Hyponatremia is the most common electrolyte disorder in hospitalized patients. Hospital-associated hyponatremia includes admission hyponatremia (community-acquired hyponatremia) and hospital-acquired hyponatremia. The reported incidence of hospital-associated hyponatremia ranges between 10% and 30%, depending on the definition, patient population, and case mix. It is associated with increased mortality, hospital length of stay, hospital costs, intensive care unit (ICU) days, and chance of readmission (1). Acute onset or rapid correction of severe chronic cases can cause extensive or fatal brain damage, but even mild chronic cases can have adverse outcomes, such as decreased cognition, osteoporosis, increased risk for falls, and fractures (2).

The CME quiz is available at www.annals.org/intheclinic.aspx. Complete the quiz to earn up to 1.5 CME credits.
Patients with no underlying disease can maintain normal plasma sodium levels. Levels are determined by the total exchangeable extracellular sodium and intracellular potassium divided by total body water. Hyponatremia is a disorder of water balance. The ability to excrete dilute urine allows people without any underlying disease to drink large amounts of water (nearly a liter an hour) without becoming hyponatremic. Maintenance of water balance requires normally functioning kidneys; sufficient urine urea (the end-product of protein metabolism); and suppressed secretion of the antidiuretic hormone, arginine vasopressin (AVP), when plasma sodium levels fall below 135 mEq/L. Hyponatremia develops if more water is ingested than can be excreted by the kidneys or if the ability to excrete a large volume of dilute urine is compromised because of kidney disease, diuretics, low protein intake, or the presence of AVP. The amount of free water excreted is determined by urine volume, sodium, and potassium. If the sum of urinary sodium and potassium is less that of plasma sodium, free water is excreted (3). A complete overview of sodium and water balance can be found elsewhere (4).

**Prevention**

**Who is at risk for hyponatremia?**

Up to 13% of individuals participating in endurance exercise (marathons and triathlons) develop hyponatremia, which can be severe (<120 mEq/L) when water intake exceeds water loss (5). Institutionalized patients with schizophrenia can become hyponatremic, despite an intact ability to excrete maximally dilute urine, after rapidly ingesting large quantities of water. People who consume large quantities of fluid but little protein (beer potomania, or tea and toast diet) may also become hyponatremic, because decreased excretion of urea results in limited water excretion even when urine osmolality is < 100 mOsm/kg.

Patients with severe kidney disease are unable to increase urine water loss and are susceptible to hyponatremia.

In a study of patients with chronic kidney disease and a mean estimated glomerular filtration rate (GFR) of 50.2 ± 14.1 mL/min/1.73 m², prevalence of hyponatremia was 13.6% at baseline and 26% of patients had >1 episode of hyponatremia during a follow-up period of 5.5 years (6). Diuretics impair the kidney’s ability to excrete dilute urine. Thiazides are a particularly common cause of hyponatremia—30% of thiazide-treated patients develop hyponatremia over 10 years (7). In 1 study of patients who became hyponatremic after receiving thiazides, the electrolyte disturbance developed within 2 weeks in approximately two thirds of cases and within 5 days in half (8). In another study, patients developed hyponatremia after a median of 116 days (9). Elderly patients as well as those with low body weight and hypokalemia have an increased risk for thiazide-associated hyponatremia (9). Other drugs can interfere with the ability to dilute the urine, most commonly selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), carbamazepine, and oxcarbazepine. Hyponatremia develops in 0.5%–30% of patients receiving SSRIs and SNRIs, usually within 2 weeks. Elderly patients, those who had previous episodes of hyponatremia, and patients receiving concurrent thiazide treatment are at increased risk (10).

The ability to excrete water is also limited when the posterior pituitary continues to secrete AVP despite a low plasma sodium concentration. AVP is secreted without an osmotic stimulus if circulation is inadequate, as in patients with hypovolemia or heart or liver disease. “Inappropriate secretion” of AVP occurs in the absence of both osmotic and hemodynamic stimulus. Affected patients have the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Hyponatremia due to SIADH is common in hospitalized patients because AVP is released in response to hypoxia, pain, or stress. Patients at particularly high risk include postsurgery patients, elderly persons, persons admitted to the intensive care unit, and patients with central nervous system disorders. Finally, hyponatremia is especially common among hospitalized children receiving hypotonic fluids, and fewer patients develop hyponatremia if isotonic saline rather than hypotonic saline is used to treat gastroenteritis.

