Stage Liver Disease (MELD) score.[1] In fact, the incorporation of serum sodium level into MELD (referred to as MELD-Na) has been shown to predict survival more accurately than MELD alone[10] and will likely be used soon instead of MELD for organ allocation in the United States.

Differential Diagnosis of Hyponatremia in Cirrhosis

Hyponatremia in cirrhosis may be (1) hypervolemic or dilutional as a result of water retention (in excess of sodium retention) due to AVP activation secondary to vasodilatation and decreased effective circulatory volume or (2) hypovolemic as a result of sodium and fluid losses (mainly overdiuresis). It is important to distinguish between hypervolemic and hypovolemic hyponatremia in order to provide appropriate management. As hypervolemic hyponatremia results from increased sodium and water retention, patients often have dependent edema and tense refractory ascites. The clinical hallmark of systemic vasodilatation is low MAP; patients with dilutional hyponatremia are therefore usually hypotensive and may have creatinine levels above baseline. On the other hand, in hypovolemic hyponatremia, patients are often dehydrated. They appear dry, with no ascites or edema.

Clinical Significance of Hyponatremia in Cirrhosis

Hyponatremia is associated with a significantly higher risk of death with cirrhosis. Kim and colleagues demonstrated serum sodium to be an important predictor of mortality, independent of MELD score among adult patients listed for liver transplantation.[1]

In patients with cirrhosis, hyponatremia has been noted to be an independent predictive factor for the development of hepatic encephalopathy.[11,12] An increase in ammonia and other neurotoxins along with a decrease in serum sodium are thought to act synergistically to cause a shift in the osmotic milieu of the brain, which results in cerebral edema and hepatic encephalopathy.[13] Gradual development of hyponatremia has been noted to be associated with myo-inositol and organic osmolytes in the brain as measured by magnetic resonance spectroscopy, probably as a compensatory mechanism to maintain cerebral fluid homeostasis.[11]

The presence of dilutional hyponatremia is associated with severe ascites, spontaneous bacterial peritonitis, and HRS.[9] As would be expected, patients with hyponatremia and ascites are also at high risk of having or developing HRS.[14]

Dilutional hyponatremia is associated with impaired health-related quality of life (HRQOL). In patients with cirrhosis and ascites, hyponatremia was found to be an independent predictor of decreased physical as well as mental component scores of the SF-36 questionnaire that assesses HRQOL.[15] A recent study of the effect of hyponatremia and hepatic encephalopathy on HRQOL demonstrated that patients with cirrhosis and hyponatremia but without hepatic encephalopathy have a poorer HRQOL as measured by the Sickness Impact Profile, despite better cognition, compared with those with concomitant encephalopathy.[16] Furthermore, in a prospective study, correction of hyponatremia was associated with improvement in cognitive function and HRQOL.[17]

Pretransplant hyponatremia is an independent predictor of short-term mortality after liver transplantation.[18,19] Rapid correction of hyponatremia in the postoperative period can result in central pontine demyelinolysis,[20,21] a lethal neurologic complication that can result in irreversible manifestations such as dysarthria, dysphagia, paraparesis, behavioral disturbances, and locked-in syndrome. Apart from neurologic complications, pretransplant hyponatremia has been associated with an increased risk of renal failure and bacterial infections in the first month posttransplantation.[18]

Management

Recognition of the type of hyponatremia (hypervolemic vs hypovolemic) is key in tailoring management. The easier type to treat is hypovolemic hypernatremia because removal of the precipitating factor (mainly diuretics) and administration of intravenous isotonic solutions to expand plasma volume often correct the abnormality.

On the other hand, treatment of hypervolemic hyponatremia is difficult and directed at decreasing excess free water in the circulation. Water restriction to 1 to 1.5 L/d is the current standard treatment for hypervolemic hyponatremia. However, patient compliance is very poor, and the resultant effect on serum sodium levels is modest. Potential therapeutic targets for the management of hypervolemic hyponatremia in cirrhosis are shown in Figure 2. These include increasing renal excretion of solute-free water, increasing the effective arterial blood volume, and ameliorating systemic and splanchnic vasodilatation.

