Hepatorenal Syndrome and Hyponatremia

Guadalupe Garcia-Tsao, MD
Yale University School of Medicine
New Haven, CT

Key Concepts

- Hyponatremia and hepatorenal syndrome are complications that occur in patients with cirrhosis and ascites and represent a stage of “further” decompensation of cirrhosis.
- Worsened vasodilatation with consequent non-osmotic release of arginine-vasopressin and renal vasoconstriction are the main pathogenic mechanism for hyponatremia and hepatorenal syndrome, respectively.
- Both hyponatremia and hepatorenal syndrome portend a poor prognosis in the patient with cirrhosis and ascites.
- Main therapy of hyponatremia consists of AVP receptor antagonists.
- Main therapy of hepatorenal syndrome consists mainly of vasoconstrictors.
- Both therapies are considered “bridge” therapies to liver transplantation.

Hyponatremia and hepatorenal syndrome (HRS) are part of a spectrum of complications of the patient with cirrhosis and ascites [1] (Figure 1). Since they occur in the already decompensated patients, their development represents a stage of “further” decompensation of cirrhosis.

In a prospective inception cohort study of patients with cirrhosis that had first developed ascites and were followed for a mean of 41 months, hyponatremia developed in 28% of the patients, 11% developed refractory ascites, 8% developed HRS (5% HRS-2, 3% HRS-1), suggesting a sequential process (ascites —> hyponatremia —> refractory ascites —> HRS-2 —> HRS-1) [2]. At the time of development of each of these complications patients had progressively lower values of mean arterial pressure indicative of worsening vasodilatation, progressively lower urinary sodium excretion and progressively higher Child-Pugh and MELD (Model of Endstage Liver Disease) scores indicative of worsening liver function.

Pathophysiology

As shown in Figure 1, arterial vasodilatation (splanchnic and systemic) is the most likely mechanism leading to hyponatremia and HRS, and the severity of vasodilatation represents a continuum in the pathophysiology of ascites on one extreme, and HRS on the other extreme. Arterial vasodilatation occurs after portal hypertension and portosystemic collaterals have formed. It is thought to be the result of increased nitric oxide and probably other vasodilators (e.g. vascular endothelial growth factor or VEGF). Vasodilatation results in a reduction of the “effective” arterial blood volume, which in turn leads to stimulation of several neurohumoral systems, specifically the renin-angiotensin-aldosterone system (RAAS), the sympathetic nervous system, and the nonosmotic release of antidiuretic hormone (or arginine vasopressin; AVP). Activation of RAAS and the sympathetic...
nervous system results in sodium retention and, in extreme cases, in renal vasoconstriction. Increased levels of AVP influence the activation of vasopressin-2 (V2) receptors within the renal tubules. Renin/angiotensin lead to renal vasoconstriction. Additionally, a relative decrease in cardiac output seems to be a “second hit” that further decreases renal perfusion [3].

Hyponatremia

Hyponatremia in cirrhosis has been arbitrarily defined as serum sodium ≤ 130 mEq/L and occurs in 22% of patients with cirrhosis and ascites [4]. Hyponatremia has been found to be a predictor of death in patients waiting on the liver transplant list, independent of MELD [5] and has led to proposing the MELD-Na model to improve liver transplant assignment of priority.

Patients with cirrhosis can have two types of hyponatremia – hypovolemic hyponatremia and hypervolemic hyponatremia. Hypovolemic hyponatremia, a rare occurrence, is a consequence of fluid losses either from the kidneys (most commonly from iatrogenic overdiuresis) or from gastrointestinal tract losses (i.e. diarrhea). Patients are dehydrated, have no ascites or edema and may have prerenal azotemia. In contrast, the majority of patients with cirrhosis present with hypervolemic hyponatremia. Characterized by inappropriate water retention in excess of sodium retention, resulting in expanded extracellular volume and dilutional hyponatremia. The latter is the type that results from vasodilatation.

Patients with hypervolemic hyponatremia usually have ascites (often refractory to diuretics), with or without edema and may have concurrent kidney injury.

Patients with hypovolemic hyponatremia should be treated with withdrawal of diuretics and infusion of isotonic solutions. Treatment strategy for hypervolemic hyponatremia can be done at several pathophysiological levels: restriction of free water ingestion, increase of renal excretion of solute-free water, and ultimately, amelioration of systemic and splanchnic vasodilatation and the resultant decreased effective arterial blood volume that leads to free water retention (Figure 2).