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

Clinicians should encourage runners to drink fluids only when they have increased thirst and to monitor their body weight to avoid weight gain during exercise. Plasma sodium levels should be checked 1–2 weeks after initiation of thiazide, SNRI, and SSRI therapy, especially in patients at high risk for hyponatremia. Thiazides should be avoided in persons with high fluid or low protein intake and during acute illness.

Plasma sodium levels should be measured in all hospitalized patients on admission; low sodium levels should be treated based on the underlying cause. Hypotonic fluids and thiazide diuretics should be avoided, especially in patients at increased risk for hyponatremia. Clinicians should monitor daily plasma sodium levels in patients with hyponatremia or in those at increased risk.

**Prevention...** Hyponatremia is common in patients participating in endurance exercise and those receiving thiazides, SSRIs, or SNRIs. Elderly patients; those with congestive heart failure, cirrhosis, or pneumonia; and persons admitted to the ICU are at increased risk for hospital-acquired hyponatremia. Hypotonic fluids should be avoided in hospitalized patients at increased risk.

**CLINICAL BOTTOM LINE**

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

Hyponatremic patients can be asymptomatic or have symptoms that are moderate (nausea, confusion, headache, vomiting) or severe (delirium; impaired consciousness; seizures; and, rarely, cardiorespiratory arrest). Notably, mild chronic hyponatremia (plasma sodium 125–135 mEq/L) may cause subtle neurocognitive deficits that can only be detected by careful testing; these deficits improve when the plasma sodium is normalized (12). Because hyponatremic patients are at risk for severe complications, early recognition and treatment are crucial.

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for osteoporosis, falls, and hip fractures, it should be considered in the differential diagnosis of these conditions (2).

What conditions should clinicians consider when evaluating patients with hyponatremia?

Hyponatremia can occur when release of AVP is physiologically appropriate, due to decreased effective circulating volume, or inappropriate (that is, no physiologic reason). Urine volume decreases in response to the release of AVP, and hyponatremia will develop if water intake exceeds urinary and insensible losses of water. Patients are typically classified based on their total body sodium as hypovolemic, euvolemic, and hypervolemic (Table 1).

**Hypovolemic hyponatremia**

Patients with hypovolemic hyponatremia have a loss (renal or extrarenal) of sodium and/or potassium and water. Extrarenal sodium losses can occur with excessive sweating, pancreatitis, small bowel obstruction, vomiting, and diarrhea. If these losses are not replaced, they lead to decreased effective circulating volume and nonosmotic release of AVP. Hypovolemic hyponatremia caused by diarrhea or third-space loss 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 due to increased renal chloride reabsorption, but urine sodium may not be low because of metabolic alkalosis and resulting bicarbonaturia. Renal sodium losses occur with glycosuria, cerebral salt wasting (CSW), primary adrenal insufficiency, and diuretics. Loop diuretics can cause hypovolemic hyponatremia, but patients with thiazide-associated hyponatremia are usually clinically euvolemic (see next section). CSW is uncommon and can be difficult to differentiate from SIADH. Conditions associated with CSW include 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 (also decreased reabsorption of urea and uric acid). Because it is often difficult to assess volume status in postneurosurgery patients in the ICU, finding a significant negative fluid balance on reviews of the chart—Intake/Output—may indicate CSW. In these patients, volume depletion leads to nonosmotic release of AVP and subsequent water retention. Similar to patients with SIADH, patients with CSW have decreased serum levels of sodium and increased urinary sodium and osmolality.

A rare but important cause of hypovolemic hyponatremia is primary adrenal insufficiency (loss of mineralocorticoids and glucocorticoids, also known as Addison disease). Primary adrenal insufficiency leads to renal sodium wasting with subsequent volume depletion, causing nonosmotic release of AVP. Lack of cortisol also increases AVP release (see isolated glucocorticoid deficiency in euvolemic hyponatremia). 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. However, not all patients with primary adrenal insufficiency have this classic presentation.

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 (13).

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

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

**Euvolemic hyponatremia**

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

SIADH is the most common cause of euvolemic hyponatremia. Patients with this syndrome have a decrease in total body sodium and an increase in total body water resulting in clinical euvoolemia, but they have laboratory findings (decreased uric acid and blood urea nitrogen [BUN]-creatinine ratio) consistent with slight hypervolemia (12). **Table 2** presents criteria for diagnosis of SIADH. SIADH cannot be diagnosed in patients who are receiving diuretics (particularly thiazide diuretics) or those who have severe hypothyroidism or isolated glucocorticoid insufficiency (secondary adrenal insufficiency). It is common in hospitalized patients and patients treated with SSRIs and SNRIs (10). **Table 3** presents common causes of SIADH.