Vaptans, or V2 receptor antagonists, are a class of drugs that increase renal excretion of solute-free water by blocking water reabsorption, leading to voluminous hypotonic urine output. A recent meta-analysis of randomized, controlled trials of vaptans (satavaptan, tolvaptan [Samsca, Otsuka], and lixivaptan) for hyponatremia in patients with cirrhosis, in which the primary outcome was death, showed a small transient beneficial effect on hyponatremia but no effect on mortality or renal failure.[22] The meta-analysis concluded that the data did not support the routine use of vaptans in cirrhosis. Tolvaptan is the only orally administered vaptan that is approved by the US Food and Drug Administration. Because signifi-

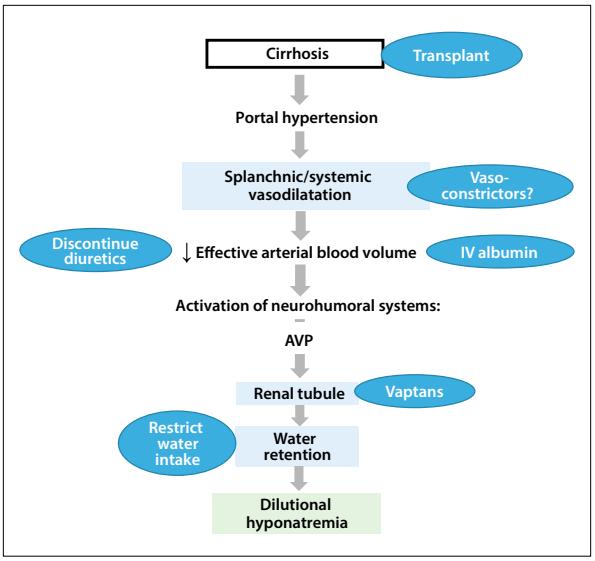

Figure 2. Potential therapeutic targets for the management of hyponatremia based on its pathophysiology.

AVP, arginine vasopressin; IV, intravenous.

cant elevations in liver enzymes have been observed with tolvaptan use in patients with autosomal dominant polycystic kidney disease, a black box warning was recently issued that precludes the use of this agent in patients with severe liver disease.[23]

Interventions to correct the decreased effective arterial blood volume in patients with hyponatremia include withdrawal of diuretics and use of intravenous albumin. Infusion of albumin in a very small number of patients was found to be useful in short-term, nonrandomized studies. However, the long-term benefit of albumin use remains unknown.[24]

Finally, the use of vasoconstrictors would be rational and, although they have not been tested specifically for hyponatremia, proof-of-concept and randomized, controlled trials of vasoconstrictors for HRS have shown that they are associated with increases in serum sodium levels.[25]

Hepatorenal Syndrome

Serum creatinine is an independent predictor of mortality in decompensated cirrhosis, such that it is a component of the MELD score, which is a robust predictor of 4-month mortality risk and, hence, is currently used for determining priority for orthotopic liver transplantation.[26] Renal dysfunction in cirrhosis is the organ failure with the highest prognostic impact in patients with acute-on-chronic liver failure.[27,28]

HRS is a type of prerenal kidney injury unique to patients with decompensated cirrhosis. As mentioned previously, HRS is functional renal failure resulting from renal vasoconstriction, which in turn is a result of extreme vasodilation in the splanchnic and systemic vascular beds. HRS is a state of effective hypovolemia associated with low MAP, relatively decreased cardiac output, and reduced systemic vascular resistance. There are 2 types of HRS: HRS-1 and HRS-2. HRS-1 is characterized by an abrupt deterioration in renal function (a form of acute kidney injury [AKI]), often precipitated by a bacterial infection such as spontaneous bacterial peritonitis. HRS-2 is a more chronic form of renal dysfunction (akin to chronic kidney disease [CKD]) that is often associated with refractory ascites. Patients with ascites have a 40% probability of developing HRS within 5 years.[14] Median survival associated with HRS-1 is shorter than with HRS-2 (1 month vs 6.7 months).[29]

