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Hyponatremia: Why it matters, how it presents, how we can manage it

■ ABSTRACT

Hyponatremia is a common electrolyte disorder among hospitalized patients and has been associated with increased mortality. Most patients are asymptomatic, but many do present with symptoms, usually of a generalized neurologic nature. Based on medical history, physical examination (including volume-status assessment), and laboratory tests, patients can be classified as having either hypervolemic, euvolemic, or hypovolemic hyponatremia. Management depends on the speed of hyponatremia onset; its degree, duration, and symptoms; and whether there are risk factors for neurologic complications. The risks of overly rapid correction must be weighed against the benefits of treating hyponatremia. Traditional therapies have significant limitations. New agents that antagonize arginine vasopressin at the V_2 receptor or both the V_{1A} and V_2 receptors show promise for treating hypervolemic and euvolemic hyponatremia, as they induce desired free water diuresis without inducing sodium excretion.

■ KEY POINTS

Hyponatremia results from changes in total body water, not body sodium content. These changes are regulated primarily by thirst, the hormone arginine vasopressin, and the kidney.

The rate of decline in plasma sodium concentration, the patient's age, and the extracellular fluid volume affect the clinical presentation in patients with hyponatremia.

Prompt, controlled correction of serum sodium is indicated for acute symptomatic hyponatremia. Hypertonic saline and a loop diuretic are often given to achieve this goal.

Potentially fatal demyelination can occur with overly rapid serum sodium correction; a moderate rate of correction (< 12 mEq/L/day) minimizes this risk.

H YPONATREMIA is common among hospitalized patients and can lead to serious complications, yet its assessment can be a challenge and strategies for its management have traditionally been suboptimal. New therapies are emerging that promise a more targeted approach to regulating body water and sodium balance in patients with this disorder. This article reviews the incidence and clinical significance of hyponatremia, discusses patient evaluation and classification, and surveys current and emerging management approaches for the various types of hyponatremia.

■ DEFINITION AND EPIDEMIOLOGY

Hyponatremia represents an excess of body water relative to body sodium content and is frequently defined as a serum sodium concentration of less than 135 mEq/L.[1,2] Abnormalities of the mechanisms that regulate body water and sodium metabolism are often present in hospitalized patients. Untreated acute severe hyponatremia is associated with an increase in mortality.[3]

Hyponatremia is the most common electrolyte disorder,[1] reported to occur in up to 6% of hospitalized patients.[4] The precise incidence of hyponatremia varies depending on the conditions underlying it and the criteria used to define it.[1] When defined as a serum sodium concentration of less than 135 mEq/L, hyponatremia has been reported in 15% to 22% of hospitalized patients.[1] In studies defining it as a concentration of 130 mEq/L or less, hyponatremia has been described in hospitalized patients at incidences of 1% to 4%.[1,5] The frequency of hyponatremia varies by clinical setting as well. In an analysis of the prevalence of hyponatremia among 120,137 patients at initial presentation to health care providers, 7.2% of patients in the

community-care setting were hyponatremic compared with as many as 28.2% of patients in the acute-care hospital setting.[6]

PHYSIOLOGY OF WATER AND SODIUM BALANCE

Hyponatremia is associated with decreased serum osmolality resulting from changes in total body water, not body sodium content.[7] These changes are regulated primarily by thirst, arginine vasopressin (AVP), and the kidney.[7] A net increase in water reabsorption, however, fails to account entirely for the decrease in serum sodium concentration seen in patients with hyponatremia.[8]

What stimulates AVP release?

AVP is synthesized in the hypothalamus and transported to the pituitary, where it is stored.[7] Changes in effective arterial volume stimulate AVP release, causing a decrease in urine flow, maximal concentration of urine, and water reabsorption. The primary stimuli of AVP release are changes in plasma osmolality and changes in effective arterial volume that are sensed by the carotid baroreceptors and left atrium. Other important stimuli causing AVP release include certain medications (eg, diuretics), pulmonary infections, nausea, and mechanical ventilation.[7]

Aging increases likelihood of hyponatremia

Several changes in the mechanisms that regulate water and sodium balance occur as a normal part of the aging process, such as decreased glomerular filtration rate, decreased renal blood flow, impaired ability to dilute urine, and impaired water excretion.[1] These physiologic changes result in an increased likelihood of developing hyponatremia with increasing age.

INITIAL PATIENT EVALUATION

The initial evaluation of a patient with known or suspected hyponatremia consists of a careful medical history and physical examination, including a thorough neurologic evaluation and clinical assessment of volume status.[1] Additionally, laboratory measurements of serum electrolytes, glucose, blood urea nitrogen, creatinine, uric acid,[1] plasma osmolality, urine osmolality,[9] and urine sodium concentration may be useful.
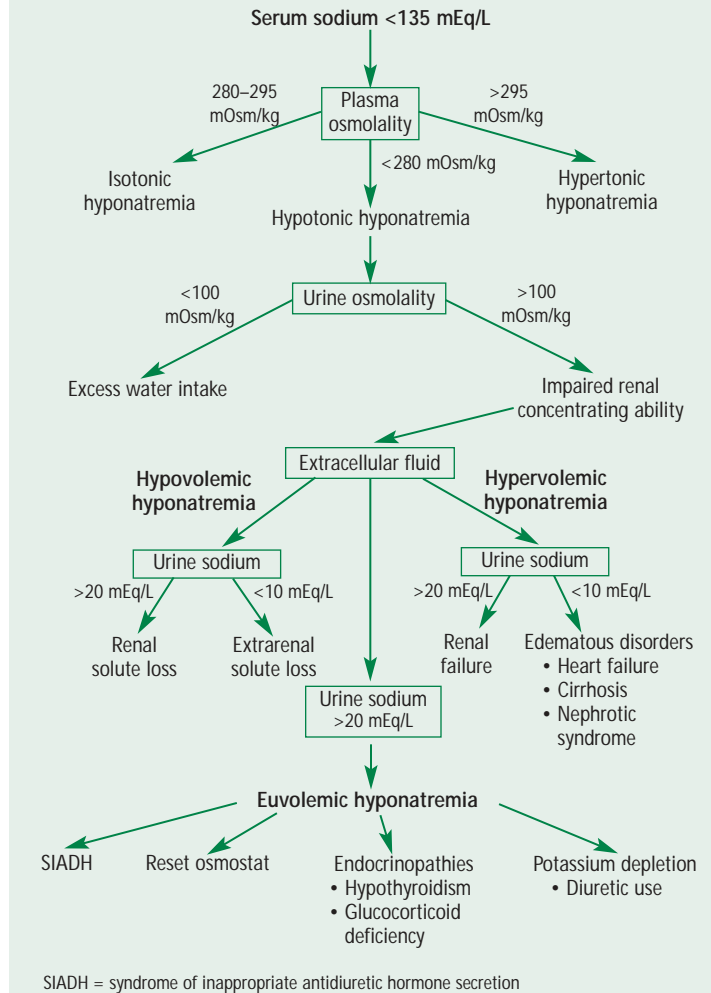

Algorithm for classifying hyponatremia

FIGURE 1. On the basis of volume status, urine osmolality, and urine sodium, patients with hypotonic hyponatremia can be categorized into one of three clinically important classes of hyponatremia: hypovolemic, euvolemic, or hypervolemic. Adapted from references 2 and 10.

Based on the initial assessment of volume status, medical history, and laboratory measurements of urine osmolality and sodium, patients with hypotonic hyponatremia can have their hyponatremia classified into one of three main categories **(Figure 1)**:[2,10]
- Hypervolemic
- Euvolemic
- Hypovolemic.

What to exclude

Because spurious (normo-osmolar) hyponatremia is a common cause of decreased serum
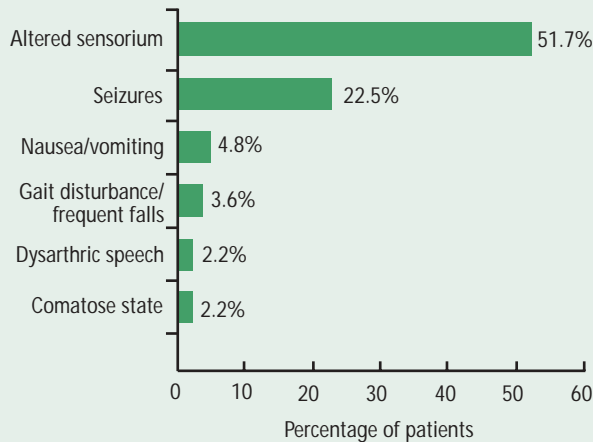
Clinical symptoms in severe hyponatremia

FIGURE 2. Incidences of symptoms observed in a retrospective study of 168 hospitalized patients with severe hyponatremia (serum sodium < 115 mEq/L) in a US medical center. Adapted from data in reference 14.

Accurate assessment of effective arterial volume is key to interpreting hyponatremic states

sodium levels, hypertriglyceridemia (> 1,500 mg/dL) and hyperproteinemia (> 10 g/dL) should be excluded in patients with compatible clinical syndromes, such as acute pancreatitis or myeloma, and in patients receiving total parenteral nutrition.

Clinical presentation

Although most hyponatremic patients may appear asymptomatic, severe symptomatic hyponatremia is a medical emergency that calls for immediate treatment. Signs and symptoms depend on several factors and vary by patient. The rate of decline in serum sodium concentration, the patient's age, and the volume of extracellular fluid (ECF) all affect the clinical presentation.[2]

CNS symptoms dominate

Symptoms are related largely to dysfunction of the central nervous system and are more evident when the decrease in the serum sodium concentration is large or fast.[11] However, patients also present with nonneurologic symptoms, such as fatigue, thirst, weakness, cramping, nausea, vomiting, bloating, swelling, and tightness of the hands and feet.

Most patients with a serum sodium concentration greater than 125 mEq/L or with chronic hyponatremia do not have neurologic symptoms, owing to volume adaptation by

the brain.[1] Gastrointestinal symptoms, such as nausea and vomiting, are more common in patients with serum sodium levels between 125 and 130 mEq/L.[12] Acute hyponatremia (< 48 hours in duration) in a previously asymptomatic young adult can cause severe central nervous system symptoms even at serum sodium levels between 125 and 130 mEq/L.[2,13] Once the level falls below 125 mEq/L, neurologic symptoms predominate.[12] Headache, muscle cramps, reversible ataxia, psychosis, lethargy, restlessness, disorientation, apathy, anorexia, and agitation are symptoms seen in patients with serum sodium levels below 125 mEq/L.[12]

Clinical signs include abnormal sensorium, hypothermia, depressed reflexes, pseudobulbar palsy, and Cheyne-Stokes respiration.[2]

Complications can be severe

Complications of severe and rapidly developing hyponatremia include seizures, coma, brainstem herniation, respiratory arrest, permanent brain damage, and death. These complications result primarily from hyponatremia-induced cerebral edema, which is most often seen in patients following surgery or in those with primary polydipsia. Menstruating women are also at elevated risk of severe neurologic complications associated with hyponatremia.[11]

Clinically important hyponatremia is a particular challenge in patients with acute neurologic diseases such as cerebral salt-wasting syndrome, syndrome of inappropriate antidiuretic hormone secretion (SIADH), anoxic or traumatic brain injury, or subarachnoid hemorrhage, since the presentations can overlap significantly.

Profile of symptoms and complications

A retrospective study of 168 patients with severe hyponatremia (serum sodium < 115 mEq/L) found that 89 patients (52.9%) developed one or more symptoms, the incidences of which are detailed in **Figure 2**.[14] The mean serum sodium level of symptomatic patients was 109 mEq/L before treatment and 120 ± 8 mEq/L after 48 hours of therapy. Twenty-eight patients (16.7%) in this cohort were considered to have chronic hyponatremia, with the remainder considered to have acute hyponatremia. The overall mortality was 20%, and

there was a trend toward increasing mortality with a slow rate of correction.

One percent of all postoperative patients are believed to develop hyponatremia, of whom approximately 15% develop symptomatic hyponatremic encephalopathy.[15]

Various comorbidities that complicate patient care have been associated with hyponatremia,[3] as detailed in **Figure 3**.[5]

■ CLINICALLY IMPORTANT TYPES OF HYPONATREMIA

A key to the interpretation of hyponatremic states is accurate assessment of the effective arterial volume. Baroreceptor sensing of arterial fullness tightly regulates autonomic outputs for vasomotor tone and neurohormonal production of AVP. *Hypervolemic* hyponatremia is associated with an increased ECF volume, indicative of total body sodium excess, whereas *hypovolemic* hyponatremia is associated with a reduction in ECF volume and often in effective arterial volume. By contrast, *euvolemic* hyponatremia involves AVP stimulation that is not volume-mediated.

Assessment of volume status in hyponatremic patients is essential in helping to differentiate the types of hyponatremia and determining the most appropriate treatment. Body weight, skin turgor, axillary and mucosal moistness, positional variation in blood pressure, and hemodynamic responses to volume challenge are useful indicators.

Hypervolemic hyponatremia

Hypervolemic hyponatremia is associated with impaired water excretion.[12] In patients with congestive heart failure, cirrhosis, or nephrotic syndrome, hypervolemia results from salt retention, increased AVP levels, and decreased glomerular filtration. This combination leads to water and salt retention,[1] which is the cause of the clinical finding of edema in patients with hypervolemic hyponatremia.

Total body sodium and total body water are increased in hypervolemic hyponatremia, with total body water exceeding total body sodium **(Table 1)**.[2] This condition is detected by the presence of edema or ascites on physical examination.[1] Edema-forming states, including congestive heart failure, liver failure, and nephrotic syndrome, are comorbidities commonly associ-
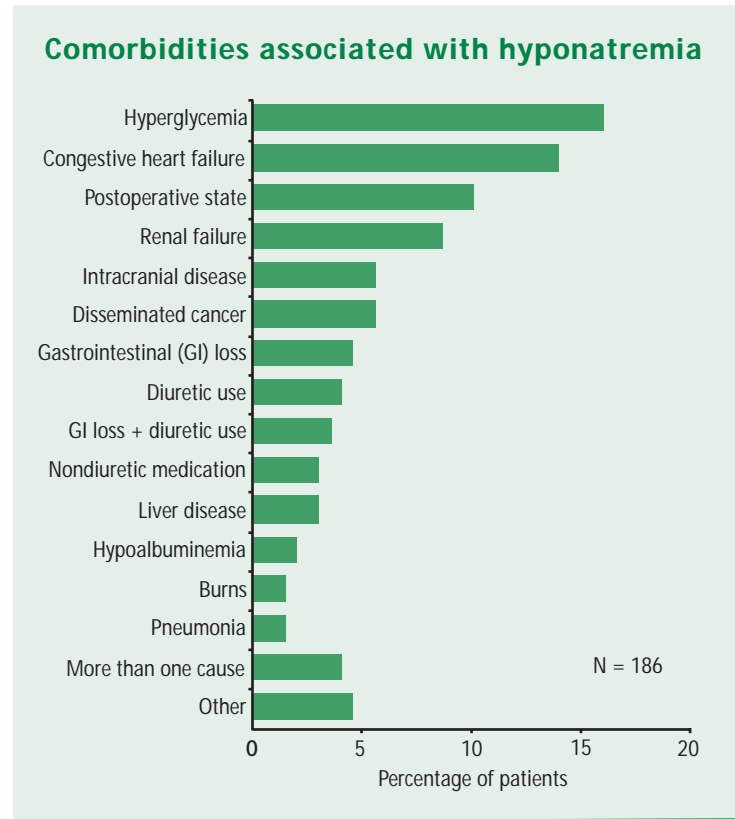

Comorbidities associated with hyponatremia

FIGURE 3. Prevalences of various comorbidities in a prospective analysis of hospitalized adults with hyponatremia at a US medical center. Adapted from data in reference 5.

ated with hypervolemic hyponatremia.[4] Despite an increased ECF volume, these disorders all have in common a decreased effective arterial blood volume or pressure, elevated plasma AVP levels leading to water retention, and concomitant hyper-reninemic hyperaldosteronism[1] with resulting sodium retention that exacerbates the dilutional state.

A typical patient with hypervolemic hyponatremia may present with complaints of dyspnea with minimal activity, orthopnea, and night-time awakening. Physical examination may reveal a lethargic, confused, cyanotic patient with nausea or vomiting, tachycardia, third heart sound, jugulovenous distension, and pitting edema in the lower extremities, highly suggestive of congestive heart failure.

Euvolemic hyponatremia

The most common form of hyponatremia in hospitalized patients is euvolemic hyponatremia.[2,4,12] AVP-mediated water retention leads to

TABLE 1

Volume status and common etiologies of major classes of hyponatremia

	HYPERVOLEMIC	EUVOLEMIC	HYPOVOLEMIC
Volume status			
Total body water	Increased	Increased	Reduced
Total body sodium	Increased	Unchanged	Reduced
Extracellular fluid	Greatly increased	Increased	Reduced
Edema	Present	Absent	Absent
Etiologies	Congestive heart failure	SIADH	Diuretic excess
	Cirrhosis	–Drugs (antidepressants, antipsychotics, barbiturates, nicotine, NSAIDs, morphine, vincristine)	Mineralocorticoid deficiency
	Nephrotic syndrome		Salt-losing nephritis
	Acute/chronic renal failure	–Physical/emotional stress	Osmotic diuresis
		Glucocorticoid deficiency	Ketonuria
			Bicarbonaturia
			Vomiting or diarrhea (extrarenal origin)
			Third-spacing (ie, burns, pancreatitis)

SIADH = syndrome of inappropriate antidiuretic hormone secretion; NSAIDs = nonsteroidal anti-inflammatory drugs
Adapted from data in references 2 and 19.

Hyponatremia in hospitalized patients is most commonly of the euvolemic form

an increase in total body water. However, patients with euvolemic hyponatremia show no indication of an increase or decrease in sodium stores.[2] In contrast to hypervolemic hyponatremia, edema is absent **(Table 1)**, hence the term *euvolemic* hyponatremia.[2]

Although urinary sodium levels vary depending on daily fluid and salt intake, patients with euvolemia have urine sodium concentrations generally greater than 20 mEq/L.[2] Normal urine sodium levels generally range from 15 to 250 mEq/L and depend on hydration status and daily sodium intake. A high urinary sodium level indicates non–volume-mediated hyponatremia similar to that in patients with SIADH.[16]

The more common etiologies of euvolemic hyponatremia **(Table 1)** result from nonosmotic stimuli for AVP release or increased receptor sensitivity to circulating AVP. SIADH is the most common cause of clinically important euvolemic hypnatremia. SIADH commonly results from medications, underlying thoracic,

intra-abdominal, or intracerebral infection, or ectopic secretion by neoplasms. Hypo-thyroidism-related hyponatremia may result from increased release of AVP or from increased renal tubular AVP sensitivity. Hypothyroidism may not be obvious in elderly patients because symptoms, such as confusion or lethargy, may be incorrectly attributed to aging.[1] Assessment of thyroid function is recommended in patients with euvolemic hyponatremia. Glucocorticoid deficiency is also associated with increased AVP release. This can result in impaired water excretion and exacerbate mineralocorticoid deficiency–mediated hypovolemic hyponatremia.[17]

Additional conditions to be considered in the differential diagnosis of euvolemic hyponatremia include secondary adrenal insufficiency, with associated low cortisol and adrenocorticotropic hormone levels, and emotional or physical stress.[2]

Euvolemic hyponatremia is commonly associated with small-cell lung carcinoma leading

to SIADH. The ectopic release of vasopressin causes a decrease in serum sodium, resulting in severe confusion and lethargy without causing edema. Regrettably, iatrogenic hyponatremia continues to be common in hospitalized patients who have a physiologic stimulus for AVP release and are also receiving significant volumes of hypo-osmolar intravenous fluids.[18]

Hypovolemic hyponatremia

Hypovolemic hyponatremia is characterized by deficits of both total body sodium and total body water, with the sodium deficit greater than the water deficit.[11] There are a number of etiologies of hypovolemic hyponatremia **(Table 1)**.[19]

Excessive use of diuretics, specifically thiazide diuretics, is responsible for most cases of hypovolemic hyponatremia and is associated with a preponderance of neurologic symptoms disproportionate to clinical signs of hypovolemia.[20] Thiazide diuretics inhibit sodium chloride reabsorption in the distal convoluted tubule and impair urinary diluting capacity, resulting in modest volume depletion, AVP secretion, and water retention, without perturbing urinary concentration capacity.[2] A recent study by Kim et al suggests additional possible mechanisms for thiazide-associated hyponatremia.[21] These researchers showed that thiazide diuretics cause upregulation of aquaporins in animals previously treated with lithium, a drug known to induce nephrogenic diabetes insipidus and to downregulate aquaporin.

Patient age, body weight, and serum potassium level were the strongest predictors of thiazide-mediated hyponatremia in a stepwise logistic regression analysis that compared 223 patients with thiazide-associated hypovolemic hyponatremia with 216 controls.[22] Loop diuretics and other medications, such as nonsteroidal anti-inflammatory drugs, were not strongly associated.[22]

Chronic renal insufficiency, such as diabetic renal disease, is commonly associated with impaired sodium reabsorption and AVP sensitivity. Patients with medullary cystic disease, chronic interstitial nephritis, polycystic kidney disease, analgesic-induced nephropathy, partial urinary tract obstruction, or chronic glomerulonephritis may in rare cases present with hypovolemic hyponatremia secondary to salt-wasting nephropathy.[2] Other situations in which electrolyte losses and depletion of ECF can occur include diabetic glucosuria, post-obstructive diuresis, and mannitol infusion therapy for intracranial hypertension without appropriate electrolyte replacement.[2]

A typical patient with hypovolemic hyponatremia is on a low-sodium diet and a thiazide diuretic for hypertension and presents with lethargy, confusion, and dizziness in the setting of a low serum sodium level. Excessive thirst, postural hypotension, and decreased skin turgor may be present, depending on fluid intake. Nonspecific signs and symptoms such as weight loss, anorexia, abdominal pain, nausea, vomiting, diarrhea, and fever may also be observed. In contrast to patients with euvolemic or hypervolemic hyponatremia, those with hypovolemic hyponatremia have decreased body sodium and water. Patients with hypovolemic hyponatremia do not present with edema.

■ MANAGEMENT OF HYPONATREMIA

To be optimal, therapy for hyponatremia must be individualized. In all patients, the risk of hyponatremia-associated complications must be balanced against the risk of serum sodium correction.[1,3] Several important factors should be considered when deciding on treatment, including the following[1,4]:

- The rapidity of onset of hyponatremia
- The degree, duration, and symptomatology of hyponatremia
- The presence or absence of risk factors for neurologic complications.

Acute symptomatic hyponatremia

Acute symptomatic hyponatremia develops in less than 48 hours. Clinical manifestations are largely related to central nervous system dysfunction resulting from brain cell swelling. Patients are at particular risk for this condition during the perioperative period.[15] Once the serum sodium level falls below 125 mEq/L, neurologic symptoms predominate.[12] In acute severe and rapidly developing hyponatremia, the risk of complications of cerebral edema exceeds the risk of osmotic demyelination associated with too-rapid correction of serum sodium, so treatment should begin promptly.[1,4]

Prompt, controlled correction of the serum

Neurologic symptoms predominate once serum sodium falls below 125 mEq/L

sodium level is indicated for patients with acute symptomatic hyponatremia. The goal is to raise the serum sodium level by 1.5 to 2 mEq/L/hour until symptoms subside[1] or until the concentration has risen to a safer level—usually greater than 118 to 120 mEq/L, with the primary focus being to minimize the risk of seizures. Even in symptomatic patients, the sodium level should not be raised by more than 12 mEq/L in the first 24 hours and by more than 18 mEq/L in the first 48 hours, in order to avoid osmotic demyelination (central pontine myelinolysis).[23]

Infusion of hypertonic saline (3%) at a rate of 1 to 2 mL/kg/hour and addition of a loop diuretic, to enhance water excretion, are commonly used to achieve this goal.[4] Hypertonic saline may be infused at a rate of 4 to 6 mL/kg/hour if severe neurologic symptoms, particularly seizures, are present.[1] Once a patient is asymptomatic and sodium levels are greater than 118 mEq/L, correction should be slowed to no more than 8 mEq/L in 24 hours to achieve a target level of 125 mEq/L.[11] In all cases, close and frequent monitoring of serum sodium and electrolytes is mandatory until sodium levels increase and symptoms subside.[4]

Chronic symptomatic hyponatremia

In hyponatremia of unknown duration, or of more than 48 hours' duration, sodium correction should be managed very cautiously because of significant osmotic adaptation of the brain to prolonged hyponatremia.[2] In patients presenting with severe symptoms, treatment should be similar to that for acute symptomatic hyponatremia: hypertonic saline plus a loop diuretic. Careful monitoring is critical because of an increased risk of irreversible osmotic demyelination. Correction should be limited to no more than 10 to 12 mEq/L on the first day of treatment and less than 6 mEq/L/day thereafter.[4] In patients presenting with mild to moderate symptoms, slower correction is required, generally 0.5 mEq/L/hour. Once the desired correction is achieved, therapy may continue in the form of fluid restriction.[2]

Adequate correction of serum sodium levels, using appropriate infusion rates, involves complex calculations. Adrogué and Madias[11] have described a useful approach using for-

mulas that allow for calculation of appropriate volume and rate of infusate for patients with or without symptoms.

Chronic asymptomatic hyponatremia

The goal in treating asymptomatic hyponatremia is to prevent a further decline in serum sodium and to maintain levels as close to normal as possible. Treatment involves a more conservative approach than for symptomatic hyponatremia. Initially, underlying causes of hyponatremia should be investigated and treated; this should include evaluation for drug-induced hyponatremia. Fluid restriction, isotonic saline, and loop diuretics may be used to treat the hyponatremia.

Euvolemic hyponatremia is the most common form of asymptomatic hyponatremia. If the underlying cause is SIADH and its etiology is unknown or cannot be effectively treated, therapy should be instituted for the hyponatremia itself.[2,4] In cases where the etiology of SIADH is known (eg, tumor), the underlying cause should be treated or removed[2] in addition to correcting the serum sodium level.

Current management options

Fluid restriction can play a role in the treatment of hypervolemic and euvolemic forms of hyponatremia. Although fluid restriction is inexpensive, it takes days for an effect to be seen. It also is associated with poor patient adherence and may prolong hospitalization.

Pharmacologic agents may be used concomitantly with fluid restriction. Demeclocycline directly inhibits AVP action at the level of the distal renal tubules and reduces urine concentration, even in the presence of increased AVP levels. The starting dose of demeclocycline ranges from 600 to 1,200 mg/day, and it may be used in patients with chronic hyponatremia.[1,2,4] However, demeclocycline is expensive, has low potency, and is rarely used because of nephrotoxicity, particularly in patients with liver cirrhosis.[2]

Lithium is also a direct competitive antagonist ofs AVP action via its induction of nephrogenic diabetes insipidus. It is rarely used, however, owing to its adverse effects.[24]

Emerging options: AVP antagonists

Traditional therapeutic options for managing AVP-induced hyponatremia are suboptimal

Do not raise serum sodium by more than 12 mEq/L in the first 24 hours

and have significant limitations, as outlined in **Table 2**.[24–26] As a result, newer agents that antagonize vasopressin receptors have been developed. These AVP antagonists, or "aquaretics," cause increased free water clearance without directly affecting tubular sodium handling. Some act at both the vasopressin type 1A (V_{1A}) and vasopressin type 2 (V_2) receptors (ie, conivaptan, recently approved by the US Food and Drug Administration for treating euvolemic hyponatremia in hospitalized patients), while others act solely at the V_2 receptor (ie, the investigational agents lixivaptan, satavaptan, and tolvaptan).

Dual V_{1A}/V_2 receptor antagonism has been shown to have favorable aquaretic effects in patients presenting with hypervolemic and euvolemic hyponatremia.[27] Vasopressin receptor antagonists may also have potential therapeutic benefit in patients with cardiovascular diseases, such as congestive heart failure. Combined V_{1A}/V_2 receptor antagonism is of particular interest because V_{1A} antagonism may provide further benefit by decreasing afterload in addition to V_2-mediated aquaresis.[27] Patients with symptomatic euvolemic hyponatremia are at particular risk of inappropriate sodium correction or seizures. These patients are especially likely to benefit from aquaretic-based correction to avoid the unpredictable effects of volume restriction and saline repletion.

Complications:
Risks and strategies for avoidance
Menstruating women, prepubescent children, and patients with preexisting hypoxic cerebral injury are thought to be at elevated risk for developing direct neurologic complications of cerebral swelling related to hyponatremia. Osmotic demyelination is a potentially fatal complication that may develop one to several days after aggressive treatment of hyponatremia. Hepatic failure, potassium depletion, and malnutrition are risks for this iatrogenic complication.[11] Demyelination may occur in the face of overly rapid correction of hyponatremia and causes brain cell shrinkage.[1,3] Oligodendrocytes are thought to be particularly sensitive to sudden osmotic shrinkage, resulting in rapid cellular apoptosis.[28] A moderate and appropriate rate of cor-

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TABLE 2

Traditional treatment options for hyponatremia

TREATMENT	MECHANISM	LIMITATIONS
Fluid restriction (most common)	Induces negative water balance Increases plasma osmolality and serum sodium	No direct inhibition of excess hormone No inhibition of hormone on kidneys Nonadherence
Demeclocycline	Impairs AVP action at renal tubules Induces nephrogenic diabetes insipidus Reduces urine concentration, even with increased AVP levels	Nephrotoxicity (cirrhosis patients) Hypersensitivity Drug interactions Unsafe in pregnancy
Urea	Decreases sodium excretion	Hypersensitivity Unsafe in pregnancy Azotemia Liver failure Can reduce effects of lithium Phlebitis, thrombosis
Lithium	Impairs AVP at renal tubules	Inconsistent results Lithium toxicity Anti-anabolic effects mainly in cirrhosis and congestive heart failure Unsafe in pregnancy
Diuretics (loop/thiazide)	Increase water excretion by inhibiting sodium and chloride reabsorption in loop of Henle and distal tubule	Hypersensitivity Hepatic coma Anuria Severe electrolyte depletion

AVP = arginine vasopressin
Data from references 24–26.

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rection (< 12 mEq/L/day), without increasing sodium to more than 125 to 130 mEq/L,[11] will minimize the likelihood of demyelination.

■ SUMMARY AND CONCLUSIONS
Hyponatremia is the most common electrolyte disorder in hospitalized patients. Severe pre-

sentations are associated with increased mortality. Hyponatremia must be managed on an individual basis, with great care taken to ensure safe and controlled serum sodium correction. Important factors to consider when managing patients with hyponatremia include the rapidity of hyponatremia onset; its degree, duration, and symptomatology; and risk factors associated with neurologic complications.

Traditional therapies for hyponatremia have limitations that make them suboptimal. These include the time to serum sodium cor-

rection with fluid restriction and the potential for additional electrolyte losses with diuretics. An ideal treatment for hypervolemic or euvolemic hyponatremia would provide solute free water excretion with prompt, controlled correction of serum sodium. With this goal in mind, new medications that antagonize AVP have been developed, including a dual V_{1A}/V_2 receptor antagonist and several V_2 receptor antagonists. These agents may represent a significant advance over current therapies for hypervolemic and euvolemic hyponatremia.

AVP antagonists increase free water clearance without affecting tubular sodium handling

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