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Diagnosis and Management of Sodium Disorders: Hyponatremia and Hypernatremia

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Hyponatremia and hypernatremia are common findings in the inpatient and outpatient settings. Sodium disorders are associated with an increased risk of morbidity and mortality. Plasma osmolality plays a critical role in the pathophysiology and treatment of sodium disorders. Hyponatremia and hypernatremia are classified based on volume status (hypovolemia, euvolemia, and hypervolemia). Sodium disorders are diagnosed by findings from the history, physical examination, laboratory studies, and evaluation of volume status. Treatment is based on symptoms and underlying causes. In general, hyponatremia is treated with fluid restriction (in the setting of euvolemia), isotonic saline (in hypovolemia), and diuresis (in hypervolemia). A combination of these therapies may be needed based on the presentation. Hypertonic saline is used to treat severe symptomatic hyponatremia. Medications such as vaptans may have a role in the treatment of euvolemic and hypervolemic hyponatremia. The treatment of hypernatremia involves correcting the underlying cause and correcting the free water deficit. (*Am Fam Physician.* 2015;91(5):299-307. Copyright © 2015 American Academy of Family Physicians.)

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Hyponatremia is a common electrolyte disorder defined as a serum sodium level of less than 135 mEq per L.[1-3] A Dutch systematic review of 53 studies showed that the prevalence of mild hyponatremia was 22.2% in geriatric hospital wards, 6.0% in nongeriatric wards, and 17.2% in the intensive care unit.[2] The prevalence of severe hyponatremia (serum sodium level less than 125 mEq per L) was 4.5%, 0.8%, and 10.3%, respectively. It is estimated that hyponatremia occurs in 4% to 7% of the ambulatory population, with rates of 18.8% in nursing homes.[2-4]

Hyponatremia is associated with increased morbidity and mortality.[1-6] In patients with heart failure who undergo cardiac surgery, hyponatremia increases rates of postoperative complications, length of hospital stay, and mortality.[5,6] Mild hyponatremia in the ambulatory setting is associated with increased mortality (hazard ratio = 1.94) compared with normal sodium levels.[3] Patients who develop hyponatremia during hospitalization have increased mortality rates compared with those who have hyponatremia on admission.[7,8] It is unclear if hyponatremia is a marker for poor prognostic outcomes or merely a reflection of disease severity. Its presence suggests a worse prognosis in patients with liver cirrhosis, pulmonary hypertension, myocardial infarction, chronic kidney disease, hip fractures, and pulmonary embolism.[1,8-10]

Etiology and Pathophysiology

The most common classification system for hyponatremia is based on volume status: hypovolemic (decreased total body water with greater decrease in sodium level), euvolemic (increased total body water with normal sodium level), and hypervolemic (increased total body water compared with sodium).[11]

Plasma osmolality has a role in the pathophysiology of hyponatremia. Osmolality refers to the total concentration of solutes in water. Effective osmolality is the osmotic gradient created by solutes that do not cross the cell membrane. Effective osmolality determines the osmotic pressure and the flow of water.[11] Plasma osmolality is maintained by strict regulation of the arginine vasopressin (also called antidiuretic hormone [ADH]) system and thirst. If plasma osmolality increases, ADH is secreted and water is retained by the kidneys, thus decreasing serum osmolality. If plasma osmolality decreases, ADH also decreases, resulting in diuresis of free water and a return to homeostasis.[12,13]

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*	*Comments*
In patients with severe symptomatic hyponatremia, the rate of sodium correction should be 6 to 12 mEq per L in the first 24 hours and 18 mEq per L or less in 48 hours.	C	13, 14	Consensus guidelines based on systematic reviews
A bolus of 100 to 150 mL of hypertonic 3% saline can be given to correct severe hyponatremia.	C	13, 14	Consensus guidelines based on small studies
Vaptans appear to be safe for the treatment of severe hypervolemic and euvolemic hyponatremia but should not be used routinely.	C	14	Consensus guidelines based on observational studies
Chronic hypernatremia should be corrected at a rate of 0.5 mEq per L per hour, with a maximum change of 8 to 10 mEq per L in a 24-hour period.	C	33	Expert opinion

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.

Diagnostic Approach to Hyponatremia

Symptoms of hyponatremia depend on its severity and on the rate of sodium decline. Gradual decreases in sodium usually result in minimal symptoms, whereas rapid decreases can result in severe symptoms. Polydipsia, muscle cramps, headaches, falls, confusion, altered mental status, obtundation, coma, and status epilepticus may indicate the need for acute intervention. Most patients with hyponatremia are asymptomatic, and hyponatremia is noted incidentally. Volume status should be assessed to help determine the underlying cause[11,13] *(Figure 1*[11-16]*)*.

The diagnostic workup should include a history and physical examination with specific attention to cardiac, cancer, pulmonary, surgical, endocrine, gastrointestinal, neurologic, and renal histories *(Table 1)*.[11-13] Diuretics, carbamazepine (Tegretol), and selective serotonin reuptake inhibitors can cause hypovolemia; therefore, medications should be reviewed. Alcohol and illicit drug use (especially beer and 3,4-methylenedioxymethamphetamine ["Ecstasy"]) can cause hyponatremia.[11-13] Athletes should be asked about training regimens because high endurance activities can lead to hyponatremia.

