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Hyponatremia

Hyponatremia is the most common electrolyte disorder in hospitalized patients. Hospital-associated hyponatremia includes community-acquired (e.g., hyponatremia on admission) and hospital-acquired hyponatremia. Acute-onset hyponatremia requires rapid treatment with hypertonic saline to decrease cerebral edema. In cases of chronic hyponatremia (>48 hours), the brain has time to normalize cell volume by losing solutes. However, even mild chronic cases can have adverse outcomes, such as decreased cognition, osteoporosis, increased risk for falls, and fractures. Hyponatremia is associated with increased hospital length of stay, readmissions, morbidity, and mortality. Prompt recognition and appropriate treatment are therefore necessary to improve outcomes.

Prevention

Diagnosis

Treatment

Practice Improvement

CME/MOC activity available at Annals.org.

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Hyponatremia is a disorder of water balance. Normal levels of plasma sodium are determined by the total exchangeable extracellular sodium and intracellular potassium divided by total body water. The ability to excrete dilute urine allows people without any underlying disease to drink large amounts of water (nearly 20 liters per day) without becoming hyponatremic. Maximum urine volume requires normally functioning kidneys, adequate solutes (urea and sodium), ability to dilute urine, and suppressed secretion of the antidiuretic hormone, arginine vasopressin (AVP), when plasma sodium levels fall below 135 mmol/L. Hyponatremia develops in patients with normal kidneys if more water is ingested than can be excreted by the kidneys. The ability to excrete a large volume of dilute urine is compromised because of kidney disease, diuretics, low solute (protein or sodium) intake, or nonosmotic release of AVP. The amount of free water excreted is determined by urine volume, sodium concentration, and potassium concentration. If the sum of urinary sodium and potassium is less than plasma sodium, free water is excreted. Regulating water intake is therefore fundamental to the management of hyponatremia.

Prevention

Who is at risk for hyponatremia?

There is a wide range in the incidence of hyponatremia, ranging from 30% over 10 years to 4% over 2 years (1, 2). A common precipitant of hyponatremia is medications. In a recent study of patients who developed hyponatremia, thiazide exposure was associated with an almost 5-times greater risk for hyponatremia than no exposure (hazard ratio, 4.95 [95% CI, 4.12–5.96]). Similarly, the risk for mild hyponatremia was more than 4.5 times higher in thiazide-exposed individuals and the risk for moderate and severe hyponatremia was 8-fold higher in individuals exposed to thiazides (3). In another study of patients initiating thiazide treatment, hospitalization risk was estimated at an odds ratio (OR) of 2.9 (CI, 2.7–3.1) (4). Patients of advanced age as well as those with low body weight and hypokalemia have an increased risk for thiazide-associated hyponatremia (5). Other drugs that can interfere with the ability to dilute the urine include selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), carbamazepine, and oxcarbazepine. In a study of individuals initiating treatment with SSRIs, risk for hospitalization for hyponatremia was estimated at an OR of 2.1 (CI, 1.0–4.2) at week 13 of therapy (6).

Up to 13% of individuals participating in marathons and triathlons develop hyponatremia, which can be severe (sodium level <120 mmol/L) (7). Patients with schizophrenia, psychoses, or primary polydipsia can become hyponatremic after rapidly ingesting large quantities of water, despite an intact ability to excrete maximally dilute urine. People who consume large quantities of fluid but little protein and/or sodium (e.g., beer potomania or a tea-and-toast diet) may also become hyponatremic, because decreased excretion of urea and sodium limits water excretion. Importantly, potomania is an underrecognized cause of hyponatremia and its risk increases with chronic kidney disease, as the diluting ability of the kidney is impaired.

In a study of patients with chronic kidney disease and a mean estimated glomerular filtration rate of 50.2 ± 14.1 mL/min/1.73 m^2, prevalence of hyponatremia was 13.6% at baseline and 26% of patients had more than 1 episode of hyponatremia during a follow-up period of 5.5 years (8).

The ability to excrete water is also limited when the posterior pituitary continues to

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secrete AVP despite a low plasma sodium concentration. AVP is secreted without an osmotic stimulus if there is a decreased effective arterial volume, such as occurs among patients with hypovolemia, congestive heart failure, and cirrhosis with ascites. Patients who secrete AVP without an osmotic or hemodynamic stimulus have the syndrome of inappropriate antidiuretic hormone secretion, more recently called the syndrome of inappropriate diuresis (SIAD). Hyponatremia due to SIAD is common in hospitalized patients because AVP is released in response to hypoxia, pain, or stress. In addition, fluid intake may be limited in inpatient settings. Postsurgical patients, patients of advanced age, those with pulmonary disease, critically ill patients, and patients with central nervous system disorders are at particularly high risk (9, 10).

What potential measures can prevent or limit the severity of hyponatremia?

Patients at risk for hyponatremia should be educated about the subtle symptoms of hyponatremia (e.g., nausea, vomiting) and told to contact their physician when experiencing these symptoms. Patients taking medications associated with hyponatremia (e.g., thiazides, SNRIs, SSRIs) should be advised of the risk and told to ingest water based on thirst. Physicians should consider checking plasma sodium levels 1 to 2 weeks after initiating therapy with these agents, especially in older patients and those with chronic kidney disease. Plasma sodium levels should be measured in all hospitalized patients on admission; hypotonic fluids should be avoided and low sodium levels should prompt an investigation.

Prevention... Hyponatremia is common in patients receiving thiazides, SSRIs, or SNRIs. Patients of advanced age, those with low solute intake (e.g., alcohol use disorder, malnourishment, congestive heart failure, cirrhosis, or pneumonia), patients with chronic kidney disease, and persons admitted to the intensive care unit are at increased risk for hospital-acquired hyponatremia. Excessive fluid intake and hypotonic fluids should be avoided in hospitalized patients.

CLINICAL BOTTOM LINE

Diagnosis

What symptoms or physical findings should alert clinicians to the diagnosis of hyponatremia?

Symptoms of hyponatremia range widely from nausea to seizures. Notably, in a study of thiazide-induced hyponatremia (sodium level <135 mmol/L), mild neurologic manifestations often appeared without clinical volume depletion. The most frequent symptoms were malaise and lethargy (49%), dizzy spells (47%), and vomiting (35%). With moderate hyponatremia, neurologic symptoms such as nausea, headache, and confusion were more common. Once plasma sodium level drops below 115 mmol/L, confusion is likely to develop. Symptoms associated with severe hyponatremia also include delirium, impaired consciousness, seizures, and, rarely, cardiorespiratory arrest (11). In a study evaluating neurologic symptoms associated with hyponatremia in hospitalized patients, impairment in neurocognitive functioning, motor performance, and mood stability were noted across a battery of tests. The scores of all tested domains were significantly worse in the hyponatremia group (median sodium level, 122 mmol/L [range, 119–126 mmol/L]) versus those with normal sodium level (12). In addition to neurologic symptoms, hyponatremic patients are at risk for osteoporosis, falls, and hip fractures. Thus, the diagnosis should also be considered in patients presenting with these conditions (13).

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What conditions should clinicians consider when evaluating patients with hyponatremia?

Hyponatremia can occur when release of AVP is physiologically appropriate (e.g., due to decreased effective arterial volume) or inappropriate (that is, in the absence of a physiologic reason). AVP leads to a decrease in urine volume, and hyponatremia will develop if water intake exceeds urinary and insensible losses. Patients are typically classified based on their total body sodium and volume status as hypovolemic, euvolemic, or hypervolemic (Table 1).

Hypovolemic hyponatremia

Patients with hypovolemic hyponatremia experience a loss of sodium and/or potassium that is greater than the loss of water. Patients may also have received hypotonic fluid replacement (either oral or intravenous), leading to decreases in sodium. Thus, hypovolemic hyponatremia can be classified as being due to renal or extrarenal losses. Extrarenal sodium losses can occur with excessive sweating, pancreatitis, small bowel obstruction, vomiting, and diarrhea. If these losses are not replaced, the resultant decrease in effective arterial volume leads to nonosmotic release of AVP. Urine electrolytes may provide clues to the cause of hyponatremia. For example, hypovolemic hyponatremia results in low urine sodium levels due to increased renal sodium reabsorption. Hypovolemia caused by gastric losses of hydrochloric acid results in low urine chloride levels due to increased renal chloride reabsorption.