Definition of Hepatorenal Syndrome

Per the International Club of Ascites consensus conference in 2007,[30] HRS is defined by a serum creatinine level of greater than 1.5 mg/dL (>133 µmol/L) and is established when there is no improvement in serum creatinine after 2 days of cessation of diuretics and adequate volume expansion with albumin in the presence of ascites and in the absence of shock, recent treatment with nephrotoxic drugs, or other parenchymal kidney diseases. Although this definition may apply to patients with HRS-2, AKI in cirrhosis has been redefined very recently, and that definition is expanded below.[31]

Hepatorenal Syndrome–1 (Acute Kidney Injury)

HRS-1 was defined by the International Club of Ascites as the doubling of initial serum creatinine concentration to a level greater than 2.5 mg/dL (>221 µmol/L) in less than 2 weeks. This criterion has been recently revised as a result of a consensus conference among members of the International Club of Ascites in 2012, taking into consideration that (1) the use of a creatinine cutoff of 1.5 mg/dL in patients with decompensated cirrhosis who are likely to have a low muscle mass and/or in a female patient with cirrhosis could already reflect markedly impaired kidney function and that (2) a time frame was necessary to distinguish between acute and chronic kidney injury.[31] Based on new definitions of AKI per nephrologic criteria from AKIN (Acute Kidney Injury Network),[32] RIFLE (Risk, Injury, Failure, Loss of Kidney Function, and End-Stage Kidney Disease),[33] and KDIGO (Kidney Disease: Improving Global Outcomes),[34] AKI in cirrhosis is now defined as follows: (1) an absolute increase in serum creatinine of at least 0.3 mg/dL (≥26.5 µmol/L) within 48 hours or (2) a percentage increase in serum creatinine of at least 50% from baseline that is known, or presumed, to have occurred within the prior 7 days. (If the baseline measurement is unavailable, a serum creatinine measure-

ment within the 3 months prior to admission can be considered as baseline.[31])

Previous studies in patients with cirrhosis in whom AKI was defined per similar AKIN criteria (an increase in serum creatinine of ≥0.3 mg/dL or ≥50% from baseline in <48 hours) showed that AKI in outpatients with cirrhosis[35] and hospitalized patients with cirrhosis[36] is associated with a high mortality rate even when serum creatinine levels are below the threshold of 1.5 mg/dL. Although the more advanced the stage of AKI, the higher the mortality rate, progression of kidney injury to higher AKIN stages is the strongest independent predictor of mortality in hospitalized patients with cirrhosis.[37] Therefore, establishing diagnosis of HRS at an earlier stage with more sensitive criteria will facilitate early diagnosis and intervention and potentially prevent progression to advanced stages.

Hepatorenal Syndrome–2 (Chronic Kidney Disease)

HRS-2 has not been as well characterized as HRS-1. HRS-2 is a functional type of CKD in which creatinine levels rise gradually. As such, it should probably be defined using the same criteria used in nephrology—that is, by a decrease in glomerular filtration rate (to <60 mL/min) for a duration of more than 3 months. It should be noted, however, that creatinine-based equations (eg, Modification of Diet in Renal Disease [MDRD]) perform poorly in patients with cirrhosis, particularly in those with decompensated cirrhosis.[38-40] Cystatin C–based equations perform better,[38,40] but, when not available, the MDRD-6 equation should be used.[39]

As nonalcoholic steatohepatitis is becoming a prominent cause of end-stage liver disease in patients with diabetes/metabolic syndrome, an increasing number of patients with cirrhosis will have structural CKD (eg, diabetic or hypertensive nephropathy), and they may then develop superimposed functional renal failure due to HRS physiology (acute-on-chronic kidney injury). These patients may not have the recognized characteristics of patients with pure HRS, as they may have high MAP, and the use of vasoconstrictors in this setting would require investigation.