Fluid restriction of one to 1.5 liters daily is currently recommended for severe hyponatremia; however, patient compliance is very poor and the resultant effect on serum sodium is modest at best.

Increasing renal excretion of free water is achieved by using vasopressin V2-receptor antagonists, the so-called “vaptans”. A recent meta-analysis of RCT of “vaptans” for hyponatremia in which the primary outcome was death, showed a small beneficial effect on hyponatremia, but no effect on mortality or renal failure [6]. The meta-analysis concluded that the data did not support the routine use of vaptans in cirrhosis. Satavaptan, the most studied vaptan, is not U.S FDA (Food and Drug Administration)-approved New Treatments in Liver Disease

Figure 1. Pathophysiology of ascites, hyponatremia and hepatorenal syndrome
and has been withdrawn in Europe. Tolvaptan, another vaptan, has been shown to have a transient beneficial effect on severe hyponatremia in patients with cirrhosis. Its use should probably be restricted to hospitalized patients with severe hyponatremia who are high on the list for liver transplantation. The U.S. FDA recently determined that tolvaptan should not be prescribed to patients with cirrhosis.

Therapies to correct the decreased effective arterial blood volume in patients with hyponatremia have been confined to the use of intravenous albumin. Infusion of albumin in a very small number of patients was found to be useful in short-term non-randomized studies [7]. However, the long-term benefit of albumin remains unknown.

Finally, the use of vasoconstrictors would be rational and, although they have not been specifically tested for hyponatremia, proof of concept and randomized controlled trials of vasoconstrictors for HRS have shown an improvement in hyponatremia [8].

**Hepatorenal Syndrome (HRS)**

Renal failure is a common complication in patients with cirrhosis and ascites and occurs in ~20% of hospitalized patients [8]. About two-thirds of the cases are pre-renal (a functional type of renal failure) while a third is intra-renal (a structural type of renal failure), most commonly acute tubular necrosis (ATN).

Patients with ascites are prone to develop prerenal (functional) failure because vasodilatation and a decrease in effective blood volume are already present and any factor that worsens either vasodilatation (infection, vasodilators, large-volume paracentesis without albumin) or effective volemia (overdiuresis, bleeding, diarrhea) will lead to vasoconstriction and renal failure.

HRS is a type of prerenal kidney injury unique to patients with cirrhosis and ascites due to extreme vasodilatation (with or without a precipitating factor) leading to maximal activation of vasoconstrictive substances that in turn cause renal vasoconstriction and decreased glomerular filtration rate (GFR). It is divided in two types: HRS-1 which is a form of acute kidney injury (AKI) and HRS-2 which is a form of chronic kidney injury. HRS-1 has a much poorer prognosis than HRS-2. Given its pathophysiology, most of the patients with HRS have refractory ascites and many have hyponatremia.

**Diagnosis**

The diagnosis of HRS is a diagnosis of exclusion and therefore it is difficult to establish. This difficulty begins with the definition of renal failure in these patients. The Ascites Club has defined renal failure as a creatinine level >1.5 mg/dL, with HRS-1 being defined as a doubling in serum creatinine to levels >2.5 mg/dL [9]. In patients with cirrhosis in whom baseline serum creatinine levels may be

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**Figure 2.** Site of action of different therapies for hyponatremia
very low given factors such as malnutrition and decreased synthesis these thresholds (and definitely the one for HRS-1) indicate severe renal dysfunction and carry not only important prognostic implications but even more important therapeutic implications as therapy would not be initiated until these thresholds are reached. Recent data obtained from outpatients [10] and from hospitalized patients with cirrhosis [11] indicate that even minor increases in serum creatinine (≥0.3 mg/dL or >50% from baseline) are clinically relevant and are associated with an increased mortality. Re-defining renal failure in cirrhosis using these criteria has been recently proposed [12].

In the chronic setting (HRS-2), when the rise in creatinine is gradual, measurements of GFR would be useful in establishing the degree and severity of chronic renal failure and the criteria used in nephrology (GFR <60 ml/min for over 3 months) could be used to establish the diagnosis. Recent studies have shown that the diagnostic performance of CKD-EPI creatinine-cystatin C equation in cirrhosis is superior to conventional equations to estimate GFR [13]. However, its diagnostic performance was worse in patients with ascites than in those without ascites and it was worse than reported in non-cirrhotic subjects [13].

In the acute setting, when the rise in creatinine is abrupt, GFR is in a non-steady state and GFR measurements are unreliable, the diagnosis would be solely based on changes in creatinine as recently defined. In this instance, and after excluding an intra-renal (structural) cause of AKI (e.g. ATN), the diagnosis of HRS-1 would be based on a lack of response to the treatment of precipitants of pre-renal AKI and a lack of response to expansion of the intravascular volume.

Unfortunately, the main differential is often between HRS-1 and ATN and, in the absence of validated markers of structural tubular injury, this differential is difficult to establish. Recent studies indicate that levels of urinary neutrophil gelatinase-associated lipocalin (uNGAL) in patients with HRS are intermediate between those with pre-renal azotemia (lowest levels as there is no tubular damage) and patients with ATN (highest levels as there is tubular damage) [14, 15]. This indicates that in some patients with HRS-1 there may be a component of tubular injury perhaps as a result of intense renal vasoconstriction [16].

**Management**

In patients with cirrhosis and ascites that develop AKI (abrupt rise in creatinine by >0.3 mg/dL or >50% from baseline), the first general measure is to investigate and treat possible precipitants. General measures include investigation (and treatment) of infection; discontinuation of any medication that can potentially induce volume depletion (e.g. diuretics, lactulose), discontinuation of any medication that can induce vasodilation (e.g. nitrates, angiotensin receptor blockers, phosphodiesterase inhibitors) or renal vasoconstriction (e.g. non-steroidal anti-inflammatory drugs) or that can cause nephrotoxicity (e.g. aminoglycosides). If the creatinine is greater than 1.5 mg/dL (indicating a more severe AKI), a bolus of saline solution can be considered, particularly if there is clear dehydration from overdiuresis or a dose of intravenous albumin can be administered.

In patients who do not respond to these measures after 2 days of observation, intravascular volume expansion with daily albumin should be performed. The recommended dose of albumin is 1 g/kg/day with a maximum of 100 g/day [9].

In patients in whom ATN is most likely, i.e. those admitted with shock (septic or hypovolemic) or those with a history of exposure to nephrotoxins/contrast agents or those with urine studies showing granular or epithelial casts (not definitive), management should be that of ATN and renal replacement therapy should be performed if clinically indicated.

HRS-1 is most likely in patients without evidence of intra-renal AKI, who have not responded to general measures described above or to intravascular expansion with albumin (after at least two days). In these patients, splanchic and/or systemic vasoconstrictors (terlipressin, norepinephrine, octreotide plus midodrine, vasopressin) are the therapy of choice at the route and doses shown in Table 1.

The bulk of evidence supports the use of terlipressin with HRS-1 reversal rates in the order of 50% and with a reduced mortality [25]. Terlipressin is considered first-line medical therapy for HRS-1 in Europe but is not yet available in the United States. Therefore, in the U.S., the combination octreotide/midodrine is considered the initial

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<td>Vasoconstrictors*</td>
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<td>+ Octreotide[21]</td>
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*All associated with daily intravenous albumin
therapy given its safety and non-ICU management. The dose of octreotide/midodrine is titrated to obtain a 15 mmHg increase in mean arterial pressure (MAP) [21]. This is rational as an increase in MAP is an indirect indicator of a desired vasoconstrictive effect. In fact, in a recent meta-analysis of vasoconstrictors in HRS, a very significant indirect correlation was found between changes in MAP and changes in serum creatinine [26]. If a MAP or creatinine response is not observed with maximal doses of octreotide/midodrine, as often occurs given a weaker vasoconstrictive effect of this combination, the patient should be transferred to the ICU for norepinephrine infusion.

Vasoconstrictor therapy is maintained for a maximum of 15 days and is associated with daily albumin infusion. With any of these vasoconstrictors, patients should be closely monitored for the development of ischemic complications (cardiovascular, intestinal, etc).

Data on vasoconstrictors in the treatment of HRS-2 is scarce. Some of the studies using different vasoconstrictors have included patients with HRS-2 and have shown reversal rates in about two thirds of the patients but with a high recurrence rate (~90%) once vasoconstrictors are discontinued. Long-term therapy with vasoconstrictors is not practical (or cost-effective) and is not recommended. Since patients with HRS-2 usually have refractory ascites and since TIPS has been shown to improve renal function, TIPS placement should be considered in selected patients with HRS-2.

Liver transplantation is the only definitive treatment for HRS, however important issues regarding changes in MELD score with therapy that will affect organ allocation and the appropriate use of liver/kidney transplant need to be addressed as reviewed recently [27].

**References**