Laboratory tests include a complete metabolic panel and urinary sodium and creatinine levels.[11,13] Serum osmolality and fractional excretion of sodium should be calculated *(eTable A)*. Measurement of thyroid-stimulating hormone, urinary uric acid, adrenocorticotropic hormone, plasma cortisol, and brain natriuretic peptide may be considered in select patients to rule out other causes.[13] The diagnosis of reset osmostat (a variation of syndrome of inappropriate antidiuretic hormone secretion [SIADH] in which ADH secretion occurs despite low plasma osmolality) may be aided using fractional excretion of urate (uric acid) in nonedematous patients who have hyponatremia that does not respond to usual treatment.[17]

Pseudohyponatremia

Pseudohyponatremia occurs when seemingly low sodium levels are actually normal. Causes include hyperglycemia, hyperproteinemia, mannitol use, or laboratory errors. Osmolality remains unchanged, and patients are usually euvolemic.[12,13] A corrected sodium calculation is needed in the setting of hyperglycemia *(eTable A)*.

Hypovolemic Hyponatremia

There are numerous causes of hypovolemic hyponatremia *(Table 1)*.[11-13] Patients typically have signs and symptoms associated with volume depletion (e.g., vomiting, diarrhea, tachycardia, elevated blood urea nitrogen–to-creatinine ratio). Urinary sodium levels are typically less than 20 mEq per L unless the kidney is the site of sodium loss. Fractional excretion of sodium is often inaccurately elevated in patients receiving diuretics because of diuretic-induced natriuresis; fractional excretion of urea can be utilized in these patients instead. Fractional excretion of urea less than 35% is more sensitive and specific for diagnosing prerenal azotemia in this setting.[18] Treatment generally consists of volume repletion with isotonic (0.9%) saline, occasional use of salt tablets, and treatment of the underlying condition.[13,14] Monitoring of urine output is recommended because output of more than 100 mL per hour can be a warning sign of overcorrection.[14]

Euvolemic Hyponatremia

Euvolemic hyponatremia is most commonly caused by SIADH, but can also be caused by hypothyroidism and glucocorticoid deficiency. Euvolemia is diagnosed by findings from the history and physical examination, low serum uric acid levels, a normal blood urea nitrogen–to-creatinine ratio, and spot urinary sodium greater than 20 mEq per L. Diuretic therapy can artificially elevate urinary sodium, whereas a low-salt diet can artificially lower urinary sodium, thus clouding the diagnosis of hypovolemia vs. euvolemia. Treatment generally consists of fluid restriction and correcting the underlying cause. Fluid restriction should be limited to 500 mL less than the daily urinary volume.[13] Salt and protein intake should not be restricted. Predictors of failure with