Diuretics commonly cause hyponatremia; thiazides are more often associated with hyponatremia than loop diuretics because unlike loop diuretics, thiazides impair the ability to excrete dilute urine while preserving the ability to concentrate the urine. Most patients with thiazide-induced hyponatremia are euvolemic (similar to SIADH). They initially lose sodium but are able to maintain sodium balance with prolonged treatment.

**Table 3. Criteria for the Diagnosis of SIADH**

<table>
<thead>
<tr>
<th>Essential</th>
<th>Supplemental</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased effective osmolality of the extracellular fluid (plasma osmolality &lt;275 mOsm/kg H$_2$O)</td>
<td>Plasma uric acid &lt;4 mg/dL</td>
</tr>
<tr>
<td>Inappropriate urine concentration (urine osmolality &gt;100 mOsm/kg H$_2$O with normal renal function) in the presence of decreased effective serum osmolality</td>
<td>Blood urea nitrogen &lt;10 mg/dL</td>
</tr>
<tr>
<td>Clinical euvoolemia, as defined by the absence of signs of hypovolemia (orthostasis, tachycardia, decreased skin turgor, dry mucous membranes) or hypervolemia (subcutaneous edema, ascites)</td>
<td>Fractional sodium excretion &gt;1%; fractional urea excretion &gt;55%</td>
</tr>
<tr>
<td>Absence of urinary sodium conservation (i.e., urinary sodium &lt;30 mmol/L) when salt and water intake are normal</td>
<td>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 &lt;100 mOsm/kg H$_2$O, or both)</td>
</tr>
<tr>
<td>Absence of other potential causes of euvolemic hyponatremia: hypothyroidism, hypocortisolism (pituitary ACTH insufficiency), and diuretic use</td>
<td>Plasma AVP level inappropriately elevated relative to plasma osmolality</td>
</tr>
<tr>
<td>No significant correction of plasma sodium with volume expansion but improvement after fluid restriction</td>
<td>No significant correction of plasma sodium with volume expansion but improvement after fluid restriction</td>
</tr>
</tbody>
</table>

**ACTH = adrenocorticotropic hormone; AVP = arginine vasopressin; SIADH = syndrome of inappropriate secretion of antidiuretic hormone.**

Although some studies indicate that chlorthalidone treatment is associated with fewer cardiovascular events than hydrochlorothiazide (HCTZ), the former is more likely to cause hyponatremia. A recent study confirmed that hyponatremia occurs more often when chlorthalidone is prescribed in the same dose as HCTZ; however, when the dose of chlorthalidone is half of the HCTZ dose (12.5 mg vs. 25 mg), there is no difference in the incidence of hyponatremia (15).

Chronic kidney disease can cause 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 for a diagnosis of SIADH.

Primary polydipsia is an unusual cause of hyponatremia; most patients with polydipsia have psychiatric disease, particularly acute

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They can develop hyponatremia through rapid ingestion of large amounts of fluid that exceed the kidney’s ability to excrete the volume. Other factors that can contribute to hyponatremia in these patients include volume depletion causing increased urine osmolality and decreased solute excretion; drugs known to cause SIADH; decreased solute intake; and acute psychosis, which itself causes an increase in AVP release (17).

Exercise-associated hyponatremia is an acute type of hyponatremia seen after vigorous endurance exercise that occurs with excessive fluid intake in the presence of increased AVP secretion.

Isolated glucocorticoid deficiency caused by lack of adrenocorticotropic hormone (ACTH) results in 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 ACTH stimulation test can diagnose secondary adrenal insufficiency, but results can be normal in patients with recent loss of ACTH.

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 and should be considered in a patient who is diagnosed with SIADH but has stable plasma sodium levels. The diagnosis is made by administering a water load to the patient. In contrast to those with SIADH, patients with reset osmostat are able to excrete free water and reduce urine osmolality.