Renal sodium loss occurs in the setting of glucosuria, cerebral salt wasting (CSW), primary adrenal insufficiency, and diuretic therapy. Although loop diuretics can cause hyponatremia, they do so less commonly than thiazide diuretics. Unlike thiazides, patients exposed to loop diuretic therapy experience hypovolemic hyponatremia (whereas thiazide-associated hyponatremia is usually clinically euvolemic). Cerebral salt wasting is an uncommon condition but can occur with head injury, subarachnoid hemorrhage, meningitis, encephalitis, and central nervous system tumors or surgery. Patients with CSW have urinary loss of sodium and water due to a proximal sodium reabsorption deficit and decreased reabsorption of urea and uric acid. Because it is often difficult to assess volume status in patients after neurosurgery in the intensive care unit, a substantial negative postoperative fluid balance should alert clinicians to the possibility of CSW. In such patients, volume depletion leads to nonosmotic release of AVP and water retention. As in cases of SIAD, patients with CSW have decreased plasma levels of sodium and increased urinary sodium and osmolality.

An important and often overlooked cause of hypovolemic hyponatremia is primary adrenal insufficiency (loss of mineralocorticoids and glucocorticoids).

Table 1. **Major Causes of Hyponatremia Based on Volume Status**

Hypovolemia
Extrarenal losses
Vomiting
Diarrhea
Pancreatitis
Sweating
Small bowel obstruction
Renal losses
Osmotic diuresis
Cerebral salt wasting
Salt-losing nephritis
Diuretics
Addison disease
Euvolemia
Primary polydipsia
Decreased solute excretion
Diuretics
Hypothyroidism
Cortisol deficiency
Syndrome of inappropriate antidiuretic hormone secretion
Hypervolemia
Heart failure
Liver disease with cirrhosis
Nephrotic syndrome
Chronic kidney disease

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Table 2. **Criteria for the Diagnosis of SIAD**

Essential Criteria
Decreased effective osmolality of the extracellular fluid (plasma osmolality <275 mmol/kg H_2O)
Inappropriate urinary concentration (urine osmolality >100 mmol/kg H_2O with normal renal function) in the presence of decreased effective serum osmolality
Clinical euvolemia, as defined by the absence of signs of hypovolemia (orthostasis, tachycardia, decreased skin turgor, dry mucous membranes) or hypervolemia (subcutaneous edema, ascites)
Absence of urinary sodium conservation (i.e., urine sodium <30 mmol/L) when salt and water intake are normal
Absence of other potential causes of euvolemic hypoosmolality: hypothyroidism, hypocortisolism (pituitary ACTH insufficiency), and diuretic use
Supplemental Criteria
Plasma uric acid <0.24 mmol/L
Blood urea nitrogen <3.57 mmol/L
Fractional sodium excretion >1%; fractional urea excretion >55%
Abnormal water load test (inability to excrete at least 90% of a 20 mL/kg water load in 4 hours, failure to dilute urine osmolality to <100 mmol/kg H_2O, or both)
No significant correction of plasma sodium with volume expansion but improvement after fluid restriction

ACTH = adrenocorticotrophic hormone; SIAD = syndrome of inappropriate diuresis.

Due to lack of aldosterone, primary adrenal insufficiency leads to renal sodium wasting with subsequent volume depletion. In turn, this leads to nonosmotic release of AVP. In addition to mineralocorticoid absence, lack of cortisol also increases AVP release. Patients with Addison disease typically present with hypovolemia, hyponatremia, hyperkalemia, decreased bicarbonate, and increased urine sodium, an inappropriate renal response in the setting of volume depletion.

In a study of 102 patients with Addison disease, 88% were hypotensive (systolic blood pressure <110 mm Hg), 12% were orthostatic, and only 66% were hyperkalemic (14).

Euvolemic hyponatremia

Euvolemic hyponatremia occurs when total body sodium content is either normal or slightly decreased while total body water is increased. The most common causes include SIAD, diuretic use, chronic kidney disease, decreased solute intake, primary polydipsia, glucocorticoid and thyroid deficiency, and reset osmostat.

SIAD is the most common cause of euvolemic hyponatremia. Patients with SIAD have a slight decrease in total body sodium and an increase in total body water resulting in clinical euvolemia. Of note, their laboratory findings of decreased uric acid and blood urea nitrogen–creatinine ratio are consistent with slight hypervolemia. **Table 2** presents criteria for diagnosis of SIAD. SIAD cannot be diagnosed in patients receiving diuretics (particularly thiazide diuretics) or those who have severe hypothyroidism or isolated glucocorticoid insufficiency (secondary adrenal insufficiency). SIAD is common in hospitalized patients and patients treated with SSRIs and SNRIs (**Table 3**).

Diuretics commonly cause hyponatremia. Loop diuretics decrease the ability to both dilute and concentrate the urine, whereas thiazides only affect the ability to dilute urine. Therefore, thiazides are more often associated with hyponatremia than loop diuretics. Most patients with thiazide-induced hyponatremia are euvolemic (as is the case in SIAD). They initially lose sodium but are able to maintain sodium balance due to increased reabsorption in other portions of the nephron.

Studies comparing risk for hyponatremia with hydrochlorothiazide versus chlorthalidone offer mixed results. One study confirmed that hyponatremia occurs more often when chlorthalidone

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Table 3. **Common Causes of SIAD**

Tumors	
	Pulmonary/mediastinal (small cell carcinoma, mesothelioma, thymoma)
	Non-chest carcinomas (duodenal, stomach, pancreatic, ureteral, prostate, bladder, uterine, nasopharyngeal)
	Lymphoma
	Ewing sarcoma
Central nervous system disorders	
	Mass lesions (tumors, brain abscesses, subdural hematoma)
	Inflammatory diseases (encephalitis, meningitis, systemic lupus, acute intermittent porphyria, multiple sclerosis)
	Degenerative/demyelinating diseases (Guillain–Barré syndrome, spinal cord lesions)
	Miscellaneous (subarachnoid hemorrhage, head trauma, acute and chronic psychosis, delirium tremens, pituitary stalk section, transsphenoidal adenomectomy, hydrocephalus, cerebrovascular accident, cavernous sinus thrombosis)
Drug-induced	
	Stimulated AVP release (narcotics, nicotine, phenothiazines, tricyclics)
	Direct renal effects, potentiation of AVP antidiuretic effects (desmopressin, oxytocin, prostaglandin synthesis inhibitors), or both
	Mixed or uncertain actions (carbamazepine and oxcarbazepine, chlorpropamide, clofibrate, clozapine, cyclophosphamide, ifosfamide, 3,4-methylenedioxymethamphetamine ["ecstasy"], serotonin reuptake inhibitors, vincristine)
Pulmonary diseases	
	Infections (tuberculosis, acute bacterial and viral pneumonia, pulmonary abscess, aspergillosis, emphysema)
	Mechanical/ventilatory (acute respiratory failure, asthma, COPD, positive-pressure ventilation)
Other	
	Rocky Mountain spotted fever
	AIDS and early symptomatic HIV infection
	Nausea, pain, stress
	Prolonged strenuous exercise (marathon, triathlon, ultramarathon, hot-weather hiking)
	Mutations of the aquaretic vasopressin receptor
	Idiopathic

AVP = arginine vasopressin; COPD = chronic obstructive pulmonary disease; SIAD = syndrome of inappropriate diuresis.

is prescribed in the same dose as hydrochlorothiazide; however, when the dose of chlorthalidone is half of the hydrochlorothiazide dose (e.g., 12.5 mg vs. 25 mg), no difference in the incidence of hyponatremia was observed (15).

Chronic kidney disease can cause both euvolemic and hypervolemic hyponatremia. Patients with chronic kidney disease have a decreased ability to dilute and concentrate urine, and urine osmolality is often fixed, which limits the ability to increase free water excretion (16). Kidney function must be normal to make a diagnosis of SIAD.

Primary polydipsia is an unusual cause of hyponatremia; most patients with this diagnosis have an underlying psychiatric diagnosis, particularly acute psychosis with schizophrenia. They can develop hyponatremia through rapid ingestion of large amounts of fluids that exceed the kidney's ability to excrete volume. Other factors that can contribute to hyponatremia in patients with psychiatric illness include volume depletion (leading to increased urine osmolality and decreased solute excretion), treatment with medications known to cause SIAD, and decreased solute intake (sodium and protein). Acute psychosis itself can also lead to an increase in AVP release (17).

Exercise-associated hyponatremia is acute and occurs after vigorous endurance exercise. Most symptomatic patients with exercise-associated hyponatremia are euvolemic and their cases

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are associated with overhydration in the presence of nonosmotic release of AVP (18).

Isolated glucocorticoid deficiency caused by lack of adrenocorticotropic hormone results in euvolemic hyponatremia because cortisol is required to inhibit AVP secretion. Aldosterone secretion is not affected because the renin–angiotensin–aldosterone system and levels of potassium control its release. An adrenocorticotropic hormone stimulation test is needed to diagnose secondary adrenal insufficiency.

Reset osmostat is a condition in which the serum osmolality required to stimulate the release of AVP is shifted to a lower serum osmolality. This condition has been described in patients with quadriplegia, tuberculosis, chronic malnutrition, and psychosis. The diagnosis should be considered when evaluating a patient who is diagnosed with SIAD with stable plasma sodium levels. The diagnosis is made by administering a water load to the patient and measuring urine output and osmolality. In contrast to patients with SIAD, patients with reset osmostat demonstrate increased free water excretion and decreased urine osmolality after a water load.

Hypervolemic hyponatremia

Conditions associated with hypervolemic hyponatremia include heart failure, cirrhosis with ascites, chronic kidney disease, and nephrotic syndrome. Patients with heart failure and cirrhosis experience decreased effective arterial volume. In patients with cirrhosis, vascular resistance decreases in the splanchnic circulation due to increased endothelial release of nitric oxide. This decrease leads to lowering of blood pressure and effective arterial volume, causing increased renin-angiotensin-aldosterone system activity, increased sympathetic nervous system activity and nonosmotic release of AVP, increased sodium and water reabsorption, and hypervolemia. Patients with nephrotic syndrome have edema due to primary sodium retention if the albumin level is greater than 17 g/L ("overfill"). Primary sodium retention is secondary to urinary plasmin activating ENaC (epithelial sodium channel). If the albumin level is less than 17 g/L, decreased effective arterial volume leads to sodium retention ("underfill") (19).

What is the overall approach to the diagnosis of hyponatremia?

Identifying the cause of hyponatremia can be challenging and requires meticulous history taking, physical evaluation of the patient, and focused laboratory testing. While algorithms exist, they must be implemented in the context of these variables.

In one study, 121 consecutive patients presenting with plasma sodium levels less than 130 mmol/L were evaluated by an inexperienced physician using an established algorithm, by a senior physician, and by a senior endocrinologist who acted as the reference standard. The agreement between the algorithm and the senior physician versus the reference standard was 71% and 32%, respectively. The main diagnostic problem was SIAD, which was often diagnosed incorrectly before hypothyroidism and secondary adrenal insufficiency were ruled out (20).

In another study, physicians attempted to diagnose challenging cases of hyponatremia using 10 clinical diagnostic algorithms. The correct diagnosis in the 3 cases by any of the 10 algorithms was only 6% to 12%. The primary obstacle was that 8 of 10 algorithms used assessment of volume status as an important variable. Other problems included failure to rule out secondary adrenal insufficiency before making the diagnosis of syndrome of inappropriate antidiuretic hormone secretion and diagnosing primary polydipsia based on urinary osmolality less than 100 mmol/kg H_2O without considering decreased solute excretion (21).

The **Figure** describes the author's preferred approach to the diagnosis

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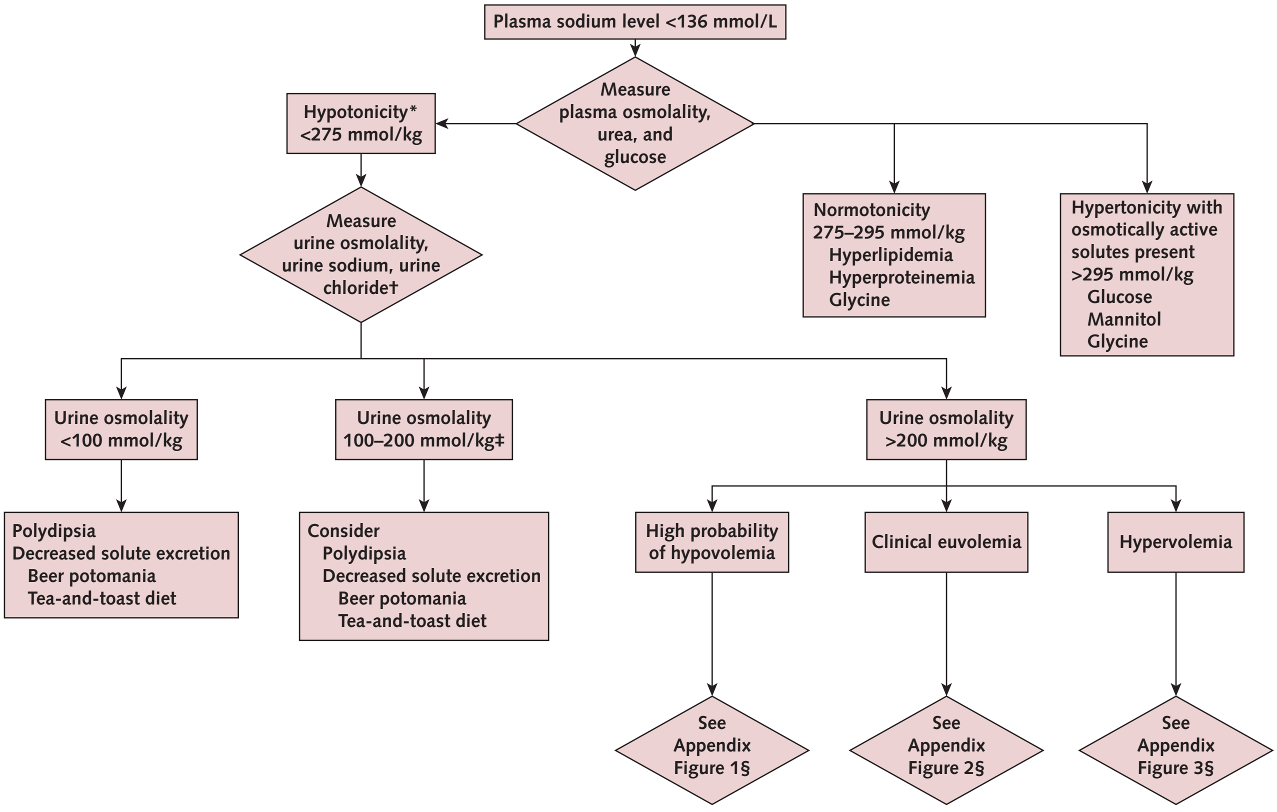
Figure. **Approach to the diagnosis of hyponatremia.**



* After correcting for any ineffective osmoles (urea, alcohol).
† If patient is vomiting, measure urine chloride level.
‡ If urinary osmolality is greater than 100 or less than 200 mmol/kg, need to rule out the syndrome of inappropriate antidiuretic hormone secretion.
§ Available at Annals.org.

of hyponatremia. As part of the initial evaluation, the patient's plasma osmolality, glucose, urea, creatinine, and potassium levels are measured. The patient's urine should be measured for osmolality, sodium, chloride (especially if the patient is vomiting), and creatinine. **Appendix Figures 1**, **2**, and **3** (available at Annals.org) show further diagnostic workups based on the initial evaluation.

