Disorders of Sodium and Water Balance

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KEYWORDS

• Dysnatremia • Water balance • Hyponatremia • Hypernatremia
• Fluids for resuscitation

KEY POINTS

- Correct hypovolemia before correcting sodium imbalance by giving patients boluses of isotonic intravenous fluids; reassess serum sodium after volume status normalized.
- Serum and urine electrolytes and osmolalities in patients with dysnatremias in conjunction with clinical volume assessment are especially helpful to guide management.
- If an unstable patient is hyponatremic, give 2 mL/kg of 3% normal saline (NS) up to 100 mL over 10 minutes; this may be repeated once if the patient continues to be unstable.
- If unstable hypernatremic patient, give NS with goal to decrease serum sodium by 8 to 15 mEq/L over 8 hours.
- Correct stable dysnatremias no faster than 8 mEq/L to 12 mEq/L over the first 24 hours.

INTRODUCTION

Irregularities of sodium and water balance most often occur simultaneously and are some of the most common electrolyte abnormalities encountered by emergency medicine physicians. Approximately 10% of all patients admitted from the emergency department suffer from hyponatremia and 2% suffer from hypernatremia.[1] Because of the close nature of sodium and water balance, and the relatively rigid limits placed on the central nervous system by the skull, it is not surprising that most symptoms related to disorders of sodium and water imbalance are neurologic and can, therefore, be devastating. Several important concepts are crucial to the understanding of these disorders, the least of which include body fluid compartments, regulation of osmolality, and the need for rapid identification and appropriate management.

The difference between a minor symptom and a life-threatening condition caused by a sodium imbalance is often a result of the rapidity of the change in sodium concentration, not necessarily the overall deficit; and how quickly the imbalance is recognized

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and then treated by clinicians. Because emergency physicians do not always have the most complete background information on their patients in acute settings, this article delineates the types of sodium and water imbalances, the symptoms and signs the clinician encounters, pitfalls and complications of correcting these imbalances too aggressively, and how to base initial management of these patients.

- Sodium and water disorders occur simultaneously and most commonly affect the neurologic system, potentially leading to devastating outcomes.

PHYSIOLOGY

Total body water (TBW) accounts for approximately 60% of the total body weight in adults (**Fig. 1**); however, this figure changes with extremes of age, and within the sexes.[2] A more accurate picture of TBW can be calculated by (Equation 1, **Table 1**):

$$\text{TBW} = \text{weight (kg)} \times \text{correction factor} \quad (1)$$

The TBW is further divided into intracellular fluid, approximately 40% of total body weight; and extracellular fluid (ECF), approximately 20% of total body weight. Of the ECF, approximately two-thirds comprises interstitial fluid and one-third comprises intravascular fluid. The intravascular fluid is correspondingly close to 5% of the total body weight. The primary solute of the ECF is sodium, with a normal concentration of 140 mEq/L. As the concentration of sodium changes, neurologic symptoms may begin to manifest because of the confining nature of the skull. These symptoms may be minor or they can lead to life-threatening conditions.

Sodium regulation primarily occurs via 2 mechanisms: vasopressin and thirst regulation. For proper fluid balance, an average healthy adult requires an intake of approximately 1 to 3 L of water per day.[3,4] This amount of water replaces the amount of water lost from the body in insensible losses and urinary output, including approximately 500 to 700 mL/d from the respiratory tract, 250 to 350 mL/d from the skin, and 100 mL/d from the feces.[3] Additional water replacement may be necessary for other excessive losses, such as sweating caused by exercise or fevers.

Water diffuses via transport channels across cellular membranes, allowing osmolality to remain relatively constant between the spaces, but in effect changing the electrolyte concentrations of these compartments. Normal osmolality of plasma is 275 to 295 mOsm/L H_2O and can be estimated by (Equation 2):

$$\text{Serum osmolality (mOsm/kg)} = 2 \times \text{Na+glucose (mg/100 mL)/18} + \text{blood urea nitrogen (mg/100 mL)/2.8} \quad (2)$$

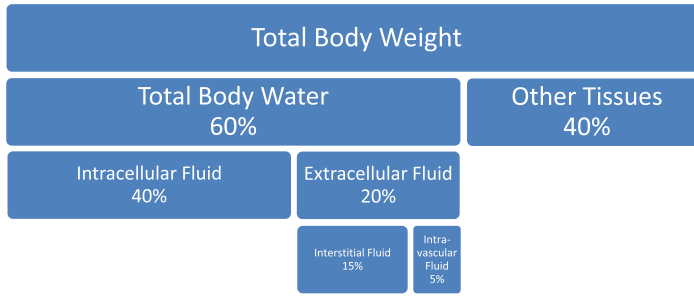

Fig. 1. Relationship of fluid compartments to total body weight. Percentages are expressed as related to total body weight.

Table 1
Correction factors to estimate TBW volume

Patient	Correction Factor
Newborn	0.8
Infant	0.7
Pediatric	0.6
Male, adult	0.6
Female, adult	0.5
Male, elderly	0.5
Female, elderly	0.45

Data from Wilson RF, Sibbald WJ. Fluid and electrolyte problems in the emergency department. JACEP 1976;5:339–46; and Kaplan LJ, Kellum JA. Fluids, pH, ions and electrolytes. Curr Opin Crit Care 2010;16:323–31.

In a healthy patient, the kidneys attempt to resorb or excrete water to preserve a normal osmolality. The primary hormone responsible for this regulation is arginine vasopressin, also referred to as antidiuretic hormone (ADH). ADH is a hormone synthesized in the posterior pituitary gland and acts on the distal convoluted tubule and the collecting duct of the nephron, resulting in increased reabsorption of free water, resulting in decreased volume of excreted urine, and concentrated urine. With this system of homeostasis, when plasma osmolality decreases, ADH is not released, water is freely excreted, and urine osmolality decreases. Conversely, when plasma osmolality increases, ADH is released, water is resorbed in the nephron, and urine osmolality increases. Plasma osmolality, with detected changes as small as 1% to 2%,[5] is the most common stimulus for ADH release; however, other factors can stimulate ADH release, including decreased intravascular volume, decreased blood pressure, pain, anxiety, nausea, pregnancy, menstruation, hypoglycemia, severe hypoxemia, hypercapnia, third spacing of fluids (eg, burns, trauma, pancreatitis), and certain drugs.[2,6,7]

The other route by which water is balanced is through the thirst mechanism. Because ADH is only able to regulate how much water the body holds onto, the thirst mechanism allows a stimulus to alter the amount of water that is consumed. Because of sensible and insensible water losses, the thirst mechanism allows the body to prevent dehydration, even under extreme water losses. Generally, the thirst mechanism determines the upper limit of the plasma osmolality, whereas the secretion of ADH determines the lower limit of the plasma osmolality.[7] If these regulation systems are functioning correctly, proper water balance is normally achieved.

HYPONATREMIA

Hyponatremia, defined as serum sodium level of less than 135 mEq/L, or severe hyponatremia as a level less than 125 mEq/L, is most commonly encountered in hospitalized patients or in patients with underlying medical diseases. The prevalence of hyponatremia is estimated to range between 3 and 6 million persons per year in the United States, and approximately one-quarter of these patients likely seek initial medical treatment in the emergency department.[8] Approximately 4% of adult medicine patients encountered in the emergency department have hyponatremia,[9] and approximately 15% of adult patients admitted to the hospital have hyponatremia.[10] Patients with hyponatremia have up to 33% higher mortality compared with normonatremic patients,[10] with an overall mortality of 3% to 29%.[11] The risk of mortality with

hyponatremia may be associated with other underlying illnesses such as heart disease, pneumonia, and liver disease; but there seems to be no correlation with the severity of hyponatremia and the risk of increased mortality.[10,11] Therefore, the recognition of all patients with hyponatremia is of utmost importance to the emergency department clinician.

Signs and Symptoms

Symptoms of hyponatremia can range from mild to severe: some patients are asymptomatic, others present with seizures. The symptoms are typically related to the level and rapidity of sodium change and to the presence and degree of cerebral edema. As water moves into brain cells, the serum sodium level decreases; patients begin to have headache, nausea, vomiting, restlessness, anorexia, muscle cramps, lethargy, and confusion. The brain attempts to adapt quickly to hyponatremia by losing other intracellular solutes to decrease the chance of cerebral edema,[12] which then becomes a factor in treatment. Most patients with symptomatic hyponatremia have some sort of neurologic complaint; however, some may present with a traumatic complaint, such as after a fall.[1] If hyponatremia is not stabilized or corrected, patients can decompensate to seizures, coma, or even death.

Evaluation and Diagnosis

When the emergency physician cares for a patient with hyponatremia, the first step is to recognize the volume status of the patient and the plasma osmolality (**Fig. 2**).[3] True hyponatremia is present with low plasma osmolality; other types of hyponatremia are caused by fluid shifts resulting from osmotically active solutes, such as glucose, urea, or mannitol, or resulting from high levels of protein or lipids.[3] Patients with hyponatremia may be hypovolemic, euvolemic, or hypervolemic; the volume status of the patient often dictates different treatment strategies: fluid resuscitation versus fluid restriction. The types of hyponatremia along with the physical and laboratory signs that often accompany each type are presented in **Table 2**.

Urine electrolytes are helpful in guiding therapy before administration of medications or fluids, and these tests should be ordered in the emergency department if possible. The serum sodium deficit can be calculated using the following equation (Equation 3):

$$\text{Total body Na deficit } (\text{mEq/L}) = (\text{desired serum Na} - \text{actual serum Na}) \times \text{TBW} \quad (3)$$

However, most equations have some downfalls and do not account for the homeostatic principles governing human physiology, leading to multiple variations of these equations.[13,14] In this matter, the body is not a closed system, so although equations are useful to roughly gauge how much solution should be used initially, the clinician must continually reevaluate the patient and adjust treatment as needed.

Hypovolemic hyponatremia

Hypovolemic hyponatremia is a loss of TBW and sodium. Usually, the patient presents with signs and symptoms suggestive of dehydration, including low blood pressure, nausea, vomiting, and tachycardia. Losses of water and sodium can be caused by renal dysfunction, or renal function may be preserved. Examples of renal water losses include overzealous diuretic use, renal tubular acidosis, renal failure, and mineralocorticoid deficiency.[3] Examples of extrarenal water losses include diarrhea, vomiting, pulmonary losses, heat exposure, sweating, biliary drains, high-output gastrointestinal fistulas, third-space losses such as burns, or pancreatitis.[3,4] Patients with renal water

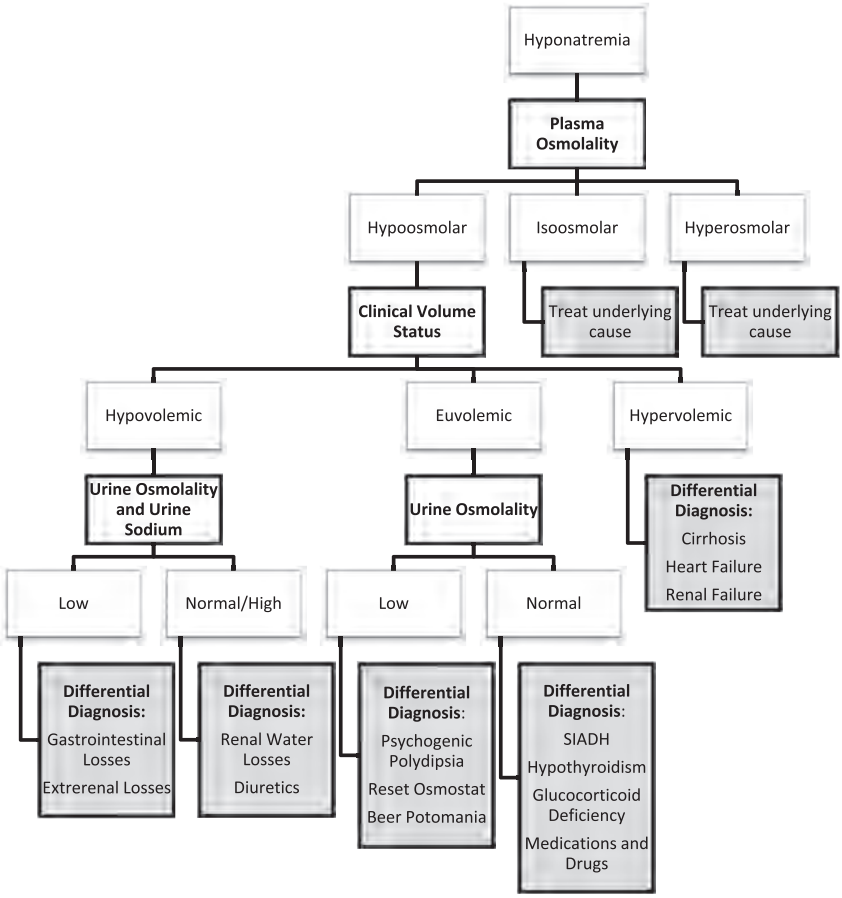

Fig. 2. Differential diagnosis of hyponatremia with serum sodium less than 135 mEq/L.

losses tend to have high urinary sodium, whereas patients with extrarenal water losses have low urinary sodium.

Hypervolemic hyponatremia

Hypervolemic hyponatremia, on the other hand, is often reflected by an increase in TBW, whereas sodium levels decrease. These patients typically present with symptoms of fluid overload, including peripheral edema, ascites, anasarca, or pulmonary edema. Commonly encountered patients with hypervolemic hyponatremia include patients with chronic renal failure, congestive heart failure, nephrotic syndrome, or cirrhosis.[3] Patients with renal failure and overload have high urinary sodium levels, whereas patients with cirrhosis, congestive heart failure, or nephrotic syndrome have low urinary sodium levels.

Euvolemic hyponatremia

Patients with euvolemic hyponatremia fall on the spectrum between hypovolemic and hypervolemic hyponatremia; they often have normal total body sodium levels, but have slightly decreased intravascular volume, without clinical signs of symptoms of dehydration.[3] The most common cause of euvolemic hyponatremia is the syndrome

Table 2
Classifications and causes of hyponatremia by volume status

Physical Signs	Laboratory Signs	Examples
Hypovolemic Hyponatremia		
Orthostasis	Low plasma osmolality	Gastrointestinal losses
Low blood pressure	Increased blood urea nitrogen level	Renal losses
Tachycardia	Hypokalemia	Diuretic use
	Low urine osmolality	Addison disease
	Low urine sodium level	Increased insensible losses
		Third-space shifts
Euvolemic Hyponatremia		
	Low plasma osmolality	Syndrome of inappropriate ADH
	High/low urine osmolality	Hypothyroidism
	High/low urine sodium level	Glucocorticoid deficiency
		Severe pain or nausea
		Trauma
		Beer potomania
		Psychogenic polydipsia
		Medications/drugs (Table 4)
Hypervolemic Hyponatremia		
Ascites	Low plasma osmolality	Cirrhosis
Edema	Low urine osmolality	Congestive heart failure
Anasarca	Low/high urine sodium level	Nephrotic syndrome
		Renal failure
Other Causes of Hyponatremia (Including High and Normal Plasma Osmolality Hyponatremias)		
Primary/secondary adipsia	Extreme hyperglycemia	Multiple myeloma
Hypodipsia	Hypertriglyceridemia	Hyperlipidemia
Increased urea level	Adrenal insufficiency	Mannitol

Data from Refs.[2,3,7,118]

of inappropriate ADH (SIADH). Causes of SIADH are varied, but include many central nervous system, pulmonary, and carcinoma causes (**Table 3**).[7,15–63] Euvolemic hyponatremia may also be caused by hypothyroidism, excessive pain, stress, nausea, or water intoxication caused by psychogenic polydipsia. Many types of medications can also cause euvolemic hyponatremia (see **Table 4**).

A subset of patients with euvolemic hyponatremia caused by SIADH have a phenomenon referred to as reset osmostat, the second most common form of SIADH.[16] These patients continue to regulate water excretion with ADH secretion, but their threshold is based around a lower serum osmolality set point, and release of ADH seems to be premature.[16] Patients are still able to suppress ADH and urinary dilution once they have retained sufficient free water, resulting in surpassing their set point and causing significant hyponatremia.[16] This preserved function is what separates these patients from other types of SIADH. The severity of hyponatremia in patients with reset osmostat is not based primarily on the amount of free water intake but also on the level of osmostat resetting.[7] The causes for having reset osmostat may be similar to those

that predispose a person to any of the causes of SIADH: pulmonary, carcinoma, or central nervous system disease.[16] The exact mechanism by which reset osmostat occurs is still unknown, but it may be caused by interruption of the afferent limb of the baroregulatory reflex that inhibits ADH secretion.[15]

Patients who have recently ingested 3, 4-methylenedioxymethamphetamine (MDMA), also known commonly as the street drug ecstasy, may also present to the emergency department with SIADH. Previously, it was believed that excessive dancing, high amounts of sweating, and intake of large amounts of free water contributed to hyponatremia in the clubbing population, who may also be exposed to MDMA.[64–66] However, 1 high-profile case in 1995 resulting in the death of Leah Betts suggested that increased ADH production was believed to contribute to the patient's severe hyponatremia and water intoxication.[67] Previous studies with rat models have shown that MDMA causes increased levels of oxytocin and ADH,[68] but a recent study by Wolff and colleagues[63] on self-described human clubbing volunteers reported results consistent with SIADH after MDMA use. Emergency clinicians must be aware of this population, because many protocols of suspected or known drug ingestions receive large amounts of intravenous fluids during resuscitation; aggressive fluid resuscitation in these individuals exacerbates hyponatremia, possibly causing seizures, coma, or cerebral edema. If MDMA ingestion is suspected, the clinician should refrain from prophylactic intravenous fluids until serum or urine studies are available.[63,69]

- Clinicians should not reflexively administer intravenous fluids to patients after ingestion. Thoroughly evaluate the patient and decide if the patient requires fluids to increase intravascular volume.