Data on HRS-2 and on acute-on-chronic CKD in cirrhosis are scarce; therefore, the remainder of this article refers to HRS-1.

Differential Diagnosis of Hepatorenal Syndrome

HRS-1 is not the only type of AKI that can complicate the condition of patients with cirrhosis. Making an accurate differential diagnosis is key in determining the most appropriate management.

AKI occurs in approximately 20% of hospitalized patients with cirrhosis.[25] Approximately two-thirds of the cases are prerenal (ie, functional), of which the majority correspond to prerenal azotemia, while HRS constitutes only a small percentage of cases (<20% of total causes of AKI); one-third of the cases are intrarenal (ie, structural), most commonly acute tubular necrosis; and less than 1% are postrenal (obstructive). The main differential of AKI in cirrhosis consists of prerenal azotemia, acute tubular necrosis, and HRS. Prerenal azotemia is caused by hypovolemia (eg, aggressive diuresis, diarrhea, and/or gastrointestinal bleeding) or by other causes of decreased effective blood volume induced by infections or vasodilators. Prerenal azotemia responds to volume expansion, but vasoconstrictors and dialysis are not required. Acute tubular necrosis mostly occurs in patients presenting with shock or a history of exposure to nephrotoxins/contrast agents. Acute tubular necrosis is treated with renal replacement therapy if indicated, but volume should not be expanded. HRS is caused by extreme vasodilatation (with or without a precipitant) with consequent renal vasoconstriction and is treated with vasoconstrictors and volume expansion.

Diagnosis of Hepatorenal Syndrome HRS remains a diagnosis of exclusion. Therefore, the first step in its diagnosis is to exclude the presence of structural kidney injury (acute tubular necrosis, glomerulonephritis, and acute interstitial nephritis) or obstructive kidney injury (obstructive uropathy) and to distinguish between prerenal azotemia and HRS (the 2 functional types of AKI in cirrhosis).

This requires taking a careful clinical history to determine whether there is evidence of infection, overdiuresis, gastrointestinal hemorrhage, recent use of vasodilators or nephrotoxins (including nonsteroidal anti-inflammatory drugs), and/or large-volume paracentesis without the use of albumin. Evidence of systemic inflammatory response syndrome and evaluation of volume status during physical examination are important. The presence of traditional urine biomarkers (urine sediment, fractional excretion of sodium [FeNa], and urine albumin) should be assessed as well as a renal ultrasound to exclude postobstructive uropathy. Workup of infection is important in the presence of AKI in cirrhosis, independent of the cause of AKI.

Recent studies demonstrate the potential utility of urinary biomarkers in differentiating acute tubular necrosis from prerenal azotemia and HRS. Urinary neutrophil gelatinase–associated lipocalin, interleukin-18, liver-type fatty acid–binding protein, and urine albumin levels are highest in patients with acute tubular necrosis, lowest in patients with prerenal azotemia, and intermediate in those with HRS.[41-43] The larger the number of urine biomarkers that are above a predetermined threshold, the higher the likelihood of acute tubular necrosis.[43] Except for urine albumin, these biomarkers are not widely available in the United States. The cutoff for urine albumin that indicates the presence of acute tubular necrosis is 44 mg/dL or greater. FeNa at the usual cutoff of 1% is of no value in the differential diagnosis of AKI in cirrhosis