Measurement of plasma osmolality can help distinguish whether the patient has true hyponatremia, pseudohyponatremia due to hyperlipidemia or hyperproteinemia, or hypertonic hyponatremia due to elevated glucose level. Because sodium, glucose, and blood urea nitrogen (BUN) are the major osmoles in plasma, osmolality is calculated using the following formula:

$$(mmol/kg\,H_2O) = 2 \times serum\,[Na^+]\,(mmol/L) + glucose\,(mmol/L)/18 + BUN\,(mmol/L)/2.8$$

Hyponatremia due to increased plasma osmolality (>295 mmol/kg H_2O) occurs when high concentrations of effective solutes increase the extracellular osmolality. As a result, intracellular water moves into the extracellular fluid, diluting plasma sodium. Hypertonic hyponatremia occurs most commonly with hyperglycemia. Misdiagnosis can be avoided by correcting the plasma sodium by a factor of 2 mmol/L for each 5.55 mmol/L increase in plasma glucose levels. Solutes that freely permeate cell membranes (urea and alcohol) are ineffective solutes, but their presence can increase plasma osmolality and should be clinically considered (and accounted for) when plasma osmolality is being calculated.

Pseudohyponatremia is characterized by normal plasma osmolality (275–295 mmol/kg H_2O) and occurs when there is marked elevation of plasma lipids, proteins, or both. The concentration of sodium per liter of plasma water is unchanged; however,

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the concentration of sodium per liter of plasma overall is decreased because of the increased relative proportion occupied by lipids or protein. Importantly, then, the measured plasma osmolality is not affected. Pseudohyponatremia can also occur in patients who undergo transurethral resection of the prostate and absorb variable amounts of glycine or sorbitol by a similar mechanism.

If plasma osmolality remains low (<275 mmol/kg H_2O) after correction for urea and glucose, the patient is confirmed to have hypotonic hyponatremia, the most common form of hyponatremia.

What is the role of volume status, urine osmolality, and urinary sodium level in the evaluation of patients with hyponatremia?

To determine the cause of hyponatremia, clinicians should classify the patient's volume status as hypovolemic, euvolemic, or hypervolemic. Patients with hypovolemic hyponatremia should be further stratified into extrarenal versus renal sodium losses. If extrarenal losses are likely (due to vomiting, diarrhea, pancreatitis, or small bowel obstruction), urinary studies should show low sodium level (<30 mmol/L) and increased osmolality. One exception is patients who have been vomiting. In these cases, urinary sodium level may be greater than 30 mmol/L due to bicarbonate loss, but urinary chloride will be less than 30 mmol/L. Renal sodium losses also occur with diuretic use, primary adrenal insufficiency, salt-losing nephritis, and CSW. In these patients, urinary sodium level will be greater than 30 mmol/L.

Clinical euvolemia can be difficult to differentiate from mild hypovolemia. Even with a history suggestive of sodium loss (e.g., diarrhea), water retention may make the patient seem euvolemic. Measurement of urinary sodium can be useful in differentiating between hypovolemia and euvolemia. Urinary sodium level less than 30 mmol/L has 63% to 80% sensitivity and 72% to 100% specificity for hypovolemia, whereas urinary sodium level greater than 30 mmol/L has 87% to 100% sensitivity and 52% to 83% specificity for euvolemia (22).

To distinguish among patients with hypovolemic hyponatremia, those with SIAD, and those with SIAD who are hypovolemic with urinary sodium level greater than 20 mmol/L and less than 40 mmol/L, administration of normal saline as a diagnostic test may be necessary. Patients with hypovolemia will initially retain administered sodium and water. This will gradually decrease nonosmotic release of AVP, resulting in increased urine volume. However, these patients will not excrete sodium until they are volume replete, with decreased renin-angiotensin-aldosterone system and sympathetic nervous system activation. In contrast, patients with euvolemic hyponatremia will initially respond with an increase in plasma sodium level, as normal saline has a higher sodium concentration than plasma sodium (154 vs. 135 mmol/L). Some physicians may misinterpret the initial increase in plasma sodium as evidence of hypovolemia. However, a patient with euvolemia will excrete the administered sodium. If the volume required to excrete the sodium is less than administered, the plasma sodium will decrease. Patients with salt-depleted SIAD will retain the administered sodium and water. Once euvolemic, they will excrete the administered sodium, and urine sodium level and osmolality will remain high.

If the patient has hypotonic hyponatremia, urine osmolality should be measured (**Figure**). If urine osmolality is less than 100 mmol/kg H_2O, then polydipsia or decreased solute excretion is usually the cause, and the clinical history should be considered. Urine osmolality less than 100 mmol/kg H_2O may also transiently occur after aggressive volume resuscitation of patients with hypovolemic hyponatremia. Some patients with primary polydipsia may also have a urine osmolality in the range of 100 to 200 mmol/kg H_2O, especially if they are taking thiazide diuretics, have concomitant volume depletion (increasing nonosmotic release of antidiuretic hormone), or are taking medications that cause SIAD.

In patients with hypervolemia due to heart failure, cirrhosis, or nephrotic syndrome, the diagnosis is usually based on history and physical examination. The urinary sodium level will be less than 30 mmol/L in such patients, unless they are receiving diuretics.

What is the role of imaging studies in the diagnosis of hyponatremia?

Patients with unexplained SIAD should undergo imaging to exclude a potential underlying malignancy. All patients should have chest radiography, and clinicians should consider ordering a chest computed tomography scan and a head computed tomography scan, especially in patients with risk factors for lung cancer.

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When should clinicians consult a nephrologist or an endocrinologist for hyponatremia?

Clinicians should consult with a nephrologist or endocrinologist in all cases with plasma sodium level less than 120 mmol/L. One study demonstrated that consulting a specialist when plasma sodium level was less than 120 mmol/L was associated with a 91% reduction in mortality (23).

Diagnosis… To determine the cause of hyponatremia, the patient's volume status should be classified as hypovolemia, euvolemia, or hypervolemia. Identifying the cause of hyponatremia can be challenging because it is often difficult to distinguish whether the patient is slightly volume depleted or euvolemic. In patients in whom volume status is uncertain, a diagnostic saline infusion followed by electrolyte monitoring may be useful. Before SIAD is diagnosed, thiazide treatment must be stopped, and secondary adrenal insufficiency and hypothyroidism must be excluded.

CLINICAL BOTTOM LINE

Treatment

What is the overall approach to treatment of hyponatremia?

The approach to treating hyponatremia depends on acuity, severity, and cause. Hyponatremia is classified as "acute" if onset is known to be less than 48 hours and "chronic" if the duration is unknown or more than 48 hours. Endurance exercise with water intoxication, psychogenic polydipsia, use of such drugs as 3,4-methylenedioxymethamphetamine (i.e., ecstasy), colonoscopy preparation, and postoperative states are examples of conditions associated with acute hyponatremia. Acute hyponatremia is characterized by swelling of brain cells and can lead to cerebral edema and brain herniation. The brain initially loses electrolytes to decrease cerebral edema. Over the next 24 to 48 hours, the brain can adapt to hyponatremia by losing osmolytes, allowing for intracellular osmolality to equal plasma osmolality. After 48 hours, this loss of solutes predisposes patients with chronic hyponatremia to brain damage if hyponatremia is corrected too rapidly.

The severity of hyponatremia is classified as mild, moderate, or severe. Guidelines released by professional societies have minor differences in sodium cut points associated with these categories. In 2013, a U.S.-based expert panel classified mild hyponatremia as a sodium level of 130 to 135 mmol/L, moderate as 120 to 129 mmol/L, and severe as less than 120 mmol/L (24). In 2014, a clinical practice guideline on diagnosis and treatment of hyponatremia from Europe classified mild hyponatremia as a sodium level of 130 to 135 mmol/L, moderate as 125 to 129 mmol/L, and severe as less than 125 mmol/L (25). Most expert recommendations use less than 120 mmol/L as the threshold for severe hyponatremia.

How rapidly should sodium levels be corrected in cases of acute and severely symptomatic hyponatremia?

Although available data come from small cohort studies, severe acute hyponatremia is associated with poor clinical outcomes. Thus, rapid treatment is warranted. In a 1986 case series of 15 women with postoperative acute hyponatremia due to SIAD, mean nadir sodium level was 108 mmol/L and one third of patients died. Importantly, no intervention was performed when overcorrection occurred, likely contributing to the increased mortality (26). Thus, in patients with acute hyponatremia, it is important to rapidly reverse cerebral edema by increasing plasma sodium by 4 to 6 mmol/L with 3% saline and treating overcorrection (if it occurs). Bolus rather than continuous infusions are recommended for such correction (27, 28).

What are manifestations of the osmotic demyelination syndrome, and who is at risk?