Treatment

Unstable patients

When patients are acutely symptomatic from their hyponatremia, the physician must quickly identify and treat the sodium imbalance, because the risks of untreated hyponatremia clearly outweigh the risks of slow correction achieved with conservative measures. In a patient who is actively seizing, is neurologically compromised, or has respiratory arrest caused by hyponatremia, a bolus of hypertonic saline, given as 3% normal saline (NS) at a dose of 2 mL/kg (maximum 100 mL) should be given.[2,7,70–72] The bolus should be given over 10 to 60 minutes and can be repeated once if severe symptoms are still evident. A bolus of 2 mL/kg increases the serum sodium level by approximately 2 mEq/L. This increase in serum sodium level should stop current symptoms and prevent other severe neurologic consequences. During infusion of hypertonic saline, the patient and the serum sodium levels much be monitored closely to look for any signs of deteriorating neurologic status or symptoms of fluid overload, which may dictate further management.

- For the unstable hyponatremic patient, give 2 mL/kg of 3% NS up to 100 mL over 10 minutes; this may be repeated once if the patient continues to be unstable.

Stable patients

The treatment of hyponatremia in stable patients is otherwise based on the volume status of the patient. In patients with hypovolemic hyponatremia, intravascular repletion of volume is paramount. In patients with hypervolemic or euvolemic hyponatremia, fluid restriction or removal of excess fluid dictates care. The goals of treatment are to increase serum sodium levels and to not exceed a correction rate of 10 mEq/L to 12 mEq/L in the first 24 hours, with some experts suggesting not

to exceed 6 mEq/L in the first 24 hours. Overall, if the patient is asymptomatic, the clinician can focus on the cause of hyponatremia and direct their efforts to correcting that medical condition, rather than aggressively treating the hyponatremia.

The mainstay of treatment of hypovolemic hyponatremia is volume expansion. Intravenous fluid resuscitation must be initiated, and any underlying problem causing the hypovolemic hyponatremia must be corrected, including the removal of any medications that may be contributing. Once the patient is clinically euvolemic, the sodium level must be reassessed. If there continues to be a sodium imbalance, the clinician must then direct their attempts at correcting the sodium level as is appropriate. Often, the initial fluid used for resuscitation is 0.9% NS in the form of

Table 3
Common causes of SIADH

Category	Cause of SIADH
Malignancy	Bladder carcinoma
	Duodenal carcinoma
	Ewing sarcoma
	Head or neck carcinoma
	Leukemia
	Lymphoma
	Mesothelioma
	Pancreatic carcinoma
	Pulmonary carcinoma
	Prostatic carcinoma
	Sarcoma
	Thymoma
	Ureteral carcinoma
Pulmonary	Acute respiratory failure
	Asthma
	Cystic fibrosis
	Empyema
	Pneumonia
	Pneumothorax
	Positive pressure ventilation
	Tuberculosis
Central nervous system	Acute intermittent porphyria
	Acute psychosis
	Agenesis of corpus callosum
	Atrophy of cerebrum or cerebellum
	Brain abscess
	Brain tumors
	Cavernous sinus thrombosis
	Cerebrovascular accidents
	Delirium tremens
	Guillain-Barré syndrome
	Encephalitis
	Head trauma
	Hydrocephalus
	Meningitis
	Multiple system atrophy
	Neonatal hypoxia
	Rocky Mountain spotted fever
	Subarachnoid hemorrhage

(*continued on next page*)

Table 3
(*continued*)

Category	Cause of SIADH
Medications/drugs	Alcohol abuse and malnutrition
	Butyrophenones
	Carbamazepine
	Cisplatin
	Chlorpropamide
	Clofibrate
	Cyclophosphamide
	Cytoxan
	Desmopressin
	Ecstasy
	Interferon α and γ
	Methotrexate
	Monoamine oxidase inhibitors
	Monoclonal antibodies
	Morphine
	Nicotine
	Nonsteroidal antiinflammatory drugs
	Opiates
	Oxcarbazepine
	Oxytocin
	Phenothiazines
	Selective serotonin reuptake inhibitors
	Sodium valproate
	Thiazide diuretics
	Tricyclic antidepressants
	Vasopressin
	Vinca alkaloids
Other	AIDS
	Glucocorticoid insufficiency
	Idiopathic
	Myxedema
	Postoperative period

Data from Refs.[7,15–63]

fluid boluses. As the intravascular volume is restored, ADH is no longer secreted, renal function improves, and excess free water given during fluid resuscitation can be excreted. Because of this homeostatic balance and the changes that continue to occur, during resuscitation, sodium levels must be carefully monitored. In addition, the clinician must ensure strict monitoring of urine output; the patient may require a Foley catheter to be placed if unable to assist with this monitoring. In patients with preserved renal function, the sodium level should increase slowly but appropriately; however, if serum sodium levels begin to increase too quickly and free water is excreted, as in the patient with recovering renal function or previous renal impairment, hypotonic fluids such as 0.45% NS or even D5W (dextrose 5% in water solution) may be necessary.

Treatment of patients with hypervolemic and euvolemic hyponatremia frequently and most commonly entails sodium and water restriction, occasionally with adjunctive use of furosemide or another loop diuretic in specific situations. However, in stable patients, optimization of the underlying medical condition usually corrects the hyponatremia. Special attention must be placed on correction of hypokalemia, because repletion of potassium also increases the serum sodium level.

Table 4
Common medications or classes of medications that may cause hyponatremia

Acetaminophen	Angiotensin-Converting Enzyme Inhibitors	Antiaggregant
ADH	Barbiturates	β-Blockers
Carbamazepine	Carboplatin	Cisplatin
Clofibrate	Colchicine	Cyclophosphamide
Desmopressin	Haloperidol	Isoproterenol
Loop diuretics	Monoamine oxidase inhibitors	Morphine
Nicotine	Nonsteroidal antiinflammatory drug	Opioids
Oxcarbazepine	Oxytocin	Phenothiazines
Proton pump inhibitors	Psychotropics	Selective serotonin reuptake inhibitors
Sodium valproate	Sulfonylureas	
Thiazide diuretics	Tolbutamide	Tricyclic antidepressants
Venlafaxine	Vinca alkaloids	Vincristine

Data from Refs.[1–3,6,15]

Another treatment modality available to treat euvolemic and hypervolemic hyponatremia is the use of vaptans. Previously, these subgroups of patients with hyponatremia had to endure uncomfortable fluid restrictions, loop diuretics such as furosemide, which can cause other electrolyte imbalances, or medications that caused additional side effects such as demeclocycline, lithium, or phenytoin.[15,73] With the advent of vasopressin receptor antagonists, also known as vaptans, patients with chronic euvolemic or hypervolemic hyponatremia have another option for treatment. Vaptans bind to vasopressin type 1 (V1) or type 2 (V2) receptors; V2 receptors are expressed in the renal collecting duct cells. Vaptans block the binding of ADH onto V2 receptors, preventing free water reabsorption and causing increased urine volume.[73] The diuresis caused by vaptans is similar in quantity to the diuresis induced by furosemide, but there is not an increase in excretion of electrolytes.[73] This diuresis of water with relative sparing of electrolytes by vaptans is termed aquaresis; aquaresis decreases urine osmolality and causes an increase in serum sodium.[73] Two options are available in the United States: an intravenous preparation, conivaptan, and an oral preparation, tolvaptan.[72] Conivaptan is a combined vasopressin receptor antagonist to V1 and V2 receptors and is indicated for short-term treatment of hospitalized patients.[72] Tolvaptan is a selective V2 receptor antagonist, but per the US Food and Drug Administration should not be used for longer than 30 days.[72] Side effects include dry mouth, thirst, and increased urination. Both of these vaptans have the possibility of causing hepatic injury, and caution should be used when administering the medication to patients with known liver disease.[72] Frequent monitoring of liver enzymes is warranted in all patients receiving the medications, and total therapy length should be limited in patients with any evidence of emerging liver disease.[72]

Vaptans may play a role in the treatment of chronic euvolemic and hypervolemic hyponatremia, but there have been no studies that have evaluated their use in the setting of acute hyponatremia that is seen in the emergency department and there is no current role in the treatment of acute symptomatic hyponatremia.

- Stable patients with hyponatremia should have their serum sodium level corrected no faster than 10 mEq/L to 12 mEq/L over the first 24 hours.

Cerebral Edema

Cerebral edema through the shift of water from extracellular stores occurs to balance out the relative hyponatremia in the vascular space. Patients particularly at risk for cerebral edema include postmenopausal women, women on thiazide diuretics, children, psychiatric patients with polydipsia, and hypoxemic patients.[71] To combat this shift from causing too many homeostatic changes, the brain quickly loses solutes to try to prevent profound cerebral edema.[12] However, if the hyponatremia is corrected too quickly with these homeostatic balancing mechanisms intact, brain cells can shrink as serum sodium is repleted.[7] From multiple studies, it has been well established that correction of the sodium should not occur quicker than approximately 0.5 to 1 mEq/L/h or a total of 10 to 12 mEq/L per 24 hours,[3,70,71,74–77] again with some experts recommending not to exceed 6 mEq/L. Once a hyponatremic patient has been identified and treatment has started, the clinician should check electrolyte levels frequently; in the most symptomatic of patients, checking levels of sodium every 2 hours is prudent and allows close guidance of medical therapy. It has been shown in case reports that if the patient's sodium level begins to correct too quickly and adjustment of the intravenous fluids is not adequate to slow the change, the hyponatremic patient may require infusion of hypotonic fluids to decrease the sodium level again.[78–80] These measures are to prevent the most dreaded complication known as osmotic demyelination syndrome.

Osmotic Demyelination Syndrome

Osmotic demyelination syndrome was first described in the medical literature in 1959[81] and is the iatrogenic irreversible clinical syndrome of neurologic symptoms that occurs after too rapid of a correction of serum sodium.[77] A subset of this syndrome is known as central pontine myelinolysis, when the effects are primarily seen from damage in the brainstem; however, many patients with the syndrome have other foci of demyelination within the central nervous system anywhere throughout the nervous system.[77,82] This severe complication is caused by exceeding generally agreed safe limits of serum sodium correction, with corrections greater than 12 mEq/L in 24 hours, 25 mEq/L in 48 hours, or inadvertent hypernatremia during correction of hyponatremia.[77,83] The nervous system damage is postulated to be caused by rapid swelling of brain and nervous system parenchyma during fluid resuscitation, because this tissue cannot adapt quick enough to the changing osmolality. Patients with chronic hyponatremia may be particularly susceptible to osmotic demyelination syndrome, especially those with underlying alcoholism, malnutrition, toxins, hypoxia, other central nervous system disease, or other metabolic syndromes.[3,7,71,74,77,81–83] Symptoms of osmotic demyelination syndrome include fluctuating levels of consciousness or confusion, behavioral changes, dysarthria, mutism, dysphagia, and seizures.[3,77,82] These symptoms may culminate in a devastating condition, including a locked-in state, in which the patients are awake but unable to move or communicate, or quadriparesis.[3,77]

Despite the severity of osmotic demyelination syndrome, and the devastating results that may ensue, the possibility of the syndrome should not prevent a clinician from aggressively treating symptomatic patients with hyponatremia. Most neurologic symptoms associated with hyponatremia are from cerebral edema and herniation,[71,84–86] so patients with symptomatic hyponatremia require immediate treatment. Without prompt treatment, patients may progress to severe seizures, coma, or death; the risk to the patient outweighs the risk of osmotic demyelination syndrome when they are severely symptomatic.

Pediatric Considerations

In general, any child who requires intravenous fluid administration should be considered to be at risk for development of hyponatremia.[87] The use of intravenous fluids in the pediatric population should be considered an invasive treatment and the same amount of care and attention should be applied as when administering any other medication.[87]

Children may be at higher risk for development of cerebral edema because of the physiologic nature of a higher ratio of brain volume to skull size.[71] The true incidence of symptomatic hyponatremia in children is not known because of lack of prospective studies.[87] However, 1 retrospective review[88] found approximately 22% of children who were admitted to the hospital had hyponatremia, and symptomatic hyponatremia was found in 10% of children younger than 2 years presenting to the emergency department with seizures.[89] Of those children with hyponatremia, 53% to 78% with serum sodium level less than 125 mEq/L developed symptomatic hyponatremia.[70,90,91] Children particularly at risk for hyponatremia include those younger than 16 years and children with hypoxia.[87] Hypoxia is the strongest predictor of mortality in pediatric patients with symptomatic hyponatremia.[92] Hyponatremia from SIADH is particularly noxious in children with neurologic injury such as encephalitis; mild hyponatremia has been associated with significant neurologic sequelae, including herniation.[93,94] Special attention and close monitoring of serum sodium level in any child at risk for hyponatremia or with any of these conditions is necessary to prevent serious neurologic complications.

Symptomatic hyponatremia should always be aggressively treated with the use of hypertonic 3% saline.[87] The serum sodium level should be increased by approximately 1 mEq/L per hour until the patient is seizure free, the serum sodium has corrected to 125 to 130 mEq/L, or the serum sodium level has increased by 20 mEq/L.[70,71,83,95,96] The optimal rate of correction of serum sodium level seems to be between 15 and 20 mEq/L over the first 48 hours, because patients with this range of correction have lower mortality and better neurologic outcome compared with those with slower correction.[83,86]

- Hypotonic fluids are no longer recommended for maintenance fluids in the pediatric population because of iatrogenic hyponatremia.

HYPERNATREMIA

Hypernatremia is defined as serum sodium level greater than 145 mEq/L and is less common than hyponatremia. Most commonly, hypernatremia occurs in hospitalized patients, but it can also occur in approximately 0.2% of patients who present to the emergency department.[97]

Hypernatremia is always associated with intracellular dehydration caused by decrease of TBW and is always associated with decreased intake of free water. As a result of losses through bowel, urine, and pulmonary losses, without adequate water intake to overcome these losses, a patient becomes more and more dehydrated and hypernatremic unless the patient ingests enough free water, even if the renal function is intact.[7] Hypernatremia commonly occurs in patients with impaired thirst mechanisms, or inability to acquire adequate free water, such as in the elderly, infants, or otherwise impaired individuals (eg, patients on a ventilator, in a coma). Excessive water loss may further contribute to hypernatremia, but again, unless the thirst mechanism or access to water is limited, the patient should be able to compensate with increased ingestion of free water.[7,98]

Signs and Symptoms

Symptoms of hypernatremia are similar to those of hyponatremia, because of effects that are again based primarily on the central nervous system.[1,99] During hypernatremia, brain cells shrink substantially as water moves into the extracellular space. This situation can cause intracerebral hemorrhage as a result of tearing of cerebral blood vessels.[3,100] Other consequences of hypernatremia include decreased left ventricular contractility, hyperventilation, impaired glucose use, muscle cramps, and rhabdomyolysis.[99] Patients may present with lethargy, weakness, or restlessness; infants may present with irritability. Neurologic examination may show increased tone, nuchal rigidity, brisk reflexes, myoclonus, asterixis, chorea, or seizures.[87] If not assessed and treated appropriately, the patient may progress to seizures, coma, or death.[3,12,101] One study[1] found that patients with hypernatremia are less likely to receive specific care for the dysnatremia, and have higher in-hospital mortality. Symptoms are again related not only to the absolute increase in serum sodium levels but also to the rapidity at which the increase occurs, because this correlates with the speed of brain cell dehydration.[7]

Evaluation and Diagnosis

The initial step in evaluating a patient with hypernatremia is to again start with the volume status of the patient. The volume status then helps guide the clinician to specific treatments (**Fig. 3**).

Hypovolemic hypernatremia

Hypovolemic hypernatremia is usually caused by an inability to detect or respond to the sensation of thirst. Primary adipsia or hypodipsia is caused by damage of the

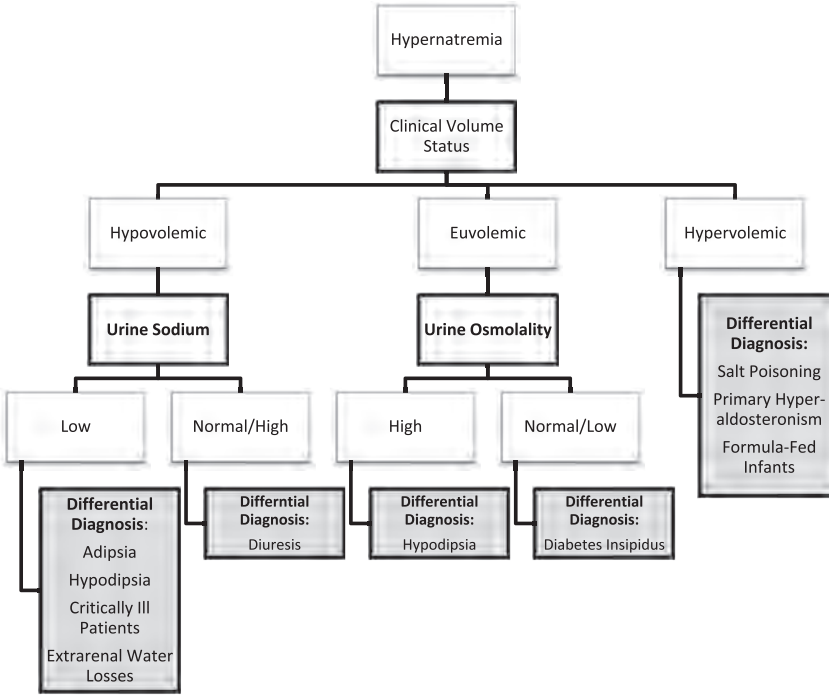

Fig. 3. Differential diagnosis of hypernatremia with serum sodium greater than 145 mEq/L.

hypothalamic osmoreceptors that cause the thirst mechanism when plasma osmolality begins to increase.[102,103] This situation typically occurs in alert and awake patients without neurologic defects and without limited access to free water. The cause of hypernatremia in these patients tends to be the limited ingestion of free water. Critically ill patients are at a high risk for the development of hypernatremia. In these patients, careful monitoring of serum sodium and water intake and output is necessary to prevent unwanted neurologic consequences.[104]

Another cause of hypovolemic hypernatremia is from secondary adipsia or hypodipsia resulting from lesions that spare the hypothalamic osmoreceptors but affect consciousness, speech, physical ability, or prevent absorption of water from the gastrointestinal tract.[7] Most commonly, these patients are obtunded because of medical conditions such as hyperglycemia, or patients who have suffered strokes, or postoperative patients with increased renal or extrarenal losses along with decreased mentation or limited water intake.[7]

- Critically ill patients and those patients at risk for developing decreased water intake should have electrolytes monitored frequently to ensure that serum sodium levels are not increasing.

Hypervolemic hypernatremia

Hypervolemic hypernatremia is almost never sporadic, but usually is the result of iatrogenic complications, or accidental or intentional poisoning. Examples of hypervolemic hypernatremia include the administration of sodium bicarbonate during cardiac arrest or during the treatment of acidosis, the previous use of hypertonic saline during therapeutic abortions, and the improper preparation of solutions for enteral or parenteral feedings, or peritoneal dialysis.[3,105–107] Infants seem to be the population most at risk for hypervolemic hypernatremia, because they are less able to excrete a high sodium load, and they are unable to ask for or acquire water. In addition, infants who are fed formula may accidently ingest a hyperosmolal solution as a result of an improperly prepared solution. Primary hyperaldosteronism can also lead to hypervolemic hypernatremia; however, the level of hypernatremia is typically milder and does not lead to neurologic symptoms.

- Formula-fed infants with neurologic changes should have serum sodium levels checked, and caregivers should be questioned about how they prepare formula.

Euvolemic hypernatremia

Euvolemic hypernatremia is most often caused by diabetes insipidus. In this disease, the body does not respond to ADH, either peripherally or centrally. Because of the lack of ADH response, the patient continues to make maximally dilute urine with low urine osmolality. Sodium excretion in the urine continues, but is less than the overall amount of water excreted, thus resulting in hypernatremia. Causes of diabetes insipidus are divided into 2 categories: central and nephrogenic. Common causes of central diabetes insipidus are trauma, pituitary surgery, and malignancies.[3] Common causes of nephrogenic diabetes insipidus include renal disease, medications, and genetic disorders.[3]

Treatment

Unstable patients

Acute hypernatremia carries mortality between 28% and 70%.[1,3,7] Symptoms most often are caused by the rapidity of change of sodium level, not necessarily the overall deficit; therefore, sodium correction should occur over roughly the same time period that it occurred. The fear of cerebral edema should be displaced by the clinician when

treating the patient with acute hypernatremia; idiogenic osmoles, organic molecules that attempt to maintain brain cell hydration, have not had time to appear in brain cells, and the risk of cerebral edema with fast correction is minimal compared with the mortality and morbidity associated with acute hypernatremia.[3,12] Correction of hypernatremia should be initiated with isotonic fluids and should occur over a minimum of 48 hours. The serum sodium level should not decrease by more than 8 to 15 mEq/L in any 8-hour period if the patient is symptomatic.[4,100,108,109] Overly rapid correction of hypernatremia with the use of hypotonic fluids may lead to seizures, permanent brain damage, or death.[7,100,108,110]

If the patient with hypernatremia shows evidence of dehydration, fluid resuscitation should take first priority, and the patient should be provided with adequate amounts of intravenous fluid to restore plasma volumes. Isotonic solutions should be used in these situations, because the patient normally has hypernatremia as a result of hypovolemia and isotonic solutions are likely still relatively hypotonic compared with the patient's serum. However, the serum sodium must be closely monitored to prevent correction from happening too quickly and leading to additional neurologic problems.[7] Approximately half of the water deficit should be provided in the first 12 to 24 hours, and the other half should be provided over the next 24 hours.[4] The free water deficit in adults can be calculated by the following equation (Equation 4):

$$\text{Water deficit (L)} = [(\text{measured Na}/\text{normal Na}) - 1] \quad 4$$

Again, frequent measurements of serum sodium to allow quick tailoring of therapy are necessary, because patients often do not precisely follow the guidelines used by the clinician. If correction occurs too rapidly, or if the patient begins to show symptoms of cerebral edema or hyponatremia, the clinician should immediately stop treatment of hypernatremia, and treat the patient as if they have hyponatremia with fluid restriction or addition of electrolytes/saline to the fluid infusion.

- Unstable patients with hypernatremia should receive isotonic fluids, with a goal to lower the serum sodium by 8 mEq/L to 15 mEq/L over the first 8 hours.

Stable patients

Chronic or slowly occurring hypernatremia does not cause as many symptoms and does not carry as high mortality, because of the presence of idiogenic osmoles.[3,12] Because of the brain's self-preservation strategy by production of idiogenic osmoles that allows relative maintenance of brain cell hydration,[3,12] rapid restoration of serum sodium levels to normal in patients with chronic hypernatremia may cause further complications because of resultant cerebral edema caused by these organic molecules. In the asymptomatic patient, correction of the serum sodium level should occur slowly, at a rate no greater than 0.5 mEq/L/h and no more than 8 mEq/L to 15 mEq/L per day.[3,4,99,100]

The specific causes of hypernatremia also have specific treatments tailored to the nature of the serum sodium excess. In cases of accidental excess sodium excretion, removal of sodium is the goal of treatment. If the patient is asymptomatic and has normal renal function, then the clinician may wait for natural excretion, which should not cause large shifts in brain cell hydration status. If renal function is impaired, then excess sodium needs to be removed through phlebotomy or dialysis. In patients with adipsia or hypodipsia, whether primary or secondary, patient, family, and caregiver education is paramount. The patient, family, or caregiver needs explanation about sensible and insensible water losses, the need for replacement daily of these losses, and how to monitor and accurately adjust water needs on a day-to-day basis.

With adequate education and frequent follow-up visits assessing hydration and serum sodium levels, these patients may remain eunatremic and euvolemic.

- Stable patients with hypernatremia should have serum sodium corrected by 8 mEq/L to 15 mEq/L per day until the sodium has normalized.

Pediatric Considerations

Hypernatremia in pediatric populations is rare outside other medical problems. Hypernatremia was found to occur in approximately only 0.004% of newborns and accounts for only approximately 0.04% of pediatric hospital admissions.[111] However, hypernatremia is associated with mortality of 15% in children,[18] and when encountered by the clinician, it should be taken seriously. Mild hypernatremia should not be considered benign, but rather should prompt further investigation and prompt attention to free-water administration.[87] Children that have particularly high mortality and morbidity associated with hypernatremia are infants with hypernatremic dehydration and children with end-stage liver disease.[111–114]

The outpatient pediatric group at highest risk of developing hypernatremia is breast-fed infants.[115] Infants that are primarily breast-fed and have more than 7% weight loss or who have jaundice should undergo prompt evaluation for hypernatremia.[87] Dehydration caused by diarrhea is another cause of acute hypernatremia[111]; however, because of the widespread availability of oral rehydration solutions, clinicians are seeing these patients less commonly.[87]

Pediatric patients with hypernatremia often have hypovolemia, and attention must first focus on correction of volume status. Once oral hydration can be tolerated, it should be used because oral hydration allows acute hypernatremia to be corrected faster, and leads to fewer seizures.[116]

- Breast-fed infants are one of the highest-risk groups for developing hypernatremia caused by dehydration; when possible, oral rehydration is preferred, because of decreased risk of complications.

FLUIDS USED FOR RESUSCITATION

In most cases of sodium imbalance, intravascular volume is depleted. The first priority of management in a patient with dysnatremia when associated with hypovolemia is restoration of the intravascular space. Infusion of isotonic 0.9% NS is the best initial fluid choice. In patients with preserved renal function, the patient excretes either excess sodium or water through the urine.[2,7] Even if the patient does not have normal renal function, intravascular volume takes priority over sodium balance.

The clinician should be aware of the fluids available for treatment (**Table 5**), should recognize the importance of the composition of each of the different types of fluids, and should treat intravenous fluids as any other medication prescribed to the patient.[4] Many complications can occur in electrolyte and water balance if a patient receives all of their fluids intravenously,[4] and the clinician should be aware of these possible complications.

Normotonic or isotonic fluids, such as 0.9% NS and lactated Ringer solution, are so named because they have an osmolality similar to that of plasma, approximately 275 to 295 mOsm/L H_2O. Because of the risk of osmotic demyelination syndrome associated with overly rapid correction of hyponatremia,[77] hypertonic saline greater than 3% NS is rarely used for correction. Some recommend initial intravascular volume repletion with solution closer to the electrolyte balance of plasma such as

Table 5
Sodium concentrations in fluid compartments and commonly used intravenous fluids

Fluid	Sodium Concentration (mEq/L)
Plasma	140
0.9% NS	154
0.45% NS	77
3% NS	513
Lactated Ringer solution	130
D5W	0
0.45% NS + 75 mEq sodium bicarbonate	152

lactated Ringer solution,[2] but most use 0.9% NS as the primary resuscitation fluid.[7] D5W, 0.45% NS, or any other hypotonic fluids should not be used as primary resuscitation fluids, because these fluids can lead to osmotic diuresis; instead, they should be preserved for maintenance fluids only.[4]

The clinician must seriously consider the amount and type of intravenous fluid used in treatment of pediatric patients. Hypotonic fluids, once routinely recommended for use in pediatric patients,[117] have been linked to more than 50 deaths or neurologic injuries in children after resultant hyponatremia.[87] Recommendations now exist that hypotonic fluids should be avoided in the pediatric population unless there is a well-established free-water deficit, hypernatremia, or ongoing water losses.[87,88] Most children evaluated in the emergency department and found to be in need of intravenous fluids have some signs of volume depletion.[87] Current recommendations state that these children should receive isotonic intravenous fluids, similar to the recommendations in adults.[87,88] Isotonic fluid administration in children, as in adults, should not result in hypernatremia or fluid overload unless there is a defect in excretion of excess sodium or free water.[87]

SUMMARY

Disorders of sodium and water occur simultaneously. The emergency physician must be aware of these disorders to quickly and accurately identify them in life-threatening situations. Often, disorders of sodium and water are chronic, but acute cases require rapid intervention. Before evaluation or possible correction of a sodium imbalance, the clinician must correct any intravascular volume losses. This correction is best achieved by infusion of isotonic NS. If depleted intravascular volume is the main cause of the sodium imbalance and renal function remains normal, the sodium imbalance should autocorrect without any neurologic side effects.

Overall, hyponatremia is often caused by a defect in water excretion, whereas hypernatremia is often caused by a defect in thirst regulation or water acquisition. Because of dreaded neurologic complications, the imbalance in the serum sodium should be corrected in approximately the same time frame as it initially occurred. Overly rapid correction may cause osmotic demyelination syndrome in patients with hyponatremia, or cerebral edema in patients with hypernatremia. Narrow control of the disorder of sodium balance should be the goal of the clinician. Emergency physicians should be aware that these imbalances of water and sodium are frequently encountered in the emergency department and should be aware of the pathophysiology that regulates them and the appropriate treatments based on patient symptoms and the underlying cause of the dysnatremia.

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