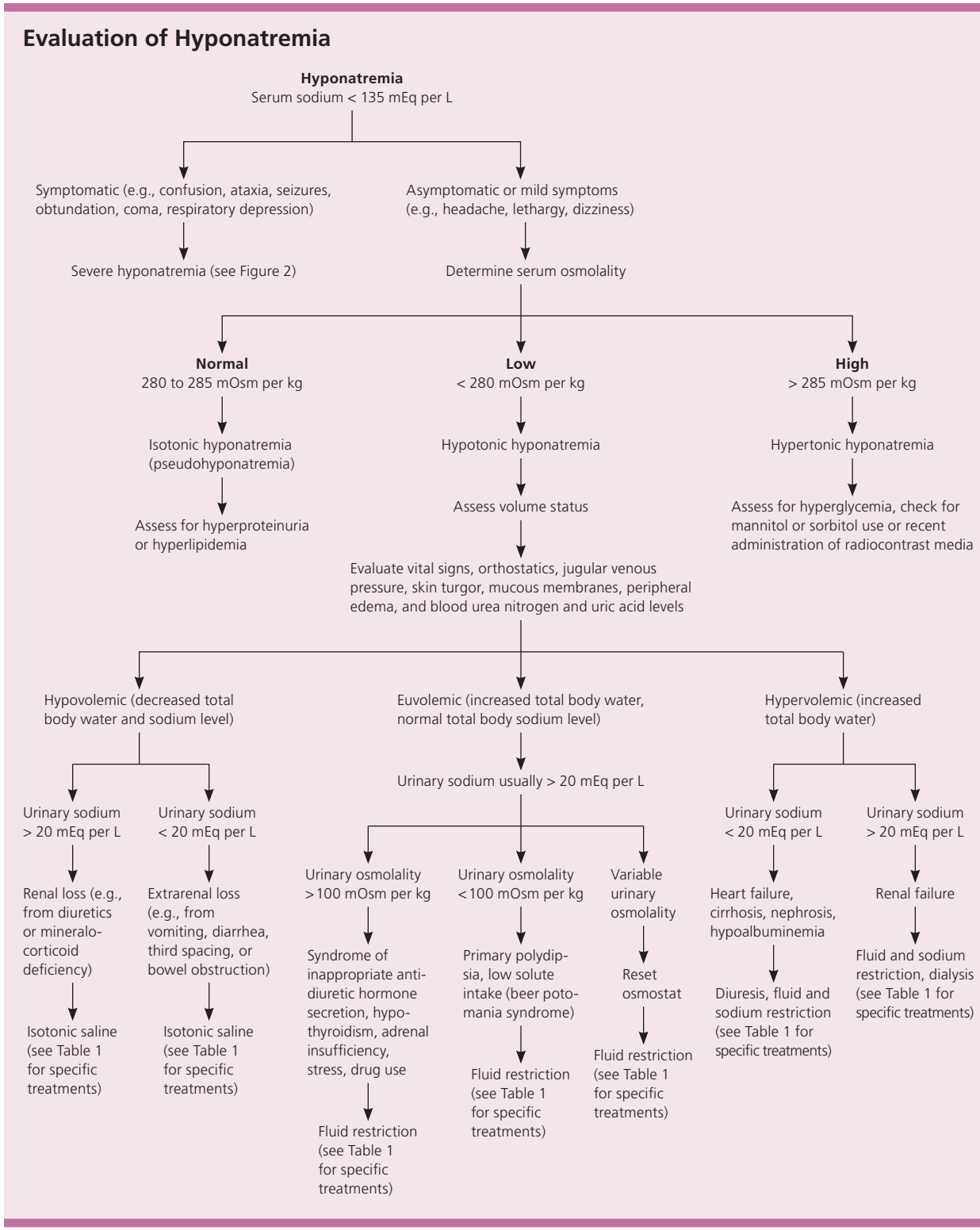

Figure 1. Algorithm for the evaluation of hyponatremia.

Information from references 11 through 16.

fluid restriction include urinary osmolality greater than 500 mOsm per kg, 24-hour urinary volume less than 1.5 L, an increase in the serum sodium level of less than 2 mEq per L within 24 to 48 hours, and a serum sodium level less than the sum of the urinary sodium and potassium levels.[13] Volume status can be difficult to determine; therefore, a trial of intravenous fluids may be warranted.[11] Sodium levels in patients with SIADH will decrease

Table 1. Differential Diagnosis and Treatment of Hyponatremia

Condition	*Diagnosis*	*Treatment*
Pseudohyponatremia		
Hyperglycemia (e.g., in diabetic ketoacidosis)	Elevated glucose levels (> 400 mg per dL [22.2 mmol per L]), elevated anion gap	Insulin, intravenous fluids, isotonic saline
Hyperlipidemia	Elevated total and low-density lipoprotein cholesterol levels	Statin therapy
Hyperproteinemia (e.g., in multiple myeloma)	Serum and urinary monoclonal protein, bone marrow biopsy, lytic bone lesions detected on radiography	Chemotherapy
Laboratory errors	Repeat sodium levels	—
Hypovolemic hyponatremia		
Cerebral salt wasting	Diagnosis of exclusion (e.g., head injuries, intracranial hemorrhage); urinary sodium > 20 mEq per L	Isotonic or hypertonic saline
Diuretic use	Clinical; urinary sodium > 20 mEq per L	Stop diuretic therapy
Gastrointestinal loss (e.g., diarrhea, vomiting)	Clinical; urinary sodium < 20 mEq per L	Intravenous fluids
Mineralocorticoid deficiency (e.g., Addison disease [primary], pituitary failure [secondary], hypothalamic failure [tertiary])	Low aldosterone and morning cortisol levels, hyperkalemia, increased plasma renin level, low or increased adrenocorticotropic hormone level (cause-dependent), urinary sodium > 20 mEq per L, positive results on cosyntropin stimulation test, 21-hydroxylase autoantibodies (Addison disease), computed tomography of adrenal glands to rule out infarction	Steroid replacement therapy
Osmotic diuresis	Elevated glucose level, mannitol use	Correct glucose level, stop mannitol use
Renal tubular acidosis	Urinary osmolar gap, increased urinary pH, urinary sodium > 25 mEq per L, fractional excretion of bicarbonate > 15% to 20%, hyperchloremic acidosis, decreased serum bicarbonate level, potassium abnormalities (type dependent)	Correct acidosis, sodium bicarbonate
Salt-wasting nephropathies	Urinary sodium > 20 mEq per L	Correct underlying cause
Third spacing (e.g., bowel obstruction, burns)	Clinical; computed tomography	Intravenous fluids, relieve obstruction
Euvolemic hyponatremia		
3,4-methylenedioxymethamphetamine ("Ecstasy") use	Urine drug screen	—
Beer potomania syndrome	Excessive alcohol consumption, low serum osmolality	Therapy to decrease alcohol use and nutritional counseling to increase protein intake

continues

further with intravenous fluid administration. The use of demeclocycline (Declomycin) and lithium is not recommended because of an increased risk of harm.[14]

Hypervolemic Hyponatremia

Hypervolemic hyponatremia occurs when the kidneys cannot excrete water efficiently. In volume overload states, the effective arterial blood volume is decreased compared with venous volume, resulting in excess ADH secretion. The most common causes of hypervolemic hyponatremia are heart failure, cirrhosis, and kidney injury. Treatment consists of correcting the underlying cause, sodium and fluid restriction, and diuretic therapy to increase excretion of solute-free water.[13,14] A randomized controlled trial of 46 patients with heart failure showed that restricting fluid intake to 1 L per day improved quality of life 60 days after discharge.[19]

Severe Symptomatic Hyponatremia

Severe symptomatic hyponatremia occurs when sodium levels decrease over less than 24 hours. Severe symptoms (e.g., coma, seizures) typically occur when the sodium level falls below 120 mEq per L, but can occur at less than 125 mEq per L. Severe symptomatic hyponatremia must be corrected promptly because it can lead to cerebral edema, irreversible neurologic damage, respiratory

Table 1. Differential Diagnosis and Treatment of Hyponatremia *(continued)*

Condition	*Diagnosis*	*Treatment*
Euvolemic hyponatremia *(continued)*		
Exercise-associated hyponatremia	Clinical	Isotonic or hypertonic saline, depending on symptoms
Glucocorticoid deficiency	Low aldosterone, morning cortisol, and adrenocorticotropic hormone levels, hyperkalemia, increased plasma renin level	Steroid replacement therapy
Hypothyroidism	Elevated thyroid-stimulating hormone level, low free thyroxine level	Thyroid replacement therapy
Low solute intake	Clinical	Increase sodium intake
Nephrogenic SIADH	Same as SIADH, with low vasopressin levels	Fluid restriction, loop diuretics
Psychogenic polydipsia	History of schizophrenia with excessive water intake	Psychiatric therapy
Reset osmostat	Free water challenge test, normal fractional excretion of uric acid (urate)	Treat underlying disease
SIADH	Decreased osmolality, urinary osmolality > 100 mOsm per kg, euvolemia, urinary sodium > 20 mEq per L, absence of thyroid disorders or hypocortisolism, normal renal function, no diuretic use	Fluid restriction, consider vaptans
SIADH secondary to medication use (e.g., barbiturates, carbamazepine [Tegretol], chlorpropamide, diuretics, opioids, selective serotonin reuptake inhibitors, tolbutamide, vincristine)	SIADH with use of causative agent	Stop causative medication
Water intoxication	Clinical; excessive water intake	Diuresis
Hypervolemic hyponatremia		
Heart failure	Clinical (e.g., jugular venous distention, edema), elevated B-type natriuretic peptide level, echocardiography, urinary sodium < 20 mEq per L	Diuretics, angiotensin-converting enzyme inhibitors, beta blockers
Hepatic failure/cirrhosis	Elevated liver function tests, ascites, elevated ammonia level, biopsy, urinary sodium < 20 mEq per L	Furosemide (Lasix), spironolactone (Aldactone), transplant
Nephrotic syndrome	Urinary protein, urinary sodium < 20 mEq per L	Treat underlying cause
Renal failure (acute or chronic)	Blood urea nitrogen–to-creatinine ratio, glomerular filtration rate, proteinuria, urinary sodium > 20 mEq per L	Correct underlying disease with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers

SIADH = syndrome of inappropriate antidiuretic hormone secretion.

Information from references 11 through 13.

arrest, brainstem herniation, and death. Treatment includes the use of hypertonic 3% saline infused at a rate of 0.5 to 2 mL per kg per hour until symptoms resolve. At this time, vaptans have no role in the treatment of symptomatic hyponatremia because of the potential for overcorrection of sodium and variable sodium fluctuations.[13] Loop diuretics may be needed in patients with concurrent symptomatic hyponatremia and volume overload. The rate of sodium correction should be 6 to 12 mEq per L in the first 24 hours and 18 mEq per L or less in 48 hours.[12-14] An increase of 4 to 6 mEq per L is usually sufficient to reduce symptoms of acute hyponatremia.[20] Rapid correction of sodium can result in osmotic demyelination (previously called central pontine myelinolysis). Overcorrection is common and is typically caused by rapid diuresis secondary to decreasing ADH levels. Every attempt should be made not to overcorrect sodium levels. One study of 25 patients with severe symptoms and sodium levels less than 120 mEq per L showed that concurrent treatment with a weight-based dose of 3% saline and 1 to 2 mcg of desmopressin every six to eight hours resulted in a rate of correction of 3 to 7 mEq per L per hour without causing overcorrection.[21] Another study used a 100-mL bolus of 3% saline infused over 10 minutes

in marathon runners; symptoms improved without overcorrecting. This method increased sodium levels by 1.5 to 2.0 mEq per L per hour.[13,22,23] Guidelines from the European Society of Endocrinology recommend infusing one dose of 150 mL of 3% saline over 20 minutes, with sodium monitoring every 20 minutes until symptoms resolve.[14] This regimen may be repeated if the patient remains symptomatic or until the goal sodium target of 5 mEq per L is achieved *(Figure 2*[13,14,20-23]*)*.