If chronic hyponatremia is corrected too rapidly, osmotic demyelination syndrome (ODS) may occur. This syndrome is characterized by dysarthria, dysphagia, paraparesis or quadriparesis, confusion, obtundation, and coma typically 2 to 6 days after correction. ODS is more likely to occur if the increase in serum sodium is 10 mmol/L or greater within 24 hours or 18 mmol/L within 48 hours. Fortunately, early recognition and careful monitoring for overcorrection

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can decrease cases of ODS to 0.2% (29).

How rapidly should sodium levels be corrected in cases of chronic hyponatremia?

In patients with chronic hyponatremia who are severely symptomatic, the initial treatment is the same as in acute hyponatremia. However, given the chronicity of the derangement, plasma sodium level in patients who are not severely symptomatic should not be increased more than 10 mmol/L within 24 hours and/or more than 18 mmol/L within 48 hours to avoid osmotic demyelination. Patients with alcohol use disorder, hypokalemia, malnutrition, or liver disease or those with a plasma sodium level less than 105 mmol/L are at higher risk for demyelination; in such patients, correction should occur at a goal of 4 to 6 mmol/L per day and not exceed 8 mmol/L in any 24-hour period.

Among 56 patients with plasma sodium levels of 105 mmol/L or less, 14 developed post-therapeutic complications (10 permanent, 4 transient) after correction to a serum sodium level greater than 120 mmol/L. Eleven of these 14 patients (including 3 with documented central pontine myelinolysis) had a biphasic course in which neurologic findings initially improved and then worsened on the second to sixth day. Increased chronicity of hyponatremia and a high rate of correction in the first 48 hours were significantly associated with complications. No neurologic complications were observed among patients whose sodium levels were corrected by less than 12 mmol/L per 24 hours or by less than 18 mmol/L per 48 hours (30).

In a recent study of 23 000 patients admitted with hyponatremia (sodium level <130 mmol/L), 17.7% had rapid correction (>8 mmol/L per 24 hours). Among these, only 12 patients developed osmotic demyelination (31).

Guidance for the treatment of hospitalized patients with acute and chronic symptomatic hyponatremia from European and U.S. expert panel recommendations is summarized in **Appendix Tables 1 and 2** (available at Annals.org).

Rapidly treating hyponatremia in patients with chronic hyponatremia and avoiding overcorrection and rapidly treating it if it occurs are very important. It is also important to avoid undertreatment.

A recent meta-analysis compared rapid (>8–10 mmol/L per 24 hours) versus slow (<8 or 6–10 mmol/L per 24 hours) versus very slow (<4–6 mmol/L per 24 hours) correction of severe hyponatremia (plasma sodium level <120 mmol/L or <125 mmol/L with severe symptoms). Rapid correction was associated with 32 fewer in-hospital deaths per 1000 treated patients as compared with slow correction (OR, 0.67 [CI, 0.55–0.83]) and 221 fewer deaths as compared with very slow correction (OR, 0.29 [CI, 0.11–0.79]) (32).

In another study, 67 patients with severe hyponatremia (sodium level <120 mEq/L) were divided into 2 groups: group A consisted of 35 patients with a plasma sodium correction rate less than 0.3 mmol/L per hour, whereas group B included 32 patients with a plasma sodium correction rate ranging from less than 0.5 mmol/L per hour to 0.3 or greater mmol/L per hour. The mean plasma sodium correction rate was 4.1 ± 2 in group A and 9.84 ± 1.2 in group B. The survival rate was significantly lower in group A (25%) than in group B (60%) (P <0.001) (33).

In a retrospective cohort study of 3274 patients, a correction rate of less than 6 mmol/L per 24 hours was observed in 38%, 6 to 10 mmol/L per 24 hours was observed in 29%, and greater than 10 mmol/L per 24 hours was observed in 33%. Compared with patients whose correction rate was 6 to 10 mmol/L per 24 hours, a correction rate of less than 6 mmol/L per 24 hours exhibited higher in-hospital mortality. Also, compared with 6 to 10 mmol/L per 24 hours, a correction rate of greater than 10 mmol/L per 24 hours was associated with lower in-hospital mortality and shorter length of stay in multivariable analyses. Seven patients with central pontine myelinolysis were identified, with 5 of 7 developing central pontine myelinolysis despite a sodium correction rate of less than or equal to 8 mmol/L per 24 hours. Six of 7 patients who developed central pontine myelinolysis had alcohol use disorder, malnutrition, hypokalemia, or hypophosphatemia (29).

In view of these data, the author recommends maximum correction rates of 10 to 12 mmol/L in any 24-hour period and a minimum daily correction goal of 8 to 10 mmol/L if no risk factors for demyelination are present. In patients with risk factors for osmotic demyelination (e.g., plasma sodium level <105 mmol/L, alcohol use disorder, hypokalemia, malnutrition, or severe liver disease), a maximum correction rate of 8 mmol/L and a minimum of 6 to 8 mmol/L, as opposed to

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the current recommendation of a minimum of 4 to 6 mmol/L, is favored (24). These recommendations reflect the fact that overcorrection (should it occur) is almost always treatable with 5% dextrose in water plus desmopressin, whereas undercorrection may prove fatal.

It is extremely difficult to predict the rate of correction of plasma sodium levels. Initially, when patients are given hypertonic saline, the formula $\Delta[Na^+]s = [Na^+ + K^+]$ infusate $-$ $[Na^+]$ s/TBW $+$ 1 may be used to calculate the predicted initial increase in serum sodium level. However, this formula is based on a "closed system"—that is, the prediction does not account for ongoing urinary loss of electrolytes or water, which may influence the observed change in plasma sodium level. Given these limitations, frequent monitoring to guide the rate of sodium correction is necessary.

In a retrospective study of 62 hyponatremic patients treated with a low rate of hypertonic saline, several patients' hyponatremia was unintentionally overcorrected (11% by >12 mmol/L in 24 hours and 9.7% by >18 mmol/L in 48 hours), despite frequent adjustments in the infusion rate and/or administration of 5% dextrose in water. Using a predictive formula in patients with plasma sodium level less than 120 mmol/L, the observed increase in plasma sodium exceeded the formula's estimated increase by 74.2%. Inadvertent overcorrection was due to documented water diuresis in 40% of cases (34).

Which patients are at increased risk for overcorrection?

Patients with reversible causes of hyponatremia—such as compulsive water drinking, decreased sodium or solute intake, volume depletion, adrenal deficiency (Addison disease and secondary adrenal deficiency), hypothyroidism, and drug-related SIAD—are at the greatest risk for overcorrection. Should these conditions be suspected as the cause for hyponatremia, clinicians should implement proactive, reactive, or rescue-based strategies. Proactive strategies are designed to prevent overcorrection and mainly include administering desmopressin at the time hypertonic saline is administered. In contrast, reactive strategies are deployed when an increase in urine output or plasma sodium is first observed. Rescue strategies are deployed when plasma sodium correction limits are exceeded. In these situations, 5% dextrose in water and desmopressin are simultaneously administered to decrease the plasma sodium level to correction limits (35).

What is the treatment of hypervolemic hyponatremia in hospitalized patients?

The primary goal in treating hypervolemic hyponatremia is to reduce effective plasma volume. Patients with congestive heart failure may be treated with free water and sodium restriction and with loop diuretics. Among patients with heart failure and reduced ejection fraction, angiotensin-converting enzyme inhibitors such as captopril have been shown to increase cardiac output while decreasing norepinephrine, systemic vascular resistance, and left ventricular end-diastolic pressures. In turn, the nonosmotic release of AVP is decreased and excretion of free water is increased (36). A meta-analysis of studies in which hypertonic saline plus furosemide was administered in patients with decompensated congestive heart failure observed an increase in plasma sodium level by 6.80 mmol/L (CI, 4.92–8.69 mmol/L) and a decrease in serum creatinine level by 0.41 mg/dL (37). Thus, this strategy may be deployed in the cases of patients with acute, severe hyponatremia in whom rapid correction is needed.

The most effective treatment of hyponatremia in patients with cirrhosis and ascites is intravenous albumin. In a study of patients with cirrhosis and ascites, administration of albumin led to resolution of hyponatremia in 85% of patients and improved 30-day survival (38). Treatment with albumin also reduced the incidence of hyponatremia among patients with cirrhosis (0.51 vs. standard medical therapy) while improving cognition and quality of life (39, 40).

Patients with hyponatremia who develop or present with symptoms such as confusion, headache, vomiting, and seizures should be hospitalized. Patients with acute-onset hyponatremia (e.g., hyponatremia developing with a plasma sodium level <125 mmol/L) or those who have risk factors for ODS should also be hospitalized for close monitoring.

How should clinicians counsel patients about salt and fluid intake?

Patients with heart failure who present with hypervolemic hyponatremia should receive counseling on restricting fluid intake and limiting dietary salt to less than 3.0 g/day. Patients with SIAD should be advised to limit fluid intake to around 1000 mL/day but not restrict salt intake. Patients should seek care if they experience

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Table 4. **Treatment of Patients With Asymptomatic Chronic Hyponatremia**

Condition	Treatment
Hypovolemia due to gastrointestinal losses and sweating*	Isotonic saline; at risk for overcorrection; if overcorrects, use desmopressin and D5W
Diuretics*	Discontinue diuretics, and if no improvement, administer isotonic saline
Addison disease*	Isotonic saline; glucocorticoid and mineralocorticoid replacement
Glucocorticoid insufficiency*	Glucocorticoid replacement
Primary polydipsia*	Restrict water; discontinue diuretics and any drug known to cause SIADH; if volume-depleted or decreased solute excretion, cautiously administer isotonic saline and consider desmopressin if there is a rapid increase in urine output and/or serum sodium
Decreased solute intake*	Restrict water; discontinue diuretics and any drug known to cause SIADH; if volume-depleted or decreased solute excretion, cautiously administer isotonic saline and consider desmopressin if there is a rapid increase in urine output and/or serum sodium; increase electrolytes and protein in diet
Heart failure	Restrict water and salt; loop diuretics in cases of fluid overload† Consider loop diuretics with 3% saline and urea
Cirrhosis with ascites†	Restrict water and salt; administer diuretics; albumin infusion alone or with diuretics
Nephrotic syndrome	Restrict water and salt; albumin <17 g/L, administer albumin with diuretics; albumin >17 g/L, administer diuretics
Chronic kidney disease	Restrict water and salt; loop diuretics if fluid overload is present
SIAD	Discontinue diuretics and any drug known to cause SIADH; restrict water but not salt; consider oral urea, empagliflozin, furosemide with salt tablets; use vaptans if benefit is greater than risk, and only for 1 month if following FDA guidelines

D5W = 5% dextrose in water; FDA = U.S. Food and Drug Administration; SIAD = syndrome of inappropriate diuresis; SIADH = syndrome of inappropriate antidiuretic hormone secretion.
** All patients are at risk for rapid correction.*
† Loop diuretics should increase free water clearance.

persistent nausea, falls, or changes in mental status, as these may be symptoms of hyponatremia.

How should chronic asymptomatic hyponatremia be treated?

Consensus recommendations for the treatment of patients with chronic asymptomatic hyponatremia are presented in Table 4. The initial treatment of patients with euvolemic hypovolemia should include fluid restriction and stopping medications that may cause SIAD. Clinicians should not administer isotonic saline to patients with a plasma sodium level of 120 mmol/L or less who are euvolemic, regardless of symptoms (3). Salt should not be restricted in patients with SIAD because they effectively have decreased total body sodium.

Even though fluid restriction is the cornerstone of treatment, it is usually unsuccessful if the sum of urinary sodium concentration plus potassium is more than the plasma sodium concentration and if urinary osmolality is greater than 500 mmol/L. A recent study compared fluid restriction (<1000 or <500 mL/day) versus furosemide and furosemide with fluid restriction. Patients who received furosemide with fluid restriction more often experienced acute kidney injury without significant differences in plasma sodium at 28 days (41). Thus, caution when using diuretics is warranted.

Urea increases urine output due to osmotic diuresis and may therefore be used to treat euvolemic and hypervolemic hyponatremia. Newer formulations are more palatable than older ones, so the therapy has become more acceptable to patients. Urea costs $3 for a 15-g packet (250 mmol) and is comparable in efficacy to tolvaptan when used long-term. Side effects include increased plasma urea, which is usually asymptomatic. Urea therapy may also cause overcorrection, but to date, no cases of osmotic demyelination have been reported from this treatment (42).

What therapeutic agents may be used to treat chronic hyponatremia?

Empagliflozin decreases reabsorption of glucose in proximal tubule, resulting in osmotic diuresis. In one study, patients receiving empagliflozin experienced an increase in plasma sodium of 10 mmol/L versus 7 mmol/L in the placebo arm after 4 days (43). In another, empagliflozin treatment led to an increase in plasma sodium by 4 mmol/L with no change observed with placebo after 4 weeks (44). Major side effects of this treatment include volume

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depletion, urogenital infections including Fournier gangrene, and euglycemic diabetic ketoacidosis. In the absence of definitive studies that determine efficacy in treating chronic hyponatremia, the author recommends considering this agent for long-term therapy when plasma sodium level is greater than 130 mmol/L and fluid restriction and urea therapy have not been successful.

Demeclocycline is recommended by U.S. experts only for the treatment of chronic hyponatremia. Because the drug has a delayed onset of action and significant side effects, including acute renal failure, photosensitivity, nausea, vomiting, and diarrhea, European experts do not recommend using this agent. As safer agents such as urea and empagliflozin are available, the author also does not recommend this therapy for the management of chronic hyponatremia.

Tolvaptan blocks the action of AVP and is successful in increasing plasma sodium level in patients with SIAD, heart failure, and cirrhosis with ascites. A major concern with the use of tolvaptan is overcorrection. In a study of 1840 patients, overcorrection occurred in 13.1% of treated patients versus 3.3% of control cases (OR, 5.72 [CI, 3.38–9.70]) (45). Despite this increase, no cases of osmotic demyelination from tolvaptan have been reported. An important limitation of tolvaptan is cost (up to $300 per pill). In addition, therapy should ideally be started in the hospital under close monitoring. As long-term treatment with tolvaptan has also not been associated with mortality benefit, the U.S. Food and Drug Administration recommends limiting therapy to 30 days.

Treatment... Patients with severe hyponatremia, acute hyponatremia, or moderate to severe symptoms should be hospitalized for diagnosis and treatment. Early treatment with hypertonic saline to rapidly correct plasma sodium levels in patients with acute hyponatremia, even if asymptomatic, is warranted. Similarly, patients with moderate to severe symptoms (acute or chronic) also require early therapy. All patients should be monitored closely so as to not increase sodium levels by greater than 10 mmol/L within 24 hours or 18 mmol/L within 48 hours. The recommended rates of sodium correction are lower in patients at risk for osmotic demyelination syndrome. Fluid restriction and urea therapy and the search for culprit agents represent the mainstay in treating chronic hyponatremia. Clinicians considering tolvaptan should take into account the U.S. Food and Drug Administration recommendation not to exceed 1 month of use.

CLINICAL BOTTOM LINE

Practice Improvement

What do professional organizations recommend regarding the diagnosis and treatment of hyponatremia?

Professional organizations recommend a multipronged approach to diagnosing and treating hyponatremia, emphasizing rapid assessment, prompt treatment of severe symptoms, and careful management of correction rates to avoid complications like ODS. The 2013 U.S. Expert Panel Recommendations (24) and 2014 European Clinical Practice Guidelines (25) provide evidence-based recommendations for the diagnosis and treatment of hyponatremia.

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In the Clinic

Tool Kit

Hyponatremia

Patient Information

https://medlineplus.gov/ency/article/000394.htm

Information on low blood sodium from the National Institutes of Health's MedlinePlus.

www.kidney.org/kidney-topics/hyponatremia-low-sodium-level-blood

www.kidney.org/es/kidney-topics/hiponatremia-nivel-bajo-de-sodio-en-sangre

Patient information on hyponatremia in English and Spanish from the National Kidney Foundation.

www.mayoclinic.org/diseases-conditions/hyponatremia/symptoms-causes/syc-20373711

Information for patients on hyponatremia from the Mayo Clinic.

https://my.clevelandclinic.org/health/diseases/17762-hyponatremia

Information for patients on hyponatremia from the Cleveland Clinic.