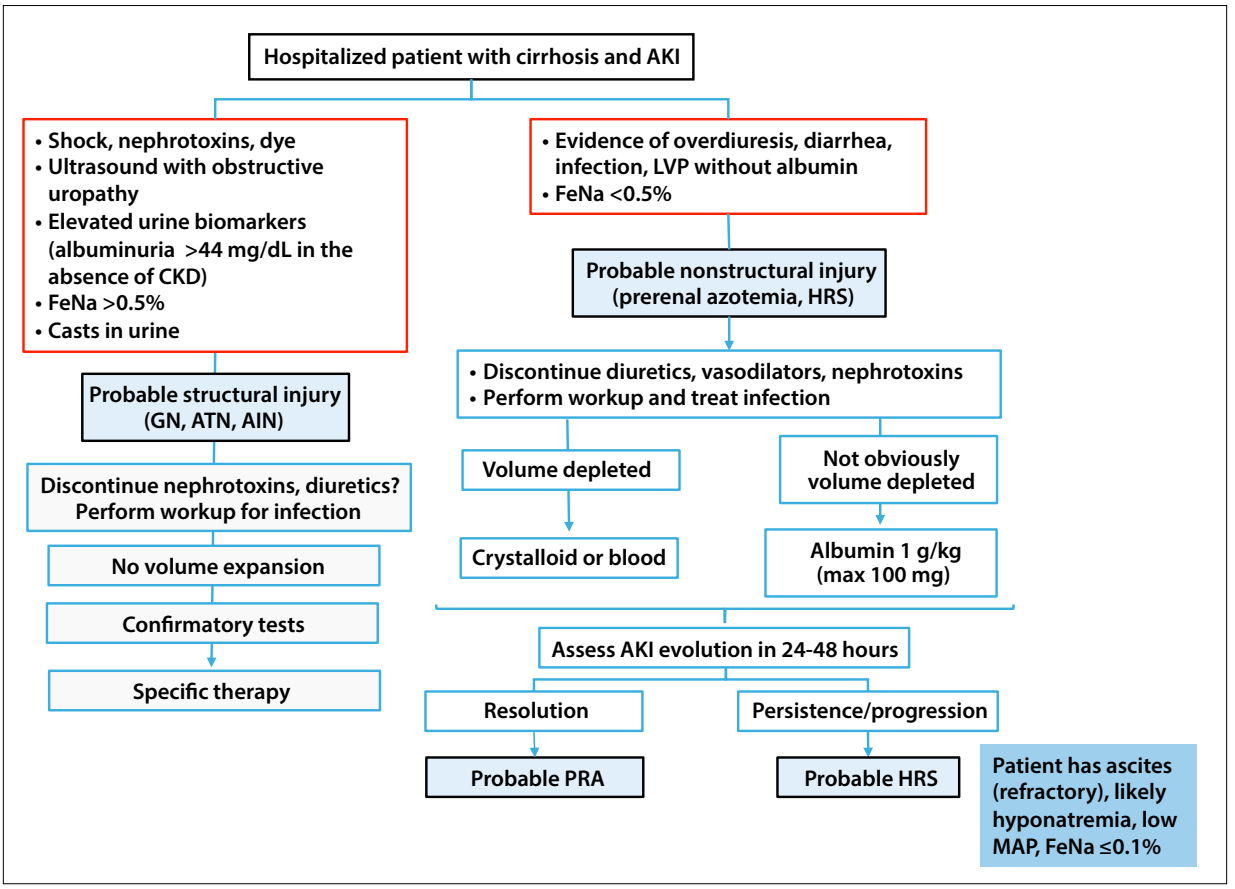

Figure 3. An approach to the hospitalized patient with cirrhosis and acute kidney injury (AKI).