Vaptans

Vaptans (conivaptan [Vaprisol] and tolvaptan [Samsca]) are vasopressin-receptor antagonists approved for the treatment of hospitalized patients with severe hypervolemic and euvolemic hyponatremia *(eTable B)*. However, their use in the management of hyponatremia is controversial. Several trials have demonstrated that vaptans increase sodium levels in patients with cirrhosis and heart failure.[24] In the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan, patients with hyponatremia and heart failure who received tolvaptan had an associated reduction in cardiovascular morbidity and mortality, although there were several confounding variables, and further study is needed.[25] The Study of Ascending Levels of Tolvaptan in Hyponatremia (SALT) trials demonstrated increased sodium levels with tolvaptan in patients with SIADH, cirrhosis, and heart failure.[26] An extension of these studies, the SALTWATER trial, showed that long-term use of tolvaptan is safe and effective in increasing sodium levels, although this study did not specify subgroups.[27,28] Regardless of their effectiveness in increasing sodium levels, vaptans—specifically tolvaptan—should not be used in patients with hepatic impairment because they may worsen liver function.[29,30] The European Society of Endocrinology recommends against the routine use of vaptans, citing a lack of reduction in overall mortality rates and increased risk of rapid overcorrection.[14] Further study is needed to clarifiy the role of vaptans.

Hypernatremia

Hypernatremia is defined as a serum sodium level greater than 145 mEq per L. It is associated with increased morbidity and mortality in the inpatient setting.[31,32] Hypernatremia is caused by net water loss (increased loss or decreased intake) or, rarely, sodium gain. Patients at increased risk include those with an impaired thirst mechanism or restricted access to water (e.g., those with altered mental status, intubated patients, infants, older adults).

Symptoms of hypernatremia in infants can include tachypnea, muscle weakness, restlessness, a high-pitched cry, insomnia, lethargy, and coma. Seizures usually occur only in cases of inadvertent sodium loading or rapid rehydration. In adults, symptoms tend to be mild and may include anorexia, muscle weakness, restlessness, nausea, and vomiting. Severe symptoms are likely to occur with acute increases in plasma sodium levels or at concentrations greater than 160 mEq per L. Hypernatremia can cause brain shrinkage, resulting in vascular rupture and intracranial bleeding.[33]

Treatment of Severe Symptomatic Hyponatremia

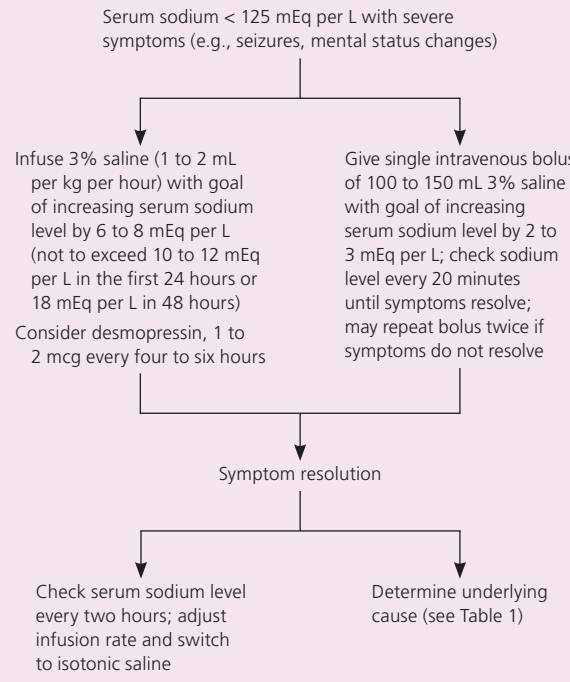

Figure 2. Algorithm for the treatment of severe symptomatic hyponatremia.

Information from references 13, 14, and 20 through 23.

DIAGNOSTIC APPROACH

The cause of hypernatremia is usually evident from the history and physical examination, and is typically water loss (e.g., gastrointestinal loss, restricted access to water) or sodium gain *(Table 2)*.[3,12,33,34] Patients are often asymptomatic but can present with irritability, nausea, weakness, altered mental status, or coma. Water loss can be pure water loss (e.g., in diabetes insipidus) or hypotonic fluid loss (e.g., renal, gastrointestinal, or cutaneous losses). Sodium gain is usually iatrogenic from the infusion of hypertonic solutions. Laboratory studies are not necessary if the cause is apparent from the history, but frequent electrolyte checks are recommended during correction. When the cause is not clear, laboratory studies should be guided by the history[12] *(Figure 3*[35]*)*.