Information for Health Professionals

https://academic.oup.com/ejendo/article/170/3/G1/6668028

Hyponatraemia Guideline Development Group clinical practice guideline on diagnosis and treatment of hyponatremia.

https://journals.lww.com/cjasn/fulltext/2024/01000/treatment_guidelines_for_hyponatremia__stay_the.21.aspx

European Clinical Practice Guidelines on diagnosis, evaluation, and treatment of hyponatremia.

www.cdc.gov/salt/php/sodium-reduction-resources/index.html

Resources for health professionals on sodium reduction from the U.S. Centers for Disease Control and Prevention.

In the Clinic

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WHAT YOU SHOULD KNOW ABOUT HYPONATREMIA

What Is Hyponatremia?

Hyponatremia is a condition that occurs when sodium levels in the body are too low. Sodium, or salt, is a mineral in the blood. Sodium helps to control the amount of water in your body. When sodium levels are low, your body holds onto too much water. Too much water in the body can be dangerous and cause serious health problems.

Low sodium levels can be caused by:

- Certain medications, like water pills (diuretics) or some antidepressants
- Some health conditions, like heart failure, kidney disease, or liver problems
- Drinking too much water after intense exercise, such as running a marathon

What Are the Warning Signs of Hyponatremia?

- Sometimes hyponatremia has no symptoms.
- Other times, symptoms include nausea, confusion, headache, or vomiting.
- On rare occasions, symptoms are more severe. Severe symptoms can include seizures, temporary loss of mental abilities, and trouble breathing.

How Is Hyponatremia Diagnosed?

- Your doctor will collect blood and urine samples to test sodium levels.
- Imaging tests may be ordered to check for signs of hyponatremia. These tests may include an x-ray to check for normal fluid levels in your lungs or an MRI of the brain to look for things that might cause hyponatremia (for example, brain tumors).

How Is Hyponatremia Treated?

- In mild cases, your doctor may simply advise you to drink less fluid or change your medications.
- Sometimes your doctor will give you a medicine that helps reduce the amount of water in your body.
- In more severe cases, you may need to go to the hospital for diagnosis and treatment. An IV filled with a salt-based fluid may be used to increase your sodium levels.

Questions for My Doctor

- Do I need to drink less water?
- Should I eat more salt?
- Do I need to change my diet?
- When can I expect my symptoms to go away?
- Could this cause any long-term problems?
- Should I change the medicines I take?
- How can I prevent this from happening in the future?
- When should I contact my doctor?

Bottom Line

- Hyponatremia is a condition that occurs when sodium levels in the body are too low. The sodium in your blood helps to control the amount of water in your body. When sodium is too low, there is too much water in your body. This can be dangerous and cause health problems.
- Symptoms of hyponatremia can range from headache or nausea to serious confusion and seizures.
- To check for hyponatremia, your doctor will collect blood and urine samples. Your doctor may also order further testing, like an x-ray or an MRI.
- Treatment will depend on how severe your symptoms are. Treatment could include using an IV to increase your sodium levels, taking a medicine to lessen the water in your body, or simply drinking less water.

For More Information

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MedlinePlus
www.nlm.nih.gov/medlineplus/ency/article/000394.htm

National Kidney Foundation
www.kidney.org/atoz/content/Hyponatremia

Cleveland Clinic
https://my.clevelandclinic.org/health/diseases/17762-hyponatremia

Patient Information

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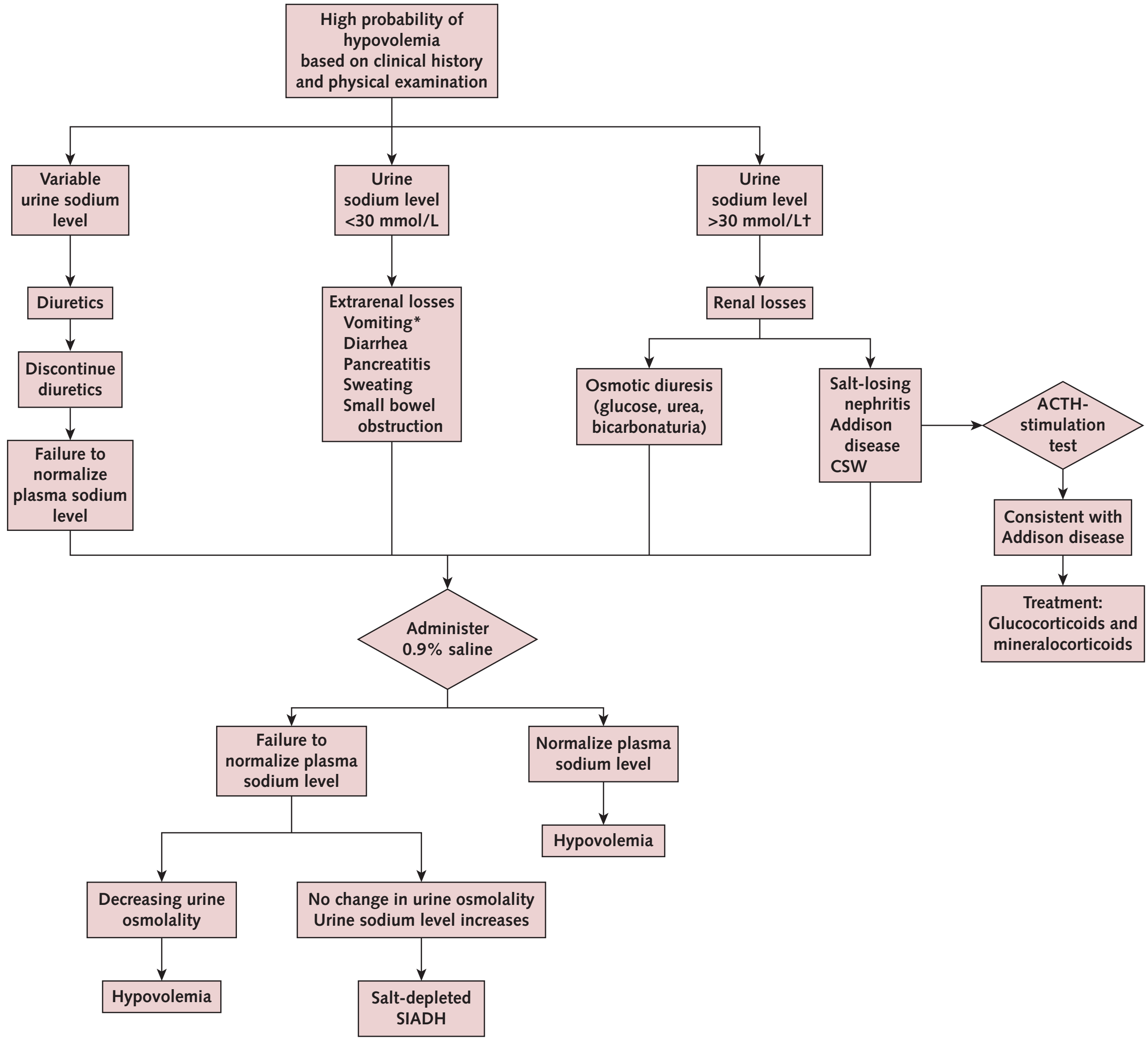
Appendix Figure 1. **Approach to the diagnosis of hypovolemic hyponatremia.**



ACTH = adrenocorticotrophic hormone; CSW = cerebral salt wasting; SIADH = syndrome of inappropriate antidiuretic hormone secretion.

* If patient is vomiting, urinary chloride level should be low.

† Older patients with volume depletion can have urinary sodium level >30 mmol/L but fractional excretion of sodium <0.5%.

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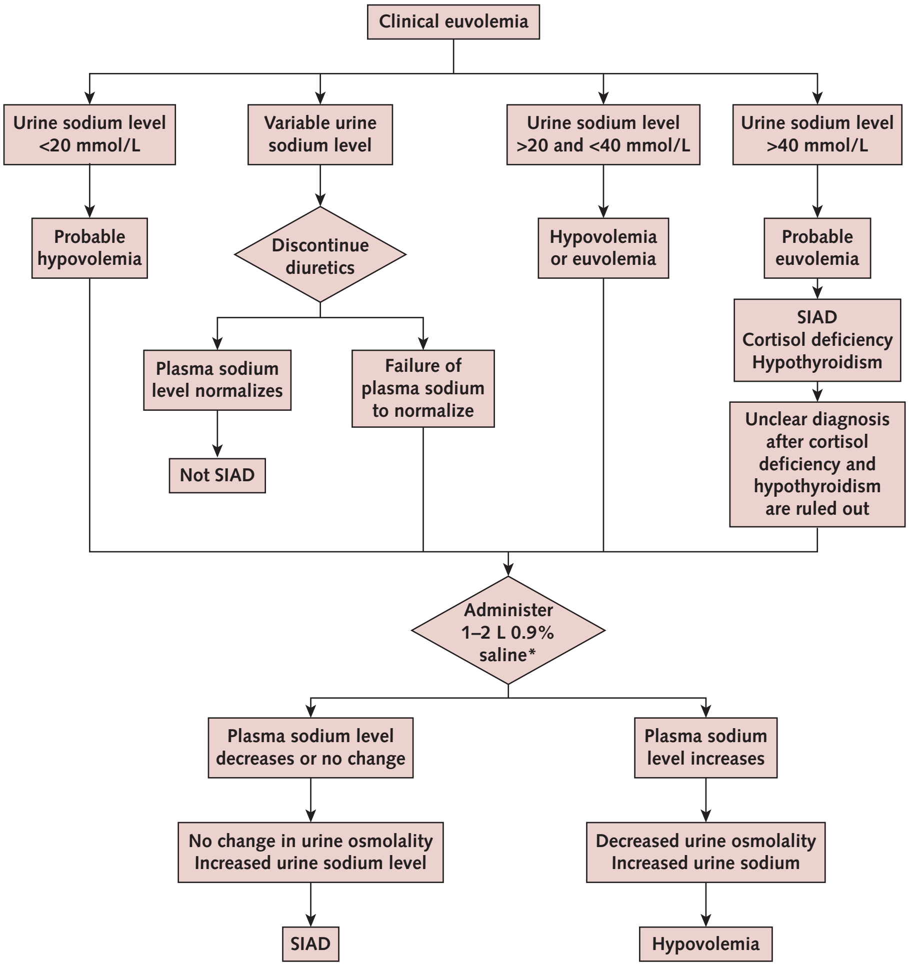
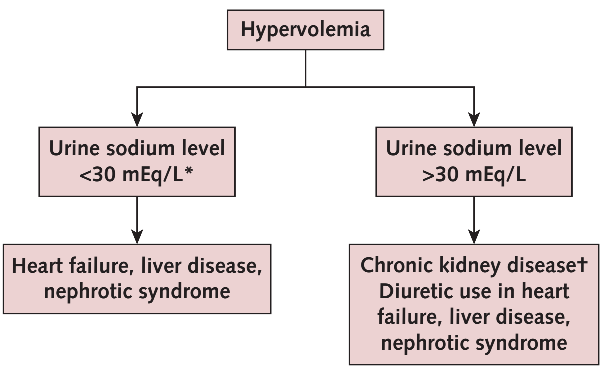
Appendix Figure 2. **Approach to the diagnosis of euvolemic hyponatremia.**



SIAD = syndrome of inappropriate diuresis.
* If plasma sodium level is <120 mmol/L, consult endocrinologist or nephrologist for guidance.

Appendix Figure 3. **Approach to the diagnosis of hypervolemic hyponatremia.**



* If patient is receiving diuretics, urinary sodium can be >30 mEq/L.
† Patients with chronic kidney disease can also be euvolemic.

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Appendix Table 1. **Drug and Nondrug Treatment of Hyponatremia**

Drug or Drug Class	*Dosing*	*Side Effects*	*Precautions*	*Clinical Use*
Furosemide (Lasix)	20–80 mg daily	Orthostatic hypotension, hyperuricemia, azotemia, ototoxicity, impaired glucose tolerance, pancreatitis	Water and electrolyte depletion; caution with sulfonamide hypersensitivity, CKD, hepatic impairment*	CHF, and liver disease with ascites Combined with sodium supplementation in SIADH
Urea	15–60 g daily	Potential for overcorrection, azotemia at higher doses	Monitor serum sodium levels	SIADH, CHF
Empagliflozin (Jardiance)	25 mg daily	Euglycemic DKA, UTI, vaginal infections, necrotizing fasciitis of perineum, polyuria, volume depletion, dizziness, stomach-area pain	Water and electrolyte depletion	SIADH, CHF
Tolvaptan* (Samsca)	15 mg daily, then 30 mg daily; maximum 60 mg daily	Xerostomia, asthenia, hyperglycemia, anorexia, hepatic disease, constipation, thirst, pollakiuria, polyuria, dehydration, orthostatic hypotension, potential neurologic sequelae when correction of serum sodium exceeds the suggested rate	Initiate and reinitiate in a hospital and monitor serum sodium levels; avoid if CrCl*	Can be useful in SIADH and CHF if benefit exceeds risk

CHF = congestive heart failure; CKD = chronic kidney disease; CrCl = creatinine clearance; DKA = diabetic ketoacidosis; SIADH = syndrome of inappropriate antidiuretic hormone secretion; UTI = urinary tract infection.
** Black box warning.*

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Appendix Table 2. **Treatment of Hospitalized Patients with Hyponatremia, According to Symptoms**

Symptoms	*Treatment*
Severe presentation (cardiorespiratory arrest, seizures, deep somnolence, and coma)	European guidelines: Administer 150 mL 3% saline over 20 min, then check serum sodium levels while repeating the infusion of hypertonic saline over 20 min; continue 3% saline with target of 5 mmol/L increase in serum sodium, then stop hypertonic saline U.S. expert panel: 100 mL of 3% saline infused over 10 min x 3 as needed with urgent correction 4–6 mmol/L Do not increase serum sodium more than 10 mmol/L in 24 h and in the next 24 h greater than 8 mmol/L For the first 24 h, monitor serum sodium levels every 6 h depending on changes; when stable, measure levels every 24 h
No improvement	European: Continue 3% saline aiming for an additional 1 mmol/L per hour increase in serum sodium Stop 3% saline infusion when symptoms improve, serum sodium level increases 10 mmol/L, or it reaches 130 mmol/L, whichever occurs first
Acute hyponatremia without severe or moderately severe symptoms	European guidelines: If acute decrease in serum infuse 150 mL 3% saline over 20 min U.S. expert panel: Mild to moderate symptoms with low risk of herniation, 3% hypertonic saline infused at 0.5–2 mL/kg per hour Monitor plasma sodium after 4, 12, and 24 h; when stable, measure plasma sodium every 24 h
Moderately severe (nausea, confusion, headache, vomiting)	European guidelines: Immediate treatment with 150 mL 3% hypertonic saline over 20 min; aim for a 5 mmol/L per 24 h increase but limit serum sodium to a 10 mmol/L increase in the first 24 h and 8 mmol/L during every 24 h thereafter until plasma sodium reaches 130 mmol/L Check plasma sodium levels after 1, 6, and 12 h U.S. expert panel: No indication for hypertonic saline; minimum correction of serum sodium by 4–8 mmol/L per day with a lower goal of 4–6 mmol/L per day if risk for ODS is high; limits should not exceed 8 mmol/L in any 24-h period if risk for ODS is high
Chronic hyponatremia without severe or moderately severe symptoms	Stop nonessential fluids, medications, and other factors that can contribute to or provoke hyponatremia. Avoid an increase in serum sodium >10 mmol/L during the first 24 h and >8 mmol/L during each 24 h thereafter. Monitor serum sodium every 6 h until the plasma sodium stabilizes.
Overcorrection	Overcorrection of hyponatremia is a medical emergency. In most cases, excessive correction results from the emergence of a water diuresis after resolution of the cause of hyponatremia. If serum sodium has increased by >10 mmol/L in 24 h or 18 mmol/L in 48 h discontinue ongoing active treatment. Consult an expert to administer 5% dextrose in water in individual doses and desmopressin to reduce urine volume until the plasma sodium is less than the limits of overcorrection. Monitor serum sodium every 2 h until it corrects, then every 4–6 h for the first 48 h.

ODS = osmotic demyelination syndrome.

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