AIN, acute interstitial nephritis; ATN, acute tubular necrosis; CKD, chronic kidney disease; FeNa, fractional excretion of sodium; GN, glomerulonephritis; HRS, hepatorenal syndrome; LVP, large-volume paracentesis; MAP, mean arterial pressure; PRA, plasma renin activity.

because practically all patients with cirrhosis and ascites have a FeNa of less than 1%. Interestingly, in a recent study, FeNa levels below 0.5% (particularly those <0.3%) were useful in identifying a prerenal cause of AKI, with levels at or below 0.1% identifying those with HRS.[43]

If there is evidence of structural injury—that is, if a patient presents with shock (septic or hemodynamic), has a history of exposure to nephrotoxins (including nonsteroidal anti-inflammatory drugs) or contrast dye, has casts present in urine, or has elevated urinary biomarkers (albuminuria >44 mg/dL in the absence of CKD) and a FeNA greater than 0.5%—or if there is evidence of obstructive uropathy on ultrasound, the patient should generally not be treated with volume expansion and should have confirmatory tests performed (including kidney biopsy if necessary) to establish the diagnosis and specific therapy. At times, the differential between acute tubular necrosis and HRS becomes difficult because, in advanced HRS, renal vasoconstriction may lead to tubular damage.

Although the same precipitants of prerenal azotemia (particularly those that worsen vasodilatation, such as infections) may also precipitate HRS, in prerenal azotemia treatment of the precipitant and volume expansion should lead to resolution of AKI. When the patient is clearly volume-depleted, volume expansion can be provided by intravenous saline solution (eg, for overdiuresis) or blood (eg, for gastrointestinal hemorrhage). If the patient does not appear volume-depleted and/or has evidence of systemic inflammatory response syndrome, the best volume expander is intravenous albumin at a recommended empiric dose of 1 g/kg of body weight per day (which could be divided into 2 doses), with a maximum dose of 100 g/d. Once volume expansion and antibiotics have been initiated (in those with suspected or confirmed infection), the course of AKI should be reevaluated in 24 to 48 hours. If the serum creatinine level has improved significantly or returned to baseline, therapy should continue, as this is likely to be prerenal azotemia. If the creatinine level has decreased only slightly, patient management should be individualized and may include repeating the AKI workup. If the creatinine level is unchanged or has worsened, the patient likely has HRS, and specific therapy can be initiated. It is important to note that at least

2 days of observation would have elapsed from the time of AKI diagnosis to the initiation of treatment for HRS.

It is also important to remark that patients with HRS have advanced liver disease (median Child-Pugh score, 11.2), low MAP (median MAP, 74 mmHg), low serum sodium (median serum sodium, 127 mEq/L), and ascites, commonly refractory to diuretics.[25] Additionally, and as mentioned previously, a FeNA of 0.1% or less is strongly suggestive of HRS.[43] Figure 3 delineates an approach to establish the most probable cause of AKI in a patient with cirrhosis.

Treatment of Hepatorenal Syndrome–1

Liver transplantation is the definitive treatment for HRS because it is the only therapeutic option associated with improved survival.[44-46] However, attaining reversal of HRS is important prior to transplantation, as pretransplant renal function is an independent predictor of short-term as well as long-term mortality and graft survival posttransplantation.[47] Patients with HRS treated with vasopressin have been noted to have posttransplant outcomes similar to those in patients without HRS undergoing transplantation. The American Association for the Study of Liver Diseases recommends that all patients with HRS have an expedited referral for liver transplantation.[48,49]

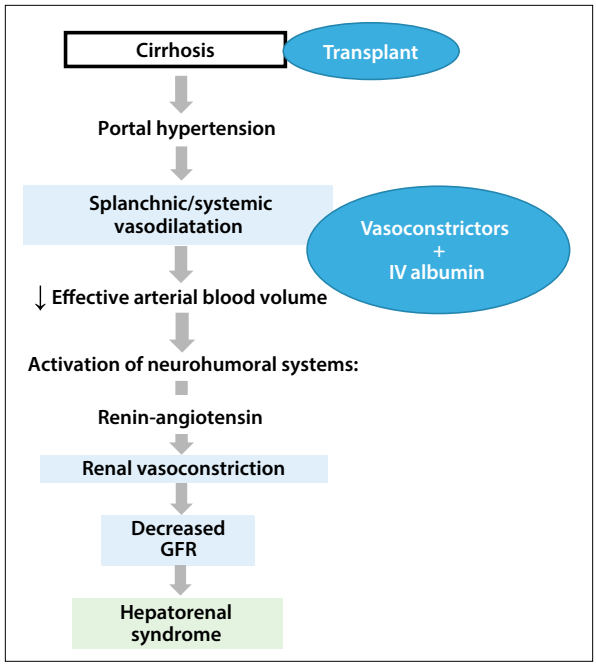

Figure 4. Management of hepatorenal syndrome based on reversing the main pathophysiologic mechanisms.