**Hypervolemic hyponatremia**

Conditions associated with hypervolemic hyponatremia include heart failure, cirrhosis with ascites, chronic kidney disease, and the nephrotic syndrome. Patients with the former two conditions have a decreased effective circulating volume. In patients with cirrhosis, decreased effective circulating volume is a result of arterial vasodilation of the splanchic circulation, which is probably due to increased endothelial release of nitric oxide. Patients with the nephrotic syndrome have edema usually due to primary sodium re-

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**Table 3. Common Causes of SIADH**

<table>
<thead>
<tr>
<th>Tumors</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Pulmonary/mediastinal (small cell carcinoma, mesothelioma, thymoma)</td>
<td></td>
</tr>
<tr>
<td>Nonchest carcinomas (duodenal, stomach, pancreatic, ureteral, prostate, bladder, uterine, nasopharyngeal)</td>
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</tr>
<tr>
<td>Lymphoma</td>
<td></td>
</tr>
<tr>
<td>Ewing sarcoma</td>
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</table>

<table>
<thead>
<tr>
<th>Central nervous system disorders</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Mass lesions (tumors, brain abscesses, subdural hematoma)</td>
<td></td>
</tr>
<tr>
<td>Inflammatory diseases (encephalitis, meningitis, systemic lupus, acute intermittent porphyria, multiple sclerosis)</td>
<td></td>
</tr>
<tr>
<td>Degenerative/demyelinating diseases (Guillain-Barré syndrome, spinal cord lesions)</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous (subarachnoid hemorrhage, head trauma, acute and chronic psychosis, delirium tremens, pituitary stalk section, transsphenoidal adenomectomy, hydrocephalus, cerebrovascular accident, cavernous sinus thrombosis)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug-induced</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Stimulated AVP release (narcotics, nicotine, phenothiazines, tricyclics)</td>
<td></td>
</tr>
<tr>
<td>Direct renal effects, potentiation of AVP antidiuretic effects (desmopressin, oxytocin, prostaglandin synthesis inhibitors), or both</td>
<td></td>
</tr>
<tr>
<td>Mixed or uncertain actions (carbamazepine and oxcarbazepine, chlorpromamide, clofibrate, clozapine, cyclophosphamide, ifosfamide, 3,4-methylenedioxymethamphetamine [&quot;ecstasy&quot;], serotonin reuptake inhibitors, vincristine)</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Pulmonary diseases</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections (tuberculosis, acute bacterial and viral pneumonia, pulmonary abscess, aspergillosis, emphysema)</td>
<td></td>
</tr>
<tr>
<td>Mechanical/ventilatory (acute respiratory failure, asthma, COPD, positive pressure ventilation)</td>
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</table>

<table>
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<tr>
<th>Other</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Rocky Mountain spotted fever</td>
<td></td>
</tr>
<tr>
<td>AIDS and early symptomatic HIV infection</td>
<td></td>
</tr>
<tr>
<td>Nausea, pain, stress</td>
<td></td>
</tr>
<tr>
<td>Prolonged strenuous exercise (marathon, triathlon, ultramarathon, hot-weather hiking)</td>
<td></td>
</tr>
<tr>
<td>Mutations of the aquaretic vasopressin receptor</td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td></td>
</tr>
</tbody>
</table>

AVP = arginine vasopressin; COPD = chronic obstructive pulmonary disease; SIADH = syndrome of inappropriate secretion of antidiuretic hormone.

tention that results in overfilling of the intravascular volume.

**What is the overall approach to the diagnosis of hyponatremia?**

Two papers have highlighted the difficulties in identifying the cause of hyponatremia.

*In the first study,* 121 consecutive patients presenting with plasma sodium levels <130 mEq/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 algorithm and senior physician with the reference standard was 71% and 32%, respectively. The main diagnostic problem was SIADH, which was often diagnosed incorrectly before hypothyroidism and secondary adrenal insufficiency were ruled out (18).

*In the second 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%–12%. The primary obstacle was that 8 of 10 algorithms used assessment of volume status as an important variable; other problems were failure to rule out secondary adrenal insufficiency before making the diagnosis of SIADH and diagnosing primary polydipsia based on urinary osmolality <100 mOsm/kg H$_2$O but not considering decreased solute excretion (19).

The **Figure** describes an approach to the diagnosis of hyponatremia. As part of the initial evaluation, clinicians should measure the patient’s plasma osmolality, glucose, urea, creatinine, and potassium. Urine should be measured for osmolality, sodium, and chloride (if the patient is vomiting). **Appendix Figures 1 through 3** (available at www.annals.org) show further diagnostic workups based on the results of the initial evaluation.

