

## REVIEW

# Managing Hyponatremia in Cirrhosis

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The development of hyponatremia represents an ominous event in the progression of cirrhosis to end-stage liver disease. It usually develops in those with refractory ascites and is a manifestation of the non-osmotic release of arginine vasopressin (AVP). In the hospitalized cirrhotic patient, hyponatremia is associated with increased disease severity and mortality. In this article, we review the pathophysiology of hyponatremia, its clinical implications, evaluation, and treatment. *Journal of Hospital Medicine* 2010;5:S8–S17. © 2010 Society of Hospital Medicine.

**KEYWORDS:** hyponatremia, common electrolyte disorder, cirrhosis, portal hypertension, cirrhosis, liver failure.

The serum sodium (Na) level is the major determinant of serum osmolality. In normal physiologic states is tightly regulated between 135 mEq/L to 145 mEq/L despite variable intake of water and solute through the interaction of osmoreceptors in the hypothalamus where arginine vasopressin (AVP) is synthesized and then released by the posterior pituitary and the binding of AVP with V2 AVP receptors on the basolateral surface of the principal cells within the collecting duct of the kidney. Binding of AVP to the V2 receptors promotes the translocation and fusion of cytoplasmic vesicles which carry the water channel protein aquaporin 2 (AQP2) to the apical membrane of the cell and, in this manner, increases water permeability and absorption.<sup>1,2,3</sup>

Patients with hyponatremia, defined by a serum Na level <135 mEq/L, can be broadly classified by their volume status into those who are euvolemic, hypervolemic, and hypovolemic (Table 1). In patients with euvolemic hyponatremia such as those with Syndrome of Inappropriate Antidiuretic Hormone (SIADH), total body Na is nearly normal, but total body water is increased. In patients with hypervolemic hyponatremia, both total body Na and water are increased, but water to a much greater degree. These patients typically have increased extracellular fluid such as edema and/or ascites. The most common conditions associated with this condition are cirrhosis, congestive heart failure (CHF), and renal failure. In contrast, hypovolemic hyponatremia is associated with a reduction in both total body Na and water, but Na to a greater degree. This condition is encountered in patients with excessive fluid losses such as those with overdiuresis, excessive gastrointestinal losses, burns, and pancreatitis.<sup>4</sup>

Hyponatremia is the most common electrolyte abnormality seen in general hospital patients.<sup>5</sup> In a database of over 120,000 patients, a serum sodium level of <136mEq/L was observed in 28.2%.<sup>6</sup> Hyponatremia is associated with selected medical conditions (especially cirrhosis and CHF),

the extremes of age, and those receiving selected medications, including several that are commonly administered to cirrhotic patients (diuretics, selective serotonin reuptake inhibitors, opiates, proton-pump inhibitors).<sup>7,8</sup> Hyponatremia is associated with increased total costs per hospital admission.<sup>5,9</sup> In an analysis of the effect of hyponatremia on length of stay in a retrospective cohort study of hospitalized patients derived from a large administrative database of 198,281 discharges from 39 US hospitals, mean length of stay was significantly greater among patients with hyponatremia than those with normal Na levels ( $8.6 \pm 8.0$  vs.  $7.2 \pm 8.2$  days). After adjusting for confounders that may be associated with more severe disease and hyponatremia (age, gender, race, geographic region, teaching status of the hospital, admission source, principal payer, comorbidity index score and primary diagnosis), the presence of hyponatremia contributed an increase in length of stay of 1.0 day. Patients with hyponatremia are more frequently admitted to the intensive care unit (ICU) and require mechanical ventilation. In patients with CHF, the presence of hyponatremia at discharge is associated with increased risk for early mortality and rehospitalization.<sup>10</sup>

Although frequently asymptomatic, hyponatremia may be associated with a range of findings, from subtle and non-specific complaints, including headache, fatigue, confusion, malaise, to severe and life-threatening manifestations with lethargy, seizures, brainstem herniation, respiratory arrest and death.<sup>11</sup> The most important complications are neurologic consequences related to cerebral edema. However, there is increased morbidity even in hyponatremic patients considered to be asymptomatic. Patients with low serum sodium have attention deficits, and falls are common. In a study of 122 patients who were considered to have chronic "asymptomatic hyponatremia," the incidence of falls was significantly higher at 21.3% compared to only 5.3% in a control population.<sup>12</sup>

**TABLE 1. Classification of Hyponatremia: Sodium and Water Changes in the 3 Different Types of Hyponatremia**

	Dilutional Hyponatremia		
	Euvolemic	Hypervolemic	Depletional Hyponatremia
Total body water	↑	↑↑	↓
Total body Na	normal	↑	↓↓
Common etiologies	SIADH	cirrhosis/CHF	vomiting, diarrhea

In hyponatremia, water enters into the cells to attain osmotic balance, resulting in cellular swelling.<sup>4</sup> To avoid cerebral edema, the brain is capable of adapting to hyponatremia by regulating its volume to avoid swelling, especially when hyponatremia is chronic. In acute hyponatremia, astrocytes and neurons adapt through osmoregulatory mechanisms by extruding intracellular electrolytes such as potassium.<sup>13</sup> Chronically, adaption occurs through the loss of low-molecular weight organic compounds termed organic osmolytes including myoinositol, glutamine, choline and taurine. As a result, both the severity and the rate of its development are critical factors in determining the neurologic manifestation of hyponatremia in a given patient.<sup>14</sup>

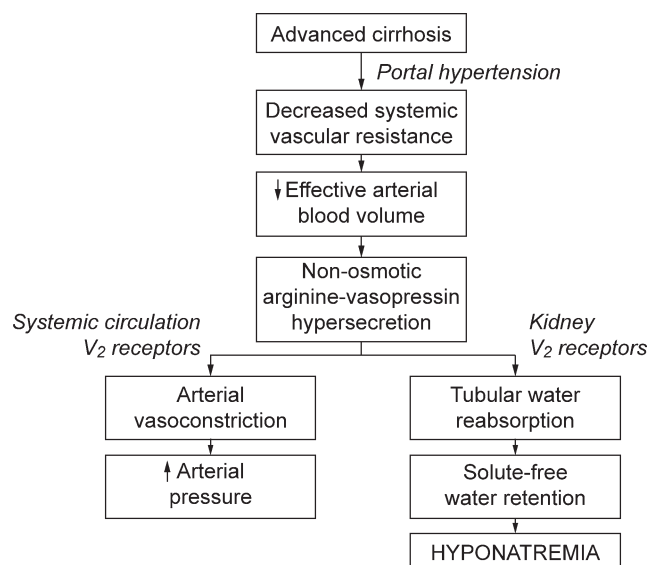
### Dilutional Hyponatremia and Cirrhosis

Patients with hyponatremia who are either euvolemic or hypervolemic are considered to have dilutional hyponatremia (DH). Management of these patients is distinct from those who are hypovolemic in whom appropriate therapy consists of the administration of normal saline. The remainder of this article addresses the pathogenesis, management and treatment of cirrhotic patients with DH.

### Pathogenesis

The development of hyponatremia in cirrhosis is intimately related to the pathophysiology of portal hypertension and the non-osmotic release of AVP<sup>3,15</sup> (Figure 1). In the early phases of cirrhosis, portal hypertension is the result of an increase in intrahepatic resistance. With the development of porto-systemic collaterals, a hyperdynamic splanchnic circulation develops as a result of splanchnic arterial vasodilation and increased vascular capacity. Nitric oxide, an endothelial derived relaxing factor, is the critical mediator of this process, and upregulation of its expression is pivotal in the pathogenesis of portal hypertension.

Multiple factors are related to the development of DH in cirrhosis. A reduction of effective central blood volume due to the development of porto-venous collaterals and arterial splanchnic vasodilation, leading to baroreceptor-mediated nonosmotic release of AVP, is considered the initiating and most important factor. Patients with cirrhosis and DH have higher plasma and urine vasopressin levels, higher plasma renin activity, and decreased plasma levels of atrial natriuretic factor than those with normal serum sodium concen-



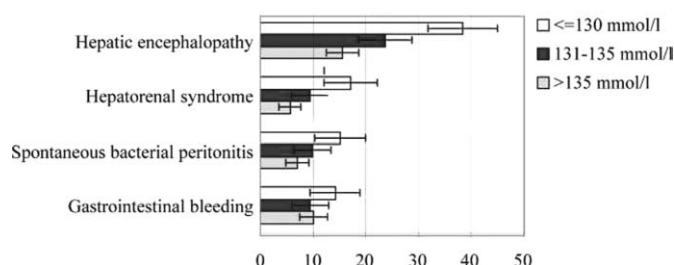
**FIGURE 1.** Proposed mechanism of hypersecretion and renal and systemic effects of vasopressin in cirrhosis with ascites. Gines P, Guevara M. Hyponatremia in cirrhosis: pathogenesis, clinical significance, and management. *Hepatology*. 2008;48:1002–1010. Copyright 2008 John Wiley & Sons, Inc. Reprinted with permission of John Wiley & Sons, Inc.

trations, findings consistent with the presence of a decreased effective plasma volume.<sup>16</sup> Arterial underfilling is sensed by baroreceptors located in the left ventricle, aortic arch, carotid sinus and renal afferent arterioles. Decreased activation leads to neurohumoral compensatory responses which include non-osmotic release of vasopressin from the neurohypophysis and increased levels. Impaired catabolism of AVP that has been correlated with the severity of liver dysfunction may further contribute to increased levels.<sup>17</sup> Initially, the increased AVP maintains arterial circulatory integrity by inducing splanchnic, peripheral and renal arterial vasoconstriction through its action on the V1a receptors and expansion of blood volume through renal water retention by its action on the V2 receptors located on the collecting ducts.

The initial adaptive response which leads to increased central blood volume can chronically result in detrimental effects, including the development of fluid overload with ascites, edema, and hyponatremia.<sup>16,18</sup> Additional factors that contribute to hyponatremia include decreased glomerular filtration rate (GFR) and/or increased proximal reabsorption of sodium (that reduce the distal delivery of filtrate and the potential for water reabsorption) and decreased cardiac function that further impairs effective central blood volume.<sup>19</sup> In addition, urinary levels of AQP2 are increased in cirrhotic patients, especially those with decompensated disease with higher Child-Pugh scores and ascites, and provide another potential mechanism to increase water reabsorption.<sup>20</sup>

### Prevalence and Prognostic Significance

Hyponatremia in cirrhosis is a common finding. In a survey of 997 cirrhotic patients with ascites from 28 centers in



**FIGURE 2.** Percentage of patients with complications of cirrhosis classified according to serum sodium concentration. Angeli P, Wong F, Watson H, et al. Hyponatremia in cirrhosis: results of a patient population survey. *Hepatology*. 2006; 44:1535–1542. Copyright 2006 John Wiley & Sons, Inc. Reprinted with permission of John Wiley & Sons, Inc.