GFR, glomerular filtration rate; IV, intravenous.

Vasoconstrictors and Albumin Splanchnic and systemic vasodilatation and resultant renal vasoconstriction are the main mechanisms for development of HRS. Use of vasoconstrictors in HRS is aimed at ameliorating splanchnic and/or systemic vasodilatation, improving effective blood volume, and decreasing activation of renal vasoconstrictors, thus improving renal perfusion. Vasoconstrictors are used in conjunction with albumin in therapy for HRS. Albumin acts as a plasma expander and, by binding vasodilator substances such as nitric oxide and by improving cirrhotic cardiomyopathy, may provide a beneficial effect that goes beyond volume expansion.[50,51] Therefore, concomitant to vasopressor use, daily albumin infusions are recommended (1 g/kg on day 1, followed by 25-50 g/d).[25,52] Albumin should be discontinued if there is evidence of volume overload or if albumin concentration is greater than 3.5 g/dL.

Vasoconstrictors that have been used in patients with HRS include terlipressin, norepinephrine, octreotide plus midodrine, and vasopressin. In proof-of-concept studies, the use of these agents for more than 3 days has been associated with improvement in MAP, glomerular filtration rate, and serum sodium levels, with a decrease in plasma renin activity.[53-58] A systematic review assessing the effect of vasoconstrictor drugs in HRS on mortality demonstrated a lower risk of death with vasoconstrictor use as compared with using placebo or albumin (odds ratio, 0.82; 95% CI, 0.70-0.96).[59] Vasoconstrictors are often started at the lowest effective dose titrated to achieve a 10 to 15 mmHg increase in MAP. This is supported by a pooled analysis of 21 studies evaluating vasoconstrictor use in HRS that showed a strong association of increase in MAP with improvement in renal function.[60] Figure 4 outlines the management of HRS.

Terlipressin is a longer-acting vasopressin analogue with fewer side effects than vasopressin and is the vasoconstrictor for which there are more data regarding HRS. Randomized, controlled trials comparing terlipressin and albumin to placebo showed a higher rate of HRS reversal (defined in these studies as a decrease in serum creatinine level to <1.5 mg/dL) in the terlipressin group as compared with the control group (46% vs 11%; odds ratio, 3.76; 95% CI, 2.21-6.39).[59,61-64] In patients who respond to terlipressin with reversal of HRS, survival is greater than in control subjects.[61-64] Notably, reversal of HRS occurs in less than half of the treated patients with mortality that exceeds 50%.[53] Patients who respond to vasoconstrictors have significantly greater survival, and an important predictor of response is baseline creatinine level (with lower levels predicting a better response)[63]; therefore, therapy should be started soon after a diagnosis of HRS is established.

Terlipressin is administered at a dose of 1 mg every 4 hours.[65] If, after 3 days of therapy, creatinine levels have not decreased by 25%, then the terlipressin dose may be increased to 2 mg every 4 hours. If resolution of HRS is not observed after 10 days of therapy, use of terlipressin should be discontinued.[30,65] This treatment schedule

should probably be reevaluated and correlated to changes in MAP; that is, therapy should probably be discontinued sooner in patients who do not achieve a 10 to 15 mmHg increase in MAP after reaching maximal doses of vasoconstrictors. Because it is a potent vasoconstrictor, terlipressin has been associated with significant adverse events, including cardiac and intestinal ischemia, hypertension, and arrhythmias in up to 40% of patients.

Terlipressin is not yet available in the United States. However, there are alternatives. Two small randomized studies comparing terlipressin vs norepinephrine specifically in patients with HRS-1 have shown comparable effectiveness and side-effect profiles.[66,67] Norepinephrine is administered in a continuous infusion, typically in an intensive care setting. Norepinephrine is given in doses of 0.5 to 3 mg/h, and doses are titrated to achieve an increase in MAP of 10 mmHg or an increase in 4-hour urine output to more than 200 mL. The dose is increased every 4 hours to a maximum of 3 mg/h.[56,67]

Another alternative is the combination of octreotide and midodrine, which has the advantage of oral/subcutaneous administration, which can be given in non–intensive care settings, and has a good safety profile.[53] Octreotide is a long-acting somatostatin analogue that causes inhibition of the release of vasodilator hormones, resulting in decreased splanchnic vasodilation. Midodrine is an α_1-adrenergic agonist that causes systemic vasoconstriction, improving effective circulatory volume and, hence, renal perfusion. The use of midodrine alone or octreotide alone is not associated with improvement in renal function in HRS.[68,69] However, the combined use of midodrine and octreotide along with albumin has been shown to improve renal function, although randomized, controlled trials are lacking. Despite the lack of strong evidence, the combination of octreotide, midodrine, and albumin has been adopted as first-line therapy in countries where terlipressin is not available, such as the United States. Octreotide is administered in doses of 100 μg, subcutaneously, 3 times a day and can be increased to 200 μg 3 times a day. Midodrine is given in doses of 7.5 mg 3 times a day and can be increased up to 12.5 mg 3 times a day. Because this is a weak vasoconstrictor combination, if an improvement in MAP or creatinine level is not noted within 3 days after initiating midodrine and octreotide (during which the dose should be escalated rapidly), then the patient should be transferred to the intensive care unit for administration of norepinephrine or vasopressin infusion. Terlipressin is a vasopressin analogue, so vasopressin should be as effective as terlipressin. One retrospective study compared the use of vasopressin and octreotide for management of HRS and demonstrated higher recovery rates with the use of vasopressin.[70] Vasopressin is used as a continuous infusion, starting at a low dose of 0.01 U/min and titrating up to a maximum of 0.45 U/min with close monitoring of MAP, urine output, and ischemic side effects. All patients receiving vasoconstrictor therapies should be monitored for ischemic and cardiovascular complications. Vasoconstrictor therapies are not recommended in patients with preexisting ischemic heart disease, cerebrovascular disease, peripheral arterial disease, hypertension, or asthma.

Other Therapies Transjugular intrahepatic portosystemic shunt (TIPS) and extracorporeal albumin dialysis have been evaluated in small studies as alternative therapies for HRS. Three uncontrolled studies have demonstrated decreased serum creatinine levels with TIPS in selected patients with HRS, although these studies combined patients with HRS-1 and HRS-2.[71-73] Sequential treatment with vasoconstrictors and albumin followed by TIPS showed sustained long-term improvement in renal function after TIPS in patients who had responded to vasoconstrictor therapy.[71] Extracorporeal albumin dialysis is an investigational therapy directed at removing circulating factors that can cause vasodilatation. In one small, randomized, controlled trial, extracorporeal albumin dialysis was shown to reduce 30-day mortality in patients with HRS as compared with venovenous hemofiltration alone.[74] Given the limited data, TIPS and extracorporeal albumin dialysis are not recommended for HRS at this time.

Summary

Hyponatremia and HRS are severe and ominous complications in patients with decompensated cirrhosis. Early recognition and the initiation of appropriate therapy are keys to ensure reversal or even slowing of the process. Because patients with HRS are often very sick and require treatment in an intensive care unit, coordinated multidisciplinary care with hepatologists, the transplant team, nephrologists, and critical care specialists is necessary to successfully bridge these patients to liver transplantation.

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