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

$$(\text{mOsm/kg H}_2\text{O}) = 2 \times \text{serum} [\text{Na}^+] (\text{mmol/L}) + \text{glucose (mg/dL)}/18 + \text{BUN (mg/dL)}/2.8$$

Hyponatremia due to increased plasma osmolality (>295 mOsm/kg H$_2$O) occurs when high concentrations of effective solutes increase the extracellular osmolality. As a result, intracellular water moves into the extracellular fluid, thus diluting the plasma sodium. Hypertonic hyponatremia occurs most commonly with hyperglycemia. Misdiagnosis can be avoided by correcting the plasma sodium by a factor of 1.6 mEq/L for each 100-mg/dL increase in plasma glucose levels, if glucose is <400 mg/dL. A correction factor of 2.4 mEq/L should be used if glucose level is >400 mg/dL (20). Solutes that freely permeate cell membranes (urea, alcohol, and methanol) can also increase plasma osmolality and should be considered when plasma osmolality is being calculated. The correction factors are as follows: BUN (mg/dL), 1/2.8; ethanol (mg/dL), 1/4.6; and methanol (mg/L), 1/32.

Pseudohyponatremia is characterized by normal plasma osmolality (275–295 mOsm/kg H$_2$O) 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, the concentration of sodium per liter of plasma overall is decreased because of the increased relative proportion occupied by lipids or protein. The measured plasma osmolality is not affected. Pseudohyponatremia can also be seen in patients who have transurethral resection of the prostate and absorption of variable amounts of glycine or sorbitol.

If plasma osmolality is low (< 275 mOsm/kg H₂O) after increased urea and glucose are corrected for, the patient has hypotonic hyponatremia, the most common form of hyponatremia.

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

If the patient has hypotonic hyponatremia, the next step is to measure urine osmolality (Figure). If urine osmolality is < 100 mOsm/kg H₂O, then polydipsia or decreased solute excretion is usually the cause. Urine osmolality < 100 mOsm/kg H₂O may also be found after volume resuscitation of patients with hypovolemic hyponatremia if osmolality is measured after the administration of isotonic saline.

If urine osmolality is > 200 mOsm/kg H₂O, the patient is not receiving diuretics, and kidney function is normal, then AVP is playing an etiologic role. To determine the cause of AVP secretion, the next step is to classify the patient's volume status on the basis of the history and physical examination. Volume status is typically classified into 3 categories: hypovolemia, clinical euvolemia, or hypervolemia.

Patients with hypovolemic hyponatremia are further subdivided into whether they are experiencing extrarenal or renal sodium losses. If extrarenal losses are likely (due to vomiting, diarrhea, pancreatitis, and small bowel obstruction), urinary studies should show low sodium (< 30 mEq/L) and increased osmolality. One exception is vomiting patients; in these cases, urinary sodium could be > 30 mEq/L but urinary chloride will be < 30 mEq/L. Re-
nal sodium losses occur with diuretic use, primary adrenal insufficiency, salt-losing nephritis, and CSW. In these patients, urinary sodium will be > 30 mEq/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. In these cases, measurement of urinary sodium can be very useful in differentiating between hypovolemia and euvolemia. Urinary sodium level < 30 mEq/L has 63%-80% sensitivity and 72%-100% specificity for hypovolemia, whereas urinary sodium >30 mEq/L has 87%-100% sensitivity and 52%-83% specificity for euvolemia (21-22).

Administration of normal saline as a diagnostic test may be necessary in patients with urinary sodium < 20 and > 20 mEq/L or < 40 mEq/L to distinguish between hypovolemic hyponatremia and SIADH, with coexistent salt depletion. Patients with salt-depleted SIADH do not normalize plasma sodium after administration of normal saline; urine osmolality remains high, and the administered sodium is excreted in the urine. By contrast, hypovolemic hyponatremia improves after administration of normal saline; the urine osmolality decreases, and urinary sodium does not increase until the patient becomes euvolemic.

In patients with hypervolemia due to heart failure, cirrhosis, or the nephrotic syndrome, the diagnosis is usually based on history and physical examination. The urinary sodium should be < 30 mEq/L in these patients unless they are receiving diuretics.

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

Patients with unexplained SIADH should have imaging studies to identify the potential underlying cause. All patients should have chest radiography, and clinicians should consider ordering chest computed tomography in smokers. Magnetic resonance imaging of the brain is indicated if neurologic abnormalities are found on physical examination after plasma sodium has been normalized.

When should clinicians consult a nephrologist or an endocrinologist?

Clinicians should consult with a nephrologist or endocrinologist if the cause of hyponatremia is unknown and if guidance is needed for the appropriate evaluation of SIADH. These specialists can also give advice on the use of normal saline in patients with possible SIADH and plasma sodium levels < 120 mEq/L.

Diagnosis... 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 for whom volume status is uncertain, saline infusion may be useful. Before SIADH is diagnosed, the thiazide treatment must be stopped to determine the effect on plasma sodium and to rule out secondary adrenal insufficiency and hypothyroidism.

CLINICAL BOTTOM LINE

What is the overall approach to treatment of hyponatremia?
The overall approach to hyponatremia treatment depends on acuity, severity, and cause. Hyponatremia is “acute” if the duration is known to be < 48 hours and “chronic” if the duration is unknown or > 48 hours. Endurance exercise with water intoxication, psychogenic polydipsia, use of such drugs as 3, 4-methylenedioxyamphetamines (ecstasy), colonoscopy preparation, and postoperative states are associated with acute hyponatremia. Acute hyponatremia can be characterized by swelling of brain cells and can lead to cerebral edema with risk for brain herniation. Thus, patients with acute hyponatremia require urgent normalization of sodium levels. Over 24–48 hours, the brain can adapt to hyponatremia by losing organic solutes, which allows intracellular osmolality to equal plasma osmolality without a large increase in brain cell water. 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 typically classified as mild, moderate, or severe. Guidelines released by professional societies have some minor differences in the sodium levels associated with these categories. In 2013, recommendations from a U.S.-based expert panel classified mild hyponatremia as 130–135 mEq/L, moderate as 120–129 mEq/L, and severe as < 120 mEq/L (23). In 2014, a clinical practice guideline on diagnosis and treatment of hyponatremia from the European Society of Endocrinology, the European Society of Intensive Care Medicine, and the European Renal Association-European Dialysis and Transplant Association classified mild hyponatremia as 130–135 mEq/L, moderate as 125–129 mEq/L, and severe as < 125 mEq/L (24).

How rapidly should sodium levels be corrected in acute and severely symptomatic hyponatremia, and how should they be monitored?
In patients with acute hyponatremia or severely symptomatic chronic hyponatremia (altered mental status, seizures, and frequent vomiting), it is important to rapidly reverse cerebral edema by increasing plasma sodium by 5 mEq/L. On the other hand, in patients with chronic hyponatremia, the plasma sodium level should not be raised > 10 mEq/L within 24 hours and/or > 18 mEq/L within 48 hours. These are limits that should not be exceeded rather than goals of therapy. Because it is easy to “overshoot the mark” (see below), the goal of therapy should be set well below the therapeutic limit. Recommended rates of correction in patients with chronic hyponatremia at high risk for osmotic demyelination are 4–6 mEq/L per day.

Guidance for the treatment of hospitalized patients with acute and chronic symptomatic hyponatremia, including monitoring of plasma sodium, is presented in Table 4. It is primarily based on the European recommendations (24) as well as U.S. expert panel recommendations whenever there are significant differences (23).

Data on outcomes of 56 patients with plasma sodium levels ≤ 105 mmol/L were obtained from members of the American Society of Nephrology. Increased chronicity of hyponatremia and a high rate of correction in the first 48 hours of treatment were significantly associated with complications. No neurologic complications were observed among patients corrected by < 12 mmol/L per 24 hours, or by < 18 mmol/L per 48 hours. In this cohort of patients with severe chronic hyponatremia, neurologic complications—which were probably secondary to...
pontine and extrapontine myelinolysis—were less frequent in patients whose electrolyte imbalance was corrected more slowly (25).

It is extremely difficult to predict the rate of correction of plasma sodium levels. Initially, when patients are given hypertonic saline, the formula that is often used to predict the initial increase in plasma takes into account the administered amount of volume, sodium, and potassium and total body water (based on age and sex). It should be noted that this formula is based on a “closed system” that does not take into consideration urinary loss of electrolytes or water, which substantially affects the actual change in plasma sodium.

In a retrospective study of 62 hyponatremic patients treated with a low rate of hypertonic saline, several patients were unintentionally overcorrected (11% by > 12 mEq/L in 24 h and 9.7% by >18 mEq/L in 48 h), despite frequent adjustments in the infusion rate and/or administration of 5% dextrose in water. Using a predictive formula in patients with plasma sodium < 120 mEq/L, the observed increase in plasma sodium exceeded the formula’s estimated increase in plasma sodium.

Table 4. Treatment of Hospitalized Patients With Hyponatremia, According to Symptoms

<table>
<thead>
<tr>
<th>Symptom Description</th>
<th>Treatment Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe (cardiorespiratory arrest, seizures, deep somnolence, and coma)</td>
<td>Administer 150 mL 3% saline over 20 min, then check plasma sodium levels while repeating the infusion of hypertonic saline over 20 min; continue 3% saline with target of 5-mEq/L increase in plasma sodium, then stop hypertonic saline. Expert panel: 100 mL of 3% saline infused over 10 min x 3 as needed with urgent correction 4-6 mEq/L. Do not increase plasma sodium more than 10 mEq/L in 24 h and in the next 24 h greater than 8 mEq/L. For the first 24 h, monitor plasma sodium levels every 6 h depending on changes; when stable, measure levels every 24 h.</td>
</tr>
<tr>
<td>No improvement</td>
<td>Continue 3% saline aiming for an additional 1-mEq/L/h increase in plasma sodium. Stop 3% saline infusion when symptoms improve, plasma sodium levels increases 10 mEq/L, or it reaches 130 mEq/L, whichever occurs first. Monitor plasma sodium every 4 h for the duration of hypertonic saline infusion, then every 6 h for the first 24 h; when stable, measure plasma sodium every 24 h.</td>
</tr>
<tr>
<td>Acute hyponatremia without severe or moderately severe symptoms</td>
<td>If acute, decrease in plasma sodium &gt;10 mEq/L infuse 150 mL 3% saline over 20 min. Expert panel: Mild to moderate symptoms with a low risk of herniation, 3% hypertonic saline infused at 0.5-2 mL/kg/h. Monitor plasma sodium after 4, 12, and 24 h; when stable measure plasma sodium every 24 h.</td>
</tr>
<tr>
<td>Moderately severe (nausea, confusion, headache, vomiting)</td>
<td>Immediate treatment with 150 mL 3% hypertonic saline over 20 min; aim for a 5-mEq/L/24 h increase but limit plasma sodium to a 10-mEq/L increase in the first 24 h and 8 mEq/L during every 24 h thereafter until plasma sodium reaches 130 mEq/L. Check plasma sodium levels after 1, 6, and 12 h. Expert panel: No indication for hypertonic saline; minimum correction of plasma sodium by 4-8 mEq/L per day with a lower goal of 4-6 mEq/L per day if risk for ODS is high; limits should not exceed 8 mEq/L in any 24-h period if risk for ODS is high.</td>
</tr>
<tr>
<td>Chronic hyponatremia without severe or moderately severe symptoms</td>
<td>Stop nonessential fluids, medications, and other factors that can contribute to or provoke hyponatremia. Do not treat with the sole aim of increasing the plasma sodium. Avoid an increase in plasma sodium &gt;10 mEq/L during the first 24 h and &gt;8 mEq/L during each 24 h thereafter. Monitor plasma sodium every 6 h until the plasma sodium stabilizes.</td>
</tr>
<tr>
<td>Overrapid correction</td>
<td>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 plasma sodium has increased by &gt; 10 mEq/L in 24 h or 18 mEq/L in 48 h, discontinue ongoing active treatment. Consult an expert as 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 plasma sodium every 2 h until it corrects, then every 4-6 h for the first 48 h.</td>
</tr>
</tbody>
</table>

ODS = osmotic demyelination syndrome.

How are patients with chronic asymptomatic hyponatremia treated?

Table 5 presents guidance for the treatment of patients with chronic asymptomatic hyponatremia. Recommendations are based on expert consensus. It is important not to administer isotonic saline to symptomatic or asymptomatic clinically euvolemic patients with plasma sodium $\leq 120$ mEq/L because levels may decrease if urine is hypertonic (i.e., the sum of urinary concentrations of sodium plus potassium exceeds plasma sodium concentration) (3). The initial treatment of patients with euvolemic hypovolemia includes fluid restriction and stopping any medications that could cause SIADH. Salt should not be restricted in patients with SIADH because they have decreased total body sodium. Fluid restriction alone is usually unsuccessful if the sum of urinary sodium concentration plus potassium is more than half the plasma sodium concentration (27).

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

When chronic hyponatremia is corrected too rapidly, the inability of the brain to rapidly recover organic solutes lost in the adaptation to hyponatremia may lead to the osmotic demyelination syndrome (ODS). The neurologic symptoms of this syndrome (dysarthria, dysphagia, paraparesis or quadriparesis, confusion, obtundation, and coma) typically occur 2–6 days after correction. Factors that increase risk for ODS include initial plasma sodium level < 105 mEq/L; hypokalemia; and a history of alcoholism, malnutrition, and advanced liver disease. ODS is more likely to occur if the increase in plasma sodium exceeds 10 mEq/L within 24 hours and 18 days.

74.2%. Inadvertent overcorrection was due to documented water diuresis in 40% of cases (26).
mEq/L within 48 hours. Furthermore, plasma sodium may increase more than intended if the cause of hyponatremia is reversible. When the reason for hyponatremia is removed (by volume resuscitation, discontinuation of a medication, cortisol replacement, correction of hypoxia, or recovery from stress), AVP secretion is suppressed, and excretion of dilute urine (water diuresis) results in a rapid increase in the plasma sodium concentration.

Overcorrection of hyponatremia is a medical emergency and should be avoided. If plasma sodium increases too rapidly, desmopressin (synthetic AVP) can be given to prevent further urinary water losses. Some authors have suggested that desmopressin be given as soon as the targeted daily increase in plasma sodium levels (6–8 mEq/L) has been achieved or water diuresis begins. Others suggest giving desmopressin immediately to patients with reversible causes of hyponatremia, in anticipation of, rather than in response to, an unwelcome water diuresis. Plasma sodium is then increased with a slow infusion of hypertonic saline, adjusted to correct hyponatremia by 6 mEq/L per day (28), while repeated doses of desmopressin are given to prevent urinary water losses. In a recent review (29), the authors suggested starting desmopressin along with isotonic saline in hypertensive patients with hyponatremia due to polydipsia (not currently drinking), and patients with low solute intake who have a rapid increase in urine output. The role of desmopressin in managing hyponatremia requires further research (29).

When should patients be hospitalized for management of hyponatremia?

Hyponatremic patients who are symptomatic (e.g., confusion, headache, vomiting, and seizures) and those with acute hyponatremia, plasma sodium level < 125 mEq/L, or risk factors for ODS should be hospitalized.

How should clinicians counsel patients about salt and fluid intake and when to seek clinical care?

Treatment of patients with hypervolemic hyponatremia due to heart failure includes restriction of dietary salt to 1.5 to 3.0 g/day and fluid restriction. Some studies have shown poorer clinical outcomes with lower salt intake. In general, patients should be counseled to limit fluid intake to 1.5–2 L/day unless hyponatremia worsens (30). Patients with SIADH should be advised to limit fluid intake to around 800 mL/day and not to restrict salt intake. Patients should seek care if they experience altered mental status, falls, or persistent nausea because these may be symptoms of hyponatremia.

What other therapies, including medications, are used in the management of hyponatremia?

The Appendix Table (available at www.annals.org) presents an overview of medications used to treat patients with asymptomatic hyponatremia. When fluid restriction is unsuccessful, treatment options include use of salt tablets alone or with loop diuretics (particularly if the urine osmolality is > 500 mOsm/kg). Although urea (usually 30 g/d) has been shown to be as effective as tolvaptan (31), it is not readily available in the United States and not very palatable. Demeclocycline acts on the collecting duct to decrease its response to AVP and has been used to treat hyponatremia. The European guidelines (24) recommend against demeclocycline because of its delayed onset of action and increased chance of acute kidney injury. The U.S. expert panel recommends demeclocycline as an alternative treatment.
if fluid restriction is unsuccessful. Loop diuretics can be useful in managing hyponatremia in patients with heart failure by increasing free water excretion. In severely symptomatic hyponatremic patients with congestive heart failure (CHF) and/or liver disease with ascites, administration of loop diuretics with hypertonic saline can decrease the chance of fluid overload.

**When should clinicians consider use of vasopressin-receptor antagonists?**

Vasopressin-receptor antagonists (vaptans) block the effect of AVP, leading to increased free water excretion. Conivaptan is an intravenous formulation and is approved for treatment of SIADH. Tolvaptan is an oral formulation approved for managing hyponatremia in CHF and SIADH. The 2014 European guidelines (24) recommend against vaptans for treatment of hyponatremia in patients with SIADH and expanded extracellular fluid. Although these guidelines acknowledge that vaptans increase plasma sodium in these patients, they also express concerns about the increased risk for rapid correction of plasma sodium and lack of mortality benefit. There are reports of neurologic sequelae in patients who were treated with tolvaptan whose plasma sodium correction exceeded the suggested rate and possibly increased the risk for death.

During the past year, several national recommendations and guidelines (from the United Kingdom, Sweden, and Spain) have been published on management of hyponatremia. Each recommended use of tolvaptan if fluid restriction was unsuccessful in managing plasma sodium levels in patients with hyponatremia.

The U.S. Food and Drug Administration (FDA) has limited tolvaptan use to 1 month, based on reports of hepatotoxicity associated with high doses in patients with autosomal dominant polycystic kidney disease. The FDA also limits use to patