Pathophysiology, Impact, and Management of Hyponatremia

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Hyponatremia’s effects can be insidious, particularly in patients with heart failure, cirrhosis, and pneumonia. Appreciating its prevalence in hospitalized patients, recognizing its symptoms, characterizing its etiology, and employing appropriate management promptly will help reduce morbidity and mortality among hyponatremic patients. Journal of Hospital Medicine 2012;7:S1–S5 © 2012 Society of Hospital Medicine

The high prevalence of hyponatremia in hospitalized patients has been recognized for decades. Published reports dating back to the 1960s indicate that serum sodium concentrations ([Na⁺]) tend to be lower in hospitalized patients than in outpatients in the community. Current estimates for the prevalence of hyponatremia in hospitalized patients range from 15% to nearly 40%. Several factors account for this wide range. While most studies estimate the presence of hyponatremia based on International Classification of Diseases, Ninth Revision (ICD-9) codes, accurate reporting varies widely from institution to institution. Furthermore, the definition of hyponatremia depends entirely on the cut-off value of [Na⁺] used (generally, <136 mEq/L). In addition to patients who have hyponatremia present on admission, a significant proportion develop the condition during their hospital stay. Deficits in water excretion can develop or worsen during hospitalization as a result of several factors, combined with intake of hypotonic fluid. In a study of hyponatremia in intensive care unit (ICU) patients, as many as 80% demonstrated impaired urinary dilution during their ICU course.

The prevalence of hyponatremia is significant in patients hospitalized for heart failure (HF), cirrhosis, and pneumonia. The prevalence of hyponatremia—defined as serum sodium <135 mEq/L—ranges from 18% to 25% in patients admitted for congestive heart failure. Rates of hyponatremia in patients admitted with cirrhosis are even higher on average, ranging between 18% and 49%. Hyponatremia is also common in patients with community-acquired pneumonia (CAP), with prevalence estimates ranging from 8% to 28%.

Overall, hyponatremia in each of these disease states portends worse outcome. In a retrospective study of 71 adults with pneumonia, admission serum [Na⁺] <135 mEq/L was a risk factor for in-hospital mortality. In each of these conditions, hyponatremia is associated with the need for ICU care and mechanical ventilation, increased hospital length of stay (LOS), and higher costs of care.

PATHOPHYSIOLOGY OF HYPONATREMIA

There are 2 primary stimuli for the secretion of antidiuretic hormone (ADH), otherwise known as arginine vasopressin (AVP). Osmoreceptors in the hypothalamus measure the osmolality of the plasma. When osmolality increases, AVP is secreted; alternatively, when plasma osmolality drops, secretion of AVP under normal circumstances will diminish. The other stimulus results from baroreceptors throughout the body. Decreased intravascular volume (manifested by lower blood pressure) causes activation of the renin-angiotensin-aldosterone system, the sympathetic nervous system, as well as AVP secretion. In turn, AVP acts on vasopressin V2 receptors in the kidney to encourage water reabsorption, therefore impairing the patient’s ability to excrete dilute urine.

The mechanism by which hyponatremia develops varies according to disease state. Whereas neurohormonal activation predominates in those with HF and cirrhosis, inappropriate AVP secretion (and in some cases, a resetting of the osmostat) occurs in patients with CAP. In both HF and cirrhosis, the degree of neurohormonal activation correlates with the degree of hyponatremia.

In healthy individuals, the mechanism for free water excretion is AVP suppression caused by a fall in plasma osmolality. Patients with hyponatremia, however, are unable to suppress AVP due to true volume depletion (eg, as a result of inadequate oral intake, gastrointestinal fluid loss from vomiting/diarrhea, or use of thiazide diuretics), effective volume depletion (reduced cardiac output in HF patients vs vasodilation in patients with cirrhosis), or an inappropriate increase in AVP secretion.

RISK FACTORS

The risk factors for hyponatremia are numerous. The ability to excrete water declines with increasing

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age and is exacerbated by chronic illness. Other risk factors include low body weight, low sodium diets, and residence in a chronic care facility. Patients with a low baseline serum sodium concentration also appear to be at increased risk of developing hyponatremia. Although the mechanisms by which such patients develop hyponatremia are not always clear, they generally involve an impaired ability to excrete free water due to an inability to appropriately suppress AVP secretion. Medications commonly associated with the syndrome of inappropriate ADH secretion (SIADH) include selective serotonin reuptake inhibitors (SSRIs), psychotropic drugs, non-steroidal anti-inflammatory drugs (NSAIDs), opiates, proton pump inhibitors, as well as certain chemotherapeutics. Other risk factors associated with SIADH include major abdominal or thoracic surgery, pain, nausea, and excessive administration of hypotonic intravenous fluids. Finally, diuretic use (in particular thiazides) places patients at risk to develop hyponatremia by increasing total urine volume and solute excretion without an appreciable increase in free water excretion.

**MORBIDITY**

The morbidities associated with hyponatremia vary widely in severity. Serious sequelae may occur as a result of hyponatremia itself, as well as from complications that occur due to the challenging nature of effective management. Much of the symptomatology relates to the central nervous system (CNS). Patients presenting with extremely low serum [Na+] levels (eg, <115 mEq/L) often have severe neurologic symptoms, while those with lesser degrees of hyponatremia may be asymptomatic, or present with “milder” nonspecific symptoms, such as confusion. It is important to note that the clinical presentation of hyponatremia very much depends on whether it is acute (occurring over 24–48 hours) or chronic (>48 hours).

Water shifts between the intracellular and extracellular fluid compartments are the primary means by which the body equalizes osmolality. When serum sodium changes, the ability of the brain to compensate is limited, and may result in various forms of neurologic impairment due to cerebral edema. Such patients may become disoriented, restless, unable to attend, or unable to process information cognitively. There may also be peripheral neurologic dysfunction, such as muscle weakness, blunted neuromuscular reflexes, and impaired gait. Such impairments can lead to delirium, falls, and fractures.

**HYPONATREMIA AND COGNITIVE IMPAIRMENT**

Renneboog and colleagues performed a case-control study to assess the impact of mild chronic “asymptomatic” hyponatremia (mean serum [Na+] 126 ± 5 mEq/L) in 122 patients compared with 244 matched controls (mean age 72 ± 13 years). Hyponatremic patients had significantly longer mean response times on concentration tests. Interestingly, the changes in cognitive function in hyponatremic patients were similar to healthy volunteers purposefully intoxicated with alcohol. Patients with hyponatremia have also been shown to score lower on the mental component summary of the 36-item Short-Form (SF-36) survey. With treatment aimed at improving serum sodium, these same patients demonstrated improved cognitive function, suggesting that treating even “mild” forms of hyponatremia can improve patient outcomes.

**HYPONATREMIA AND FALLS/FRACTURES**

Renneboog and colleagues also demonstrated a markedly increased risk of falls in their patients with chronic hyponatremia compared to controls. Hyponatremia increases not only the risk of falls, but also the risk of fracture following a fall. In another recent case-control study of 513 patients, the adjusted odds ratio for fracture after a fall in a patient with hyponatremia was 4.16 compared with an age-matched control with normal serum sodium who sustained a similar fall. Of note, hyponatremia was mild and asymptomatic in all patients studied. Medications (36% diuretics, 17% SSRIs) were the most common precipitating cause of hyponatremia in this study, which is notable because such risk factors should be recognized and addressed.

Although falls and fractures lead to obvious increases in morbidity and cost, delirium has also been identified as a risk factor for increased hospital LOS. Delirious patients are less likely and able to mobilize and participate in physical therapy. As such, they are more often bed-bound and at increased risk for aspiration and other preventable issues, including deep vein thrombosis, bed sores, and debility, all of which may increase their LOS and cost of care.

**MORTALITY**

Hyponatremia is associated with a significantly increased mortality risk not only during hospitalization, but also at 1 and 5 years following discharge. In a prospective cohort study of approximately 100,000 patients, even those with mild hyponatremia ([Na+] 130–134 mEq/L) had a significantly higher mortality at 5 years. The adjusted odds ratio for mortality in patients with serum sodium less than 135 mEq/L was 1.47 during hospitalization (95% CI, 1.33–1.62), 1.38 at 1 year post-discharge (1.32–1.46), and 1.25 at 5 years (1.21–1.30). The significance of hyponatremia varied according to the underlying clinical condition, with the greatest risk observed in patients with metastatic cancer, heart disease, and those who had undergone orthopedic surgery. While the association between hyponatremia and mortality is profound, most experts do not believe that hyponatremia directly causes mortality per se. Instead,
hyponatremia is felt to be a marker for increased illness severity.

It is difficult to isolate the direct costs of hyponatremia in the acute care setting because the condition is rarely treated in isolation. However, in a study of a managed-care claims database of nearly 1,300 patients (excluding Medicare patients), hyponatremia was a predictor of higher medical costs at 6 months and at 1 year.32

DIAGNOSIS

The most common presentation of hyponatremia involves nonspecific symptoms or a total lack of symptoms.19 Many patients have comorbid diseases, and symptoms of these illnesses often predominate at hospital admission. Patients with mild to moderate hyponatremia may present with nausea, weakness, malaise, headache, and/or impaired mobility. With more severe hyponatremia, more dangerous neurologic symptoms appear, including generalized seizures, lethargy, and coma.19 Once hyponatremia is identified, the next step is to determine its acuity and classify it.

Although several classification systems exist to describe hyponatremia, the most common scheme begins with assessment of plasma osmolality and volume status.19 The majority of hyponatremic patients present with hypotonic or hypo-osmolar serum (eg, plasma osmolality <275 mOsm/kg). The primary causes of hyponatremia in patients with normal or high serum osmolality are hyperglycemia, pseudohyponatremia, and advanced renal failure. Marked hyperglycemia increases plasma osmolality, and as a result, water moves out of cells into plasma and lowers serum sodium concentration in the process. Pseudohyponatremia arises from hyperlipidemia or hyperproteinememia, in which high concentrations of lipids/proteins reduce the free water component of plasma, therefore reducing the sodium concentration per liter of plasma. These patients do not have true hyponatremia since the physiologically important sodium concentration per liter of plasma water is normal. Finally, patients with advanced renal failure develop hyponatremia due to the inability to excrete water.

The first step in the diagnosis of hyponatremia is to assess the plasma osmolality and rule out the aforementioned conditions that cause normal or elevated serum osmolality. Patients with hypotonic serum must then be evaluated clinically to determine their volume status. Appropriate classification here has important implications for management.

In addition to clinical history and physical examination, additional laboratory assessments should be carried out. Thyroid dysfunction and adrenal insufficiency should be ruled out on the basis of thyroid stimulating hormone (TSH) and plasma cortisol levels. In addition, urine sodium and urine osmolality should be checked, as they can often help confirm the assessment of the patient’s volume status and assist in the classification of the hyponatremia.

Hypovolemic hyponatremia commonly results from either renal or gastrointestinal losses of solute (sodium and potassium).19,33 Such patients will typically have urine sodium values below 25 mEq/L. Hypervolemic hyponatremia occurs when both solute and water are increased, with water increases that are out of proportion to solute. It is seen in patients with HF, cirrhosis, and nephrotic syndrome.19,33 These patients often also demonstrate low urine sodium levels. Although plasma and extracellular volumes are increased in these states, patients with HF and cirrhosis experience effective arterial blood volume depletion due to reduced cardiac output and arterial vasodilatation, respectively.

In euvolemic patients, hyponatremia is most often due to the syndrome of inappropriate antidiuretic hormone secretion. Such patients typically have urine sodium levels above 40 mEq/L. Free water excretion is impaired in SIADH, as evidenced by urine osmolality levels greater than 100 mOsm/kg and often much higher. SIADH is the most common cause of hyponatremia in hospitalized patients.22 The heterogeneity of conditions that can lead to SIADH is striking, including pulmonary and CNS diseases, cancer, and various forms of endocrinopathy.22,23 Consequently, SIADH is often a diagnosis of exclusion.

Other important causes of hyponatremia in euvolemic patients include primary polydipsia and low dietary solute intake. Primary polydipsia most commonly affects those with psychiatric illness.34 Increased thirst is a common side effect of antipsychotic medications. If water intake is excessive, the ability of the kidney to excrete water is overwhelmed and hyponatremia develops. These patients manifest with low urine osmolality (less than 100 mOsm/kg). In contrast, beer drinkers and other malnourished patients often have reduced ability to excrete free water based on low solute intake.35 In order to maximize the kidney’s ability to excrete free water, a basic level of solute intake is required. Severe alcoholics (in particular beer drinkers) often do not meet this minimum solute level since beer is very low in solute. The result is markedly impaired free water excretion. Such patients develop hyponatremia with low urine osmolality (less than 100 mOsm/kg).

MANAGEMENT

Although effective management of hyponatremia can be challenging, it is important to recognize that even modest improvements in serum [Na+] are associated with survival benefits.22,36 The most important treatment factors relate to the severity of hyponatremia, its acuity, and the patient’s volume status.33,36 The first steps in effective management are to optimize treatment of any underlying disease(s) and to discontinue...
any medications that may be contributing to hyponatremia.