Table 2. Differential Diagnosis and Treatment of Hypernatremia

Condition	*Diagnosis*	*Treatment*
Hypovolemic hypernatremia		
Body fluid loss (e.g., burns, sweating)	Clinical	Free water replacement
Diuretic use	Clinical	Stop diuretic
Gastrointestinal loss (e.g., vomiting, diarrhea, fistulas)	Clinical	Free water replacement
Heat injury	Elevated temperature, myoglobinuria, elevated creatinine level	Intravenous fluids, supportive care
Osmotic diuresis (e.g., hyperosmolar nonketotic coma, mannitol use, enteral feeding)	Elevated glucose level; sodium level often elevated after correction	Correct glucose level, stop causative agent
Post-obstruction	Clinical	Supportive care
Euvolemic hypernatremia		
Central diabetes insipidus	Clinical history of central nervous system insult; urinary concentration after administration of desmopressin	Treatment is rarely required unless thirst is impaired
Fever	Clinical	Treat underlying cause
Hyperventilation/mechanical ventilation	Clinical	Adjust ventilation
Hypodipsia	Clinical	Increase free water consumption
Medications (e.g., amphotericin, aminoglycosides, lithium, phenytoin [Dilantin])	Medication review	Stop causative medication
Nephrogenic diabetes insipidus	History of nephrotoxic medication use (amphotericin, demeclocycline [Declomycin], foscarnet, lithium, methoxyflurane), failure to concentrate urine after administration of desmopressin	Stop causative medication
Sickle cell disease	Hemoglobin electrophoresis	Treat underlying disease
Suprasellar and infrasellar tumors	Magnetic resonance imaging	Treat underlying disease
Hypervolemic hypernatremia		
Cushing syndrome	24-hour urinary cortisol and adrenocorticotropic hormone levels, dexamethasone suppression test	Treat underlying disease
Hemodialysis	Clinical history	Treat underlying disease
Hyperaldosteronism	History of hypertension and hypokalemia, plasma aldosterone-to-renin ratio,[3] history of hypertension and hypokalemia	Treatment usually not needed for hypernatremia
Iatrogenic (e.g., salt tablet or salt water ingestion, saline infusions, saline enemas, intravenous bicarbonate, enteral feedings)	Recent administration of hypertonic saline, enteral feedings, sodium bicarbonate infusion, or hypertonic dialysis	Stop causative medication, rapid free water replacement

Information from references 3, 12, 33, and 34.

Diabetes insipidus is caused by a defect in ADH, either at the level of the central nervous system (central diabetes insipidus) or kidneys (nephrogenic diabetes insipidus). Inappropriately dilute urine (osmolality less than 300 mOsm per kg) in the setting of hypernatremia suggests diabetes insipidus. Hyperaldosteronism can cause mild hypernatremia but is rarely clinically relevant. Hyperglycemia can also cause hypernatremia, even after correction of glucose levels.[36]

TREATMENT

The treatment of hypernatremia involves treating the underlying cause and correcting the water deficit. Determining volume status and calculating the total body water deficit are important *(eTable A)*. When correcting the total body water deficit, oral or enteral free water should be used whenever possible. When intravenous fluids are required, hypotonic solutions should be used. Rapid overcorrection can result in cerebral edema; therefore, the

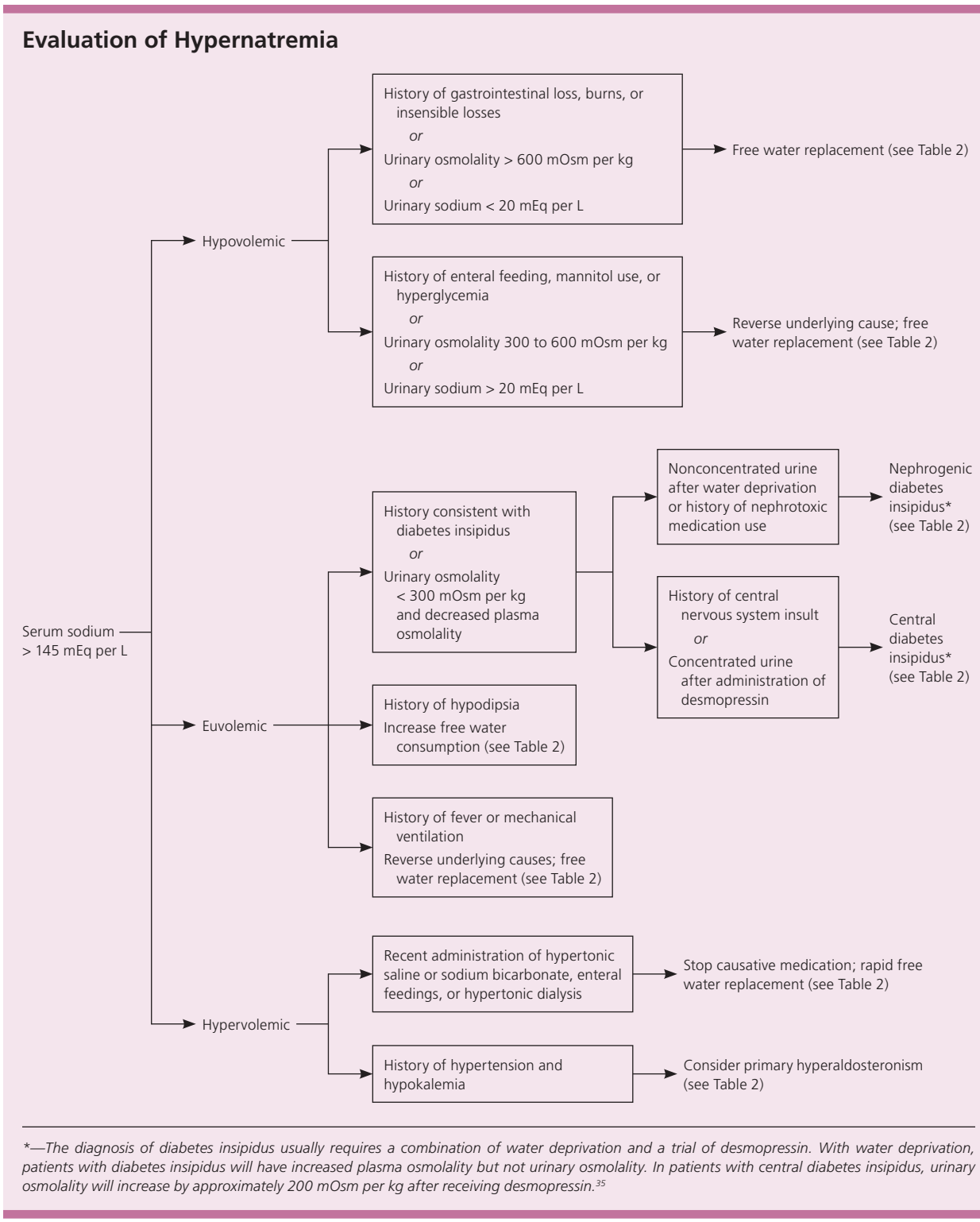

Figure 3. Algorithm for the evaluation of hypernatremia.

least amount of fluid possible should be used.[33] e*Table C* lists the sodium content of various intravenous fluids.

In patients with rapid development of hypernatremia, sodium can be corrected quickly with isotonic saline or water without increasing the risk of cerebral edema. A correction rate of 1 mEq per L per hour is considered safe in these patients.[12,36] In patients with hypernatremia that developed over a longer period, the sodium level should be corrected at a rate of 0.5 mEq per L per hour, with no more than an 8 to 10 mEq per L decrease over 24 hours.[33,36,37] The target sodium level should be 145 mEq per L.[33]

Data Sources: We searched the Cochrane database, Dynamed, PubMed, PEPID, Clinical Evidence, the National Guideline Clearinghouse, UpToDate, and OVID using the key terms hyponatremia, hypernatremia, vaptans, diagnosis, and treatment. The search included meta-analyses, randomized controlled trials, clinical trials, and reviews. Search dates: November 15, 2013; March 1, 2014; and October 5, 2014.

The views expressed are those of the authors and do not reflect the official policy of the Department of the Army, the Department of Defense, or the U.S. government.

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eTable A. Sodium Equations and Online Calculators

Measurement	*Equation*
Corrected sodium	Measured sodium + 0.024 × (serum glucose – 100)*
	or
	Measured sodium + 0.016 × (serum glucose – 100)
	Normal = 135 to 145 mEq per L
	Online calculators available at http://www.mdcalc.com/sodium-correction-for-hyperglycemia and http://www.medcalc.com/correctna.html
Fractional excretion of sodium	([Plasma creatinine × urinary sodium] / [plasma sodium × urinary creatinine]) × 100
	Prerenal < 1%, intrinsic > 1%, and postrenal > 4%
	Online calculators available at http://www.mdcalc.com/fractional-excretion-of-sodium-fena and http://www.medcalc.com/fena.html
Infusion rate of sodium	Online calculators for the rate of infusion and the concentration of sodium required are available at http://www.mdcalc.com/sodium-correction-rate-in-hyponatremia, http://www.medcalc.com/sodium.html, and http://www.nephromatic.com/sodium_correction.php
	Serum sodium correction should generally not proceed faster than 0.5 mEq per L per hour for the first 24 to 48 hours; however, in severely symptomatic patients, the rate can be 1.0 to 2.0 mEq per L per hour; these situations typically require use of 3% saline
	The goal is to raise the serum sodium level not to exceed 10 to 12 mEq per L in the first 24 hours and 18 mEq per L in the first 48 hours
	Isotonic saline contains 154 mEq of sodium per L, and 3% saline contains 513 mEq of sodium per L
Serum osmolality	(Sodium × 2) + (glucose / 18) + (blood urea nitrogen / 2.8)
	Normal = 280 to 295 mOsm per kg
	In patients with hyperglycemia, uncorrected sodium should be used to calculate the osmolality
	Online calculators available at http://www.mdcalc.com/serum-osmolality-osmolarity and http://www.medcalc.com/osmol.html
Sodium deficit	Total body water % × weight in kg × (desired sodium – actual sodium)
	For total body water %, use 0.6 for men and 0.5 for women
	Example: for a 70-kg man with a serum sodium level of 120 mEq per L and a desired serum sodium level of 140 mEq per L, the calculation is 0.6 × 70 (140 – 120) = 42 × 20 = 840 mEq
	Online calculator available at http://www.mdcalc.com/sodium-deficit-in-hyponatremia
Water deficit	Volume (L) = (total body water %) × weight in kg × [(sodium – 140) / 140]
	For total body water %, use 0.45 for women older than 65 years, 0.5 for women 65 years and younger and for men older than 65 years, and 0.6 for men 65 years and younger and for children
	Example: for a 70-kg man with a serum sodium level of 120 mEq per L, the calculation is 0.6 × 70 × ([120 – 140] / 140) = 42 × (–20 / 140) = 42 × (–1 / 7) = –6 L
	Online calculators available at http://www.mdcalc.com/free-water-deficit-in-hypernatremia and http://www.medcalc.com/freewater.html

**—A 1999 study that evaluated six healthy patients, induced hyperglycemia, and measured actual serum sodium levels found that a sodium correction factor of 2.4 mEq per L was more accurate than the traditional 1.6 mEq per L.*

Information from:

Adrogué HJ, et al. Hypernatremia. N Engl J Med. *2000;342(20):1493-1499.*

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eTable B. Summary of Vaptans

Drug	*Conivaptan (Vaprisol)*	*Tolvaptan (Samsca)*
Indications	Short-term use for hospitalized patients with hypervolemic or euvolemic hyponatremia associated with heart failure or syndrome of inappropriate antidiuretic hormone secretion with sodium < 125 mEq per L	Approved for use for up to 30 days for hypervolemic or euvolemic hyponatremia associated with heart failure or syndrome of inappropriate antidiuretic hormone secretion with sodium < 125 mEq per L
Dosing	20 mg intravenously (in 100-mL dextrose 5% solution) infused over 30 minutes as a loading dose, followed by continuous infusion of 20 mg over 24 hours for two to four days; may increase to 40 mg over 24 hours; do not exceed four days Patients with moderate hepatic impairment: 10 mg infused over 30 minutes as a loading dose, followed by a continuous infusion of 10 mg over 24 hours (0.42 mg per hour) for two to four days; may increase to a maximum dose of 20 mg over 24 hours (0.83 mg per hour) if serum sodium is not increasing sufficiently; do not exceed four days	15 mg orally once daily; after 24 hours may increase to 30 mg once daily, then titrate to desired sodium concentration (maximum of 60 mg per day)
Pharmacodynamics	Metabolized by CYP3A4 Half-life: five to eight hours Excretion: feces (83%), urine (12%, primarily as metabolites)	Metabolized by CYP3A4 Onset: two to four hours Peak: four to eight hours Half-life: five to 12 hours Excretion: feces
Safety	Adverse effects: *More common:* fever, hypokalemia, injury to intravenous site, orthostatic hypotension *Less common:* anemia, atrial fibrillation, confusion, constipation, dehydration, diarrhea, dry mouth, electrocardiographic abnormalities, erythema, headache, hematuria, hyperglycemia, hypertension, hypoglycemia, hypomagnesia, hyponatremia, hypotension, insomnia, nausea, oral candidiasis, pain, peripheral edema, pharyngolaryngitis, phlebitis, pneumonia, polyuria, pruritus, thirst, urinary tract infection, vomiting Change intravenous site every 24 hours; avoid corn products Contraindicated in patients with anuria or concurrent use of CYP3A inhibitors Not recommended for patients with creatinine clearance less than 30 mL per minute per 1.73 m^2 (0.50 mL per second per m^2)	Adverse effects: *More common:* nausea, pollakiuria, polyuria, thirst, xerostomia *Less common:* anorexia, constipation, fever, gastrointestinal bleeding, hepatotoxicity, hyperglycemia, hypernatremia, weakness Do not use for more than 30 days or in patients with underlying liver disease because of risk of hepatotoxicity; avoid consumption of grapefruit juice Liver function should be monitored frequently Contraindicated in patients with hypovolemic hyponatremia, anuria, or concurrent use of CYP3A inhibitors, or when there is an urgent need to increase sodium levels Not recommended for patients with creatinine clearance less than 10 mL per minute per 1.73^2 (0.17 mL per second per m^2)
Price*	$687 for 100 mL of solution (20 mg of conivaptan)	$3,440 for 10 15- or 30-mg tablets
Considerations	Vaptans should be initiated in the inpatient setting to monitor sodium levels No reports of osmotic demyelination; however, vaptans can rapidly overcorrect Hypovolemic hyponatremia should be ruled out before initiating therapy Should not be used in patients with severe symptomatic hyponatremia Good safety profile for limited use in current studies; further study needed to evaluate long-term use, effects, cost-effectiveness, and effects on morbidity and mortality Optimal regimens and dosages are unclear	

NOTE: *Lixivaptan is awaiting approval from the U.S. Food and Drug Administration for use in patients with euvolemia and hypervolemic hyponatremia.*

CYP = cytochrome P.

**—Estimated retail price based on information from https://online.lexi.com/crlsql/servlet/crlonline (subscription required; accessed March 1, 2014).*

Information from:

Dahl E, et al. Meta-analysis: the safety and efficacy of vaptans (tolvaptan, satavaptan and lixivaptan) in cirrhosis with ascites or hyponatraemia. Aliment Pharmacol Ther. *2012;36(7):619-626.*

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eTable C. Sodium Concentration of Intravenous Fluids

Fluid	*Sodium concentration (mEq per L)*
Dextrose 5%	0
Dextrose 5% with sodium chloride 0.2%	34
Sodium chloride 0.45%	77
Lactated Ringer solution	130
Sodium chloride 0.9%	154