Europe, North and South America, the prevalence of serum sodium concentration  $\leq 135$ , 130, 125, 120 meq/L were 49.4%, 21.6%, 5.7%, and 1.2%, respectively.<sup>21</sup> In a retrospective analysis of 188 inpatients, the prevalence of DH of  $\leq 135$ ,  $\leq 130$ , and  $\leq 125$  were 20.8%, 14.9%, and 12.2%, respectively.<sup>22</sup> The development of hyponatremia is a manifestation of increasing portal hypertension. In a natural history study of 263 patients hospitalized for first episode of significant ascites, 74 patients developed DH (Na level  $< 130$  mEq/L), including 11 patients in whom it appeared during the first episode and 63 cases during follow-up (mean period of  $40 \pm 3$  months) with a 5-year incidence of 37.1%.<sup>23</sup>

The presence of hyponatremia carries significant adverse prognostic significance. It is strongly associated with severity of liver function impairment as assessed by Child-Pugh and model for end-stage liver disease (MELD) scores.<sup>22</sup> Even mild hyponatremia is associated with severe complications such as massive ascites, severe hepatic encephalopathy, spontaneous bacterial peritonitis (SBP), and hepatic hydrothorax, and the severity of hyponatremia is directly related to the severity of these complications.<sup>21,22</sup> (Figure 2). In a natural history study of patients presenting with large volume ascites, 1-year survival after its development was reduced to only 25.6%.<sup>23</sup>

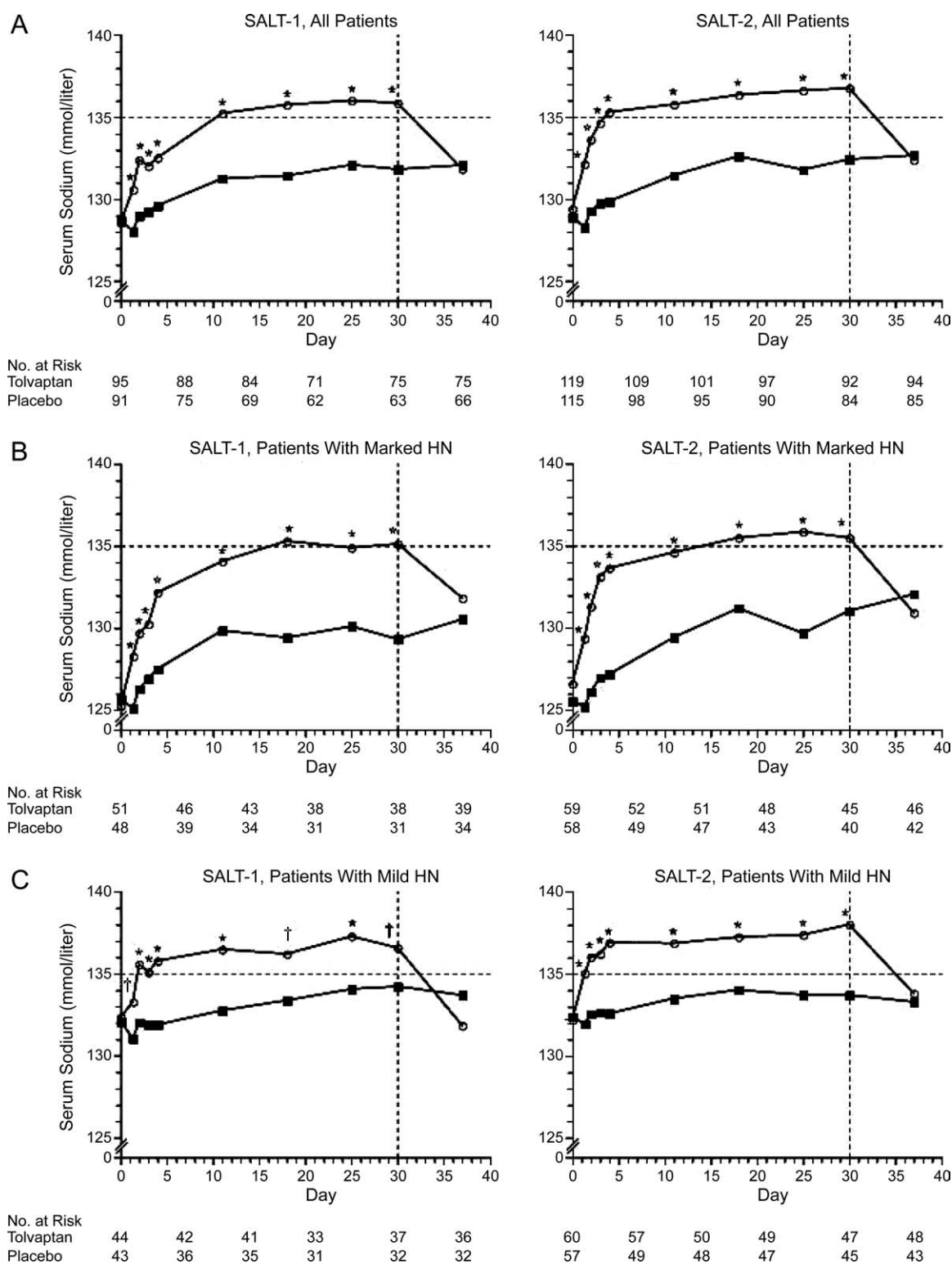
Hyponatremia is an especially poor prognostic sign for a hospitalized cirrhotic patient. In a retrospective analysis of 156 cirrhotic patients, hyponatremia—present in 57 (29.8%) of admissions—was associated with increased hospital mortality (26.3% vs. 8.9% among those with normal Na levels), and the mortality rate was even higher (48%) among the 25 patients who developed severe hyponatremia during the hospital stay.<sup>24</sup> In hospitalized patients, hyponatremia is predictive of the development of acute renal failure (73% vs. 13%).<sup>25</sup> Similarly, a low serum sodium level in critically ill cirrhotic patients admitted to the ICU is associated with complications, in-hospital mortality, and poor short-term prognosis.<sup>26</sup>

Whether hyponatremia should impact liver transplant prioritization remains an area of controversy. The United Network for Organ Sharing (UNOS) contracted by the Organ Procurement and Transplant Network (OPTN) to optimize the efficient use of deceased organs through fair and timely allocation, currently uses the MELD score, a formula that calculates the risk of death within three months from the bilirubin, creatinine, and International Normalized Ratio (INR) levels. Hyponatremia is an earlier and more sensitive marker than serum creatinine to detect renal impairment and/or circulatory dysfunction in patients with advanced cirrhosis and adds to MELD in predicting waitlist mortality.<sup>27–29</sup> In patients with a MELD score of  $< 21$ , only low serum sodium and persistent ascites are independent predictors of mortality.<sup>28</sup> To account for the importance of hyponatremia on survival, both modification of the MELD score in which the Na level is incorporated (MELD-Na model) and the MELD to serum sodium ratio (MESO) have been developed. Adding hyponatremia to the MELD score is a better predictor of death than MELD alone, particularly in patients with low MELD scores.<sup>27,29–31</sup> The OPTN/UNOS Liver and Intestinal Organ Transplantation Committee has discussed updating the liver allocation system to include the Na level. However, it was concluded that implementation of MELD-Na would change the allocation status of only 4% of candidates. Further, based on the concerns about the ability to manipulate serum sodium levels and the utility of employing resources to change the system for a relatively small number of patients, it was decided to defer incorporating the Na level pending further analysis (Report of the OPTN/UNOS Liver and Intestinal Organ Transplantation Committee To the Board of Directors, Los Angeles, California, September 17–18, 2007). At this time, the use of Na is a regional decision.<sup>32</sup> However, the OPTN/UNOS Liver and Intestinal Organ Transplantation Committee has recently solicited feedback from the transplant community about including Na in allocation for review at a forum in April 2010.

### Precipitating Factors

The most important factor related to development of hyponatremia in cirrhosis is increasing severity of portal hypertension that is associated with impaired central blood volume as a result of progressive splanchnic vasodilatation. In a study in which 170 patients with decompensated alcoholic cirrhosis were prospectively followed for  $33.9 \pm 27.9$  months, the initial hepatic venous pressure gradient (HVPG) was an independent predictive factor for the 20 patients who developed hyponatremia.<sup>22</sup>

Cirrhotic patients with ascites with hyponatremia have increased AVP secretion, higher levels of plasma renin activity, and higher serum concentrations of aldosterone and norepinephrine compared to those with normal Na levels.<sup>33</sup> Diuretic therapy is associated with the development of DH by inducing volume depletion and arterial underfilling,



**FIGURE 3.** Mean serum sodium concentrations according to the day of patient visit in the SALT-1 and SALT-2 trials. Schrier RW, Gheorghiade M, Berl T, et al. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. *N Engl J Med.* 2006;355:2099–2112. Copyright 2006 Massachusetts Medical Society. All rights reserved. Asterisks indicate  $P < 0.001$  for the comparison between tolvpaptan and placebo treated patients. Daggers indicate  $P < 0.01$  for the comparison between tolvpaptan and placebo. Tolvpaptan was discontinued on day 30. Circles denote patients receiving tolvpaptan, and squares denote patients receiving placebo. Horizontal lines indicate the lower limit of the normal range for the serum sodium concentration. Vertical lines indicate the end of the treatment period. HN denotes hyponatremia. Abbreviation: SALT-1/SALT-2, Study of Ascending Levels of Tolvaptan in Hyponatremia 1 and 2.



further activating the renin-angiotensin system (RAS) and increasing the non-osmotic release of AVP.<sup>34</sup> Although diuretics block the salt retention associated with the RAS activation, the water-retaining effects of AVP persist, and DH develops. The process is further exacerbated by a low sodium intake and a frequent uncontrollable thirst. As a result, diuretic therapy is commonly associated with the development of hyponatremia in patients with ascites.<sup>24,35</sup> Similarly, paracentesis (particularly when performed without albumin) is often associated with an increase in blood urea nitrogen and marked elevations in plasma renin activity and plasma aldosterone concentration, which may exacerbate this physiology, leading to further reduction in serum sodium concentration.<sup>36</sup> Tense ascites can contribute to DH by increasing baroreceptor mediated AVP release by increasing intrathoracic pressure.<sup>37</sup> Finally, non-steroidal anti-inflammatory drugs (NSAIDs) can cause DH by inhibiting the synthesis of renal prostaglandins (which normally function to antagonize the tubular action of AVP and are important in the maintenance of appropriate renal tubular transport of fluid and electrolytes in states of renal hypoperfusion).<sup>38</sup>

### **Medical Impact of Hyponatremia: Marker of Severe Disease or Direct Pathophysiologic Role?**

Hyponatremia is associated with severe ascites, impaired renal function, hepatic encephalopathy, SBP, and hepatorenal syndrome.<sup>3,20</sup> Because hyponatremia is frequently present in advanced liver failure, it is unclear whether it is only a marker of advanced disease or whether it plays a direct pathophysiologic role, or both. Until recently, it has not been possible to address this issue due to the inability to easily and rapidly correct the hyponatremia. However, there is increasing evidence that hyponatremia has direct impact on the severity of hepatic encephalopathy (see Hepatic Encephalopathy section). The recent introduction of tolvaptan for the treatment of hyponatremia in cirrhosis (discussed below) will allow this question to be directly answered.

### **Fluid Management and Diuresis**

The typical cirrhotic patient with DH is characterized by expanded extracellular fluid with ascites and edema. The profound vasodilation of the splanchnic arterial circulation is associated with decreased effective arterial blood volume, leading to the non-osmotic release of AVP. Diuretic therapy can further exacerbate this process. In addition, the increased water permeability induced by AVP results in reduced urine volume and fluid retention. As a result, hyponatremia directly adversely affects severity of fluid overload and limits and/or precludes diuretic treatment.

### **Hepatorenal Syndrome**

Hyponatremia is an earlier and more sensitive marker than serum creatinine to detect renal impairment and/or circulatory dysfunction and is frequently a precursor to overt hepatorenal syndrome.<sup>27</sup> Hyponatremia is predictive of the de-

velopment of acute renal failure during hospitalization, and in-hospital development of acute renal failure portends a high mortality.<sup>25</sup> In patients admitted with SBP, the presence of hyponatremia is significantly associated with higher mortality and renal failure.<sup>39</sup>

### **Hepatic Encephalopathy**

The neurologic manifestations of cerebral edema associated with hyponatremia closely mirror those of hepatic encephalopathy. In fact, a recently proposed pathogenic mechanism for hepatic encephalopathy is the development of low-grade cerebral edema associated with astrocyte swelling in response to ammonia and other precipitating factors.<sup>40</sup> DH is associated with a further reduction in brain organic osmolytes that probably reflects a compensatory osmoregulatory mechanism against cell swelling triggered by a combination of high intracellular glutamine and low extracellular osmolality.<sup>41</sup> As a result, it has been proposed that hyponatremia contributes to the development of hepatic encephalopathy through the development or exacerbation of low-grade cerebral edema. In this manner, low serum sodium acts as a “second hit” to the swelling produced by increased intracellular glutamine created by ammonia metabolism.<sup>42</sup>

Clinically, hyponatremia is a major risk factor for hepatic encephalopathy. Serum sodium and ammonia levels are the major factors that predict electroencephalographic abnormalities in cirrhotics who do not have hepatic encephalopathy.<sup>43</sup> In a prospective study of 61 patients, hyponatremia was associated with a low brain concentration of organic osmolytes as assessed by proton magnetic resonance spectroscopy (1H-MRS) and magnetic resonance imaging, and both conditions were major risk factors for the development of overt hepatic encephalopathy.<sup>44</sup> Finally, hyponatremia is a risk factor for hepatic encephalopathy in patients undergoing TIPS.<sup>45</sup>

### **Adverse Effect on Outcome After Liver Transplantation**

Hyponatremia before liver transplantation is associated with adverse post-transplant outcomes. Among patients undergoing liver transplantation, the presence of hyponatremia is associated with abnormal cardiac response in patients after reperfusion.<sup>46</sup> Pre-transplant hyponatremia is associated with longer ICU and hospital stay, higher rates of delirium and neurologic disorders, acute renal failure, acute cellular rejection, infection, and in one study a reduced 3-month survival compared to normonatremic recipients.<sup>32,47,48</sup> In 1 retrospective study that compared post-transplant outcomes of patients with corrected vs. uncorrected pre-transplant hyponatremia, patients with pre-operative correction of hyponatremia had a lower risk of prolonged post-transplant hospitalization than those with uncorrected hyponatremia.<sup>32</sup> However, both hyponatremic groups had more complicated post-transplant courses compared to those without a history of hyponatremia. However, given the small sample size, retrospective design, and the potential for confounding, the

impact of correction of pre-transplant hyponatremia remains to be determined.

## Management

Most patients with mild hypervolemic hyponatremia are asymptomatic. The initial recommended approach is fluid restriction and an Na-restricted diet. For those with severe or progressive hyponatremia, diuretics should be minimized or discontinued to avoid intravascular volume depletion.<sup>49</sup> For patients with tense ascites and severe DH, therapeutic paracentesis with plasma expanders is safe.<sup>33</sup> Unfortunately, fluid restriction is limited in efficacy and often poorly tolerated. The use of hypertonic saline is generally not recommended unless severe neurologic symptoms are present as it leads to increased ascites and edema. When administered, it is important to avoid a rapid correction of the hyponatremia to prevent the development of central pontine myelinolysis and the osmotic demyelination syndrome.

Due to the pivotal role of AVP in the pathogenesis of DH, antagonism of its action has long been proposed to be the most rational approach, but until recently, effective and specific antagonism of AVP has remained elusive. Approaches that have been attempted include interference with its secretion and actions. Intravenous albumin has been reported to improve hyponatremia in patients with cirrhosis, ascites, and hyponatremia, presumably by decreasing AVP release by plasma volume expansion.<sup>50</sup> An attempt at inhibition of central AVP release with the use of a kappa-opioid receptor agonist, niravoline, was limited by loss of efficacy and potential adverse effects.<sup>51</sup> Use of demeclocycline and lithium (which induce renal resistance to AVP and lead to a modest increase in urine volume with decreased urine osmolality and a corresponding rise in serum sodium) is limited by nephrotoxicity and hepatotoxicity.<sup>7,52</sup> Because of the important role played by prostaglandins in the maintenance of renal hemodynamics and water excretion in cirrhosis, oral misoprostol has also been evaluated but determined to be ineffective in inducing significant changes in free water clearance in patients with functional renal failure and/or DH.<sup>53</sup>

The recent introduction of vaptans, vasopressin receptor antagonists that block the physiologic action of vasopressin, represents a revolutionary and highly effective approach to the treatment of hyponatremia. Vaptans are antagonists of the V2 receptors of AVP in the principal cells of the collecting ducts. In healthy subjects, vaptans cause a dose-dependent increase in urine volume and produce a dilute urine without causing natriuresis. To date, 2 AVP antagonists, conivaptan and tolvaptan, have been Food and Drug Administration (FDA)-approved for the treatment of DH. Conivaptan, the first to be approved in 2005, is a mixed vasopressin V1a and V2 receptor antagonist that is administered intravenously for up to 4 days. In a randomized placebo-controlled study of patients with euvolemic or hypervolemic hyponatremia, intravenous conivaptan treatment increased serum Na levels by >6 mEq/L or to a serum Na >135 mEq/L in 69 to 88.5% of subjects com-

pared to 20.7% of those receiving placebo (Zeltser D, Rosansky S, Van Rensburg H, et al. Assessment of the efficacy and safety of intravenous conivaptan in euvolemic and hypervolemic hyponatremia. *American J Nephrology* 2007;27:447–457). In a pilot study involving 24 patients with end-stage liver disease, an infusion of conivaptan over 1 to 4 days was associated with an increase of serum sodium by >5 mmol/L in 60% of patients not receiving diuretics and 67% of patients on concomitant diuretic therapy by the end of treatment (O'Leary and Davis, 2009). Despite a concern about the potential for conivaptan to increase portal hypertension due to inhibition of splanchnic V1a receptors, the brief treatment appeared to be well tolerated without significant changes in systolic blood pressure, serum creatinine, variceal bleeding or worsening of ascites during the infusion period. However, approval for only 4 days of therapy and requirement for intravenous use eliminate any potential for chronic use.<sup>54</sup>

Tolvaptan is an orally available, selective V2 receptor antagonist whose efficacy was assessed in two multicenter, prospective, randomized, placebo-controlled trials, Study of Ascending Levels of Tolvaptan in Hyponatremia 1 and 2 (SALT-1 and SALT-2).<sup>55</sup> In these trials, clinically stable patients with DH (Na <135 meq/L) associated with cirrhosis (22.4% in SALT-1, 30.5% in SALT-2), CHF or SIADH were randomized in a hospital setting to receive tolvaptan 15 mg daily or placebo. Repeat Na levels were obtained at 8 hours, 2, 3, and 4 days and then weekly at days 11, 18, 25 and 30 after which study drug was discontinued and follow-up Na level was determined 7 days later. The dose was adjusted to 30 mg and then 60 mg in an attempt to achieve a Na level >135 in those in whom hyponatremia persisted. During the initial day of the titration phase, fluid restriction was not maintained, and the patients were encouraged to respond to thirst with increased water ingestion.

Tolvaptan use was associated with a prompt increase in Na level as early as 8 hours after administration of the first dose. Serum Na increased more among those receiving tolvaptan than among those receiving placebo during the first 4 days and throughout the study period regardless of baseline Na level but returned to baseline within 1 week after discontinuation (Figure 3). The main side effects were increased thirst, dry mouth and increased urination. Importantly, an increased incidence of renal failure was not observed. Based on these results, FDA approval for tolvaptan in patients with hyponatremia was obtained in May 2009 for patients with DH-associated with cirrhosis, CHF or SIADH for patients with Na levels <125 or symptomatic patients with Na levels between 125 and 135 that have not responded to fluid restriction.

## Management of the Hospitalized Cirrhotic Patient With Hyponatremia: Recommendations

Hyponatremia in hospitalized cirrhotic patients is a marker for severe disease and high risk of hospital mortality.<sup>24</sup> As a result, prompt evaluation and treatment is imperative. The

**TABLE 2. Patient Selection for Tolvaptan Therapy for Hospitalized Patients With Cirrhosis and Hyponatremia**

Hospital setting
Euvolemia or hypervolemia
Absence of recent weight loss, decrease in ascites, edema
Absence of excessive vomiting, diarrhea
Consider discontinuation of diuretic therapy prior to initiation of tolvaptan
Consider evaluation after limited volume expansion, especially with salt poor albumin prior to initiation of tolvaptan
Presence of clinically significant hyponatremia: 125mEq/L or less severe but symptomatic hyponatremia (125 to 134 mEq/L) that has resisted fluid restriction
Absence of severe neurologic symptoms attributable to hyponatremia
No co-administration with intravenous saline
Ability to respond to thirst
No co-administration with strong CYP 3A inhibitors (ketoconazole)
Absence of kidney failure with anuria

availability of tolvaptan potentially revolutionizes the manner in which these patients are treated. In the SALT trials, only clinically stable patients were enrolled. In this last section, a guideline for the evaluation and treatment of acutely ill, hospitalized cirrhotic patients with DH is presented.

### Evaluation

Determination of volume status is paramount but frequently problematic in the hospitalized cirrhotic patient. Due to the vasodilated state present in severe portal hypertension that is characterized by a relative hypotension and resting tachycardia, the usual hemodynamic parameters of blood pressure and heart rate can be difficult to interpret. Although significant extravascular volume in the form of ascites and edema may be present, patients may be intravascularly depleted due to previous diuretic use and extra-renal losses due to impaired oral intake, vomiting, lactulose-induced diarrhea, and gastrointestinal bleeding. Infection is a commonly associated condition, and endotoxin mediated splanchnic vasodilatation, especially in the setting of SBP, can adversely affect central blood volume status in the presence of severe ascites. Also, due to the Na avidity of the kidney and previous diuretic use, renal electrolytes can be difficult to interpret.

For patients in whom there is strong clinical concern about intravascular depletion (history of impaired oral intake, excessive vomiting and/or diarrhea, rapid weight loss, small volume ascites with history of large volume, azotemia), administration of limited intravenous normal saline (0.5-1 L) should be considered. Patients with severe neurologic symptoms should receive normal saline or hypertonic saline. Unless severe neurologic symptoms associated with profound hyponatremia is present, however, intravenous normal saline should not be administered for the hyponatremia alone. Administration of salt poor albumin (25%), especially for those with marked fluid overload and ascites, is an effective means to expand the central blood volume without exacerbating ascites and edema. After evaluation for and/or treatment of hypovolemia, all patients

should receive a Na restricted diet (<2000 mg daily) and placed on fluid restriction (see below for liberalization of fluid restriction upon initiation of tolvaptan therapy).

Diagnostic paracentesis should be performed for those with ascites to rule out the presence of SBP, and antibiotics administered to those with evidence of infection. High dose intravenous salt poor albumin should also be administered, especially to those at high risk of renal failure as determined by the presence of azotemia (Cr > 1.0 mg/dL) or severe liver insufficiency (TBili > 4.0 mg/dL).<sup>56,57</sup> Finally, all medications should be reviewed, and those associated with hyponatremia (diuretics, selective serotonin reuptake inhibitors, opiates, proton-pump inhibitors) discontinued if possible.

### Tolvaptan for DH Patient Selection

Appropriate patient selection for tolvaptan therapy is extremely important (Table 2). In the SALT trials, only clinically stable patients were enrolled. The presence of hyponatremia in a recently hospitalized cirrhotic patient, however, frequently indicates severe disease with a high risk of acute renal failure and hospital death. In the SALT trials, many received concomitant diuretic therapy. Because of the importance of avoiding tolvaptan administration to hypovolemic patients, discontinuation of diuretic therapy prior to the initiation of tolvaptan therapy and/or reevaluation after limited volume expansion should be considered.

Tolvaptan is indicated for cirrhotic patients with DH in whom the serum sodium is <125 mEq/L and in those with less severe but symptomatic hyponatremia (125-134 mEq/L) that has resisted fluid restriction. Although the definition of "symptomatic" was not specifically defined, possible considerations include symptoms of mild hepatic encephalopathy or inability to tolerate diuresis due to the presence of hyponatremia. According to FDA guidelines, tolvaptan therapy must be initiated and re-initiated in a hospital setting. Patients with severe neurologic symptoms attributable to hyponatremia in whom rapid treatment is critical should not receive tolvaptan but should rather be treated with normal saline. Similarly, patients should not receive combination therapy with tolvaptan and normal saline due to potential for a too-rapid correction of hyponatremia and the development of central pontine myelinolysis. If saline had been administered for treatment of possible hypovolemia, it should be discontinued and persistent hyponatremia confirmed before starting tolvaptan. Other factors that need to be considered before initiating tolvaptan include the ability of the patient to respond to thirst with increased water ingestion and recognition that the patient will experience increased urine volume and frequency, requiring easy access to toilet. Patients should not be fluid restricted during the first day of tolvaptan therapy, but should be instructed to respond to their thirst with increased water ingestion. As a result, caution should be exercised in administering tolvaptan to a confused, restrained,

unresponsive and/or bed-bound patient who is not able to respond appropriately to thirst or increased urination.

In the SALT trials, the incidence of hyperkalemia (5%) was similar in the tolvaptan and placebo treated patients.<sup>55</sup> However, further analysis of all multiple-dose, placebo-controlled trials, demonstrated that the aggregate incidence of hyperkalemia was slightly higher for tolvaptan-treated subjects compared with placebo-treated subjects (Otsuka). Because treatment with tolvaptan is associated with an acute reduction of the extracellular fluid volume which could result in increased serum potassium through hemoconcentration, it is recommended that serum potassium levels be monitored after initiation of tolvaptan treatment in patients with a serum potassium > 5 mEq/L as well as those who are receiving drugs known to increase serum potassium levels such as angiotensin converting enzyme inhibitors, angiotensin receptor blockers, or potassium sparing diuretics (Samsca Package Insert, Otsuka). Because tolvaptan is metabolized by the cytochrome P 3A system, patients receiving strong inhibitors such as ketoconazole should not receive tolvaptan. Anuric patients will not respond to tolvaptan. Finally, it is extremely important to administer tolvaptan only to patients with true hyponatremia and not to those with pseudohyponatremia in whom the plasma osmolality is normal but the measured serum sodium concentration artificially low due to marked elevations of other substances, such as can be seen in severe hyperglycemia, marked hyperlipidemia, or hyperproteinemia (as in multiple myeloma).

### ***Tolvaptan Administration***

The initial dose of tolvaptan is 15 mg daily. After receiving tolvaptan, many patients will develop an increased sense of thirst and need to urinate. As a result, patients should not be fluid restricted during the first day of therapy, and it is important to monitor the hemodynamics and Na level closely after initiating therapy with a repeat Na level at approximately 8 hours after the first dose. As a result, it should probably be administered early in the day and not at bedtime. The dose should be increased to 30 mg, then 60 mg in patients who do not respond by at least 5 mEq/L over the previous 24 hours and remain hyponatremic. In those with an excessive response (more than 8 meq/L during the first 8 hours or 12 meq/L on any subsequent day), the patient should be encouraged to either drink more water, or the dose should be held or reduced. After the appropriate dose has been identified, the patient may be discharged and continued on tolvaptan long-term.

With the advent of this exciting therapy, practical issues will need to be addressed, most important of which is its cost at \$250 per day (Otsuka). In addition, the current recommendation to initiate tolvaptan only in a hospital further limits its widespread use. Most important, long-term clinical benefit will need to be demonstrated. Although the SALT trials only involved treatment for up to 1 month, a multicen-

ter, open-label extension study for a mean duration of 701 days demonstrated that prolonged administration of tolvaptan maintains an increased serum sodium level.<sup>58</sup> However, at this time, tolvaptan can only be considered as one of the promising drugs whose long-term cost-effectiveness is yet to be proven. Proof will require showing that correction of the hyponatremia leads to improved clinical outcomes, such as a reduction in length of stay or frequency of hospitalization, decreased renal failure, improved hepatic encephalopathy, decreased mortality, and improved post-transplant outcomes.

### **Unanswered Questions**

The vaptans provide an important opportunity to clarify the role that hyponatremia plays in the pathogenesis of cirrhosis. In the past, DH in a cirrhotic patient represented a sign of advanced disease. With the availability of safe and effective therapy, we can now determine whether it also plays an important role in the pathophysiology of end-stage liver disease and whether its treatment will have a beneficial effect on patient outcomes.

Specific clinical questions that will inevitably be addressed over the next few years to determine whether DH is only a marker for advanced disease or whether it plays a direct but modifiable role in the pathophysiology of cirrhosis will include:

1. Role of vaptans in the management of ascites: In a 14-day randomized, trial of a satavaptan, another selective vasopressin V(2) receptor antagonist, vs. placebo with spironolactone, combination therapy was associated with improved control of ascites and improvements in serum sodium levels in hyponatremic patients with ascites.<sup>59</sup> If future similar studies demonstrate more prolonged benefits, this would constitute an important advance in the treatment of ascites in cirrhosis.
2. Effect on renal function: Prolonged use of tolvaptan leads to a compensatory increase in endogenous levels of AVP and, potentially, increased stimulation of V1a receptors, which might be helpful in the setting of portal hypertension. In patients with hepatorenal syndrome, vasopressin stimulation of splanchnic V1a receptors leads to improved renal function, presumably by decreasing splanchnic blood flow and improving central blood volume.<sup>60</sup> As a result, tolvaptan may indirectly improve kidney function in patients with advanced cirrhosis and refractory ascites. Whether long-term tolvaptan therapy will help to prevent hepatorenal syndrome through this mechanism remains to be determined but is an exciting possibility.<sup>61</sup>
3. Effect on hepatic encephalopathy: Hepatic encephalopathy is associated with poor quality of life in patients with cirrhosis. Although hepatic encephalopathy was not directly assessed in the SALT trials, the mean mental component summary of the Short Form General Health Survey, a quality of life measure, improved in cirrhotic



patients receiving tolvaptan to a greater degree than those receiving placebo.<sup>62</sup> A possible explanation for this finding is a beneficial effect of tolvaptan on hepatic encephalopathy. Confirmation of this hypothesis, however, will require prospective studies in which hepatic encephalopathy is directly assessed.

4. Effect on medical economics: Based on retrospective reviews, hyponatremia has an adverse impact on length of stay and outcomes following liver transplantation. It will be important to demonstrate in prospective studies that correction of hyponatremia with tolvaptan reduces length of stay, complications, and costs.

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