In the severe group are patients who present with either a documented acute drop in serum [Na\(^+\)] or neurologic symptoms that are not attributable to another disease process. The mainstay of therapy for this group is prompt administration of hypertonic saline to rapidly address neurologic symptoms or prevent their development. Experts recommend correcting serum [Na\(^+\)] at a rate of 2 mEq/L per hour in patients with documented severe acute hyponatremia, with the assistance of a nephrologist. Slower correction rates (0.5–1 mEq/L per hour) should be used in symptomatic patients who develop severe hyponatremia in a subacute or chronic timeframe, so as to reduce the risk of osmotic demyelination, which confers irreversible damage to neurons and serious CNS sequelae. In both cases, an initial correction of 4–6 mEq/L is generally sufficient to address neurologic symptoms. Correcting the sodium by more than 10 mEq/L in the first 24-hour period is widely felt to place the patient at risk for iatrogenic brain injury, and should therefore be avoided. Serum sodium must be monitored very frequently (up to every 2 hours) in such patients to ensure appropriate management.

Management of patients with hyponatremia of uncertain duration and nonspecific symptoms is more common, as well as more challenging. A recently published algorithm recommends looking for and promptly treating hypovolemia if it exists, and then beginning correction at a more gradual rate with normal saline (± furosemide). Appropriate management of these patients addresses the sequelae of hyponatremia while at the same time minimizing the risk of iatrogenic injury. Experts recommend therapeutic goals of 6 to 8 mEq/L in 24 hours, 12 to 14 mEq/L in 48 hours, and 14 to 16 mEq/L in 72 hours.

In asymptomatic patients with chronic hyponatremia, the aim of treatment is gradual correction of serum [Na\(^+\)]. A significant number of SIADH patients fall into this category. A common mistake seen in the management of such patients is inaccurate assessment of volume status and a blind trial of normal saline infusion. Administration of normal saline to such patients will not improve the serum sodium concentration, and may, in fact, drive it lower. While SIADH patients have a normal ability to excrete sodium, their ability to excrete water is impaired. Therefore, normal saline infusion will lead to free water retention.

For asymptomatic chronic hyponatremia patients, oral fluid restriction is the most simple and least toxic treatment. However, it is often difficult to calculate the actual fluid intake, since water present in food must be included. In addition, thirst often leads to patient nonadherence. Treatment with sodium chloride in the form of dietary salt or sodium chloride tablets is problematic in patients with hypertension, HF or cirrhosis. Demeclocycline is fairly well tolerated, but can cause nephrotoxicity and skin sensitivity. Urea, although effective, is available only as a powder that is bitter and difficult to tolerate.

AVP-receptor antagonists, commonly called “vaptans,” are the newest treatment option. Known as “aquaretic drugs,” they lead to free water excretion. Conivaptan and tolvaptan have been approved by the US Food and Drug Administration (FDA) for the treatment of hyponatremia. Conivaptan, available as an intravenous (IV) formulation only, is indicated for the acute treatment of euvolemic or hypervolemic hyponatremia in hospitalized patients for up to 4 days. Due to its additional effects on the V\(_2\) receptor, this agent can cause vasodilation and resultant hypotension. In a randomized, placebo-controlled study of patients with euvolemic or hypervolemic hyponatremia, a 4-day IV infusion of conivaptan significantly increased serum [Na\(^+\)] levels compared with placebo. Tolvaptan, available as an oral formulation, is more suitable for long-term use, but must be started in the inpatient setting. Patients started on this agent must be followed closely after discharge. Based on the results of 2 multicenter, prospective, randomized, placebo-controlled trials, tolvaptan is indicated for clinically significant euvolemic or hypervolemic hyponatremia (serum [Na\(^+\)] <125 mEq/L, or less marked hyponatremia that is symptomatic and persistent, despite fluid restriction), in patients with HF, cirrhosis, and SIADH. The vaptans are contraindicated in hypovolemic patients because they can lead to hypotension and/or acute renal failure. Fluid restrictions must also be relaxed in patients who are placed on a vaptan.

Long-term clinical studies of these agents are needed to address their optimal duration of treatment, clinical outcomes, and comparative effectiveness to other treatment approaches. Although this is expected to change, vaptans are not included in current clinical practice guidelines for the management of hyponatremia.

**SUMMARY**

Hyponatremia is associated with significant morbidity and mortality in a variety of clinical scenarios. Prompt recognition and accurate diagnosis has the potential to improve patient outcomes, as even modest improvements in serum [Na\(^+\)] are associated with survival benefits. The appropriate management of hyponatremia involves careful assessment of acuity, severity, and volume status. The recently approved vasopressin receptor antagonists show promise as a therapeutic option for this challenging clinical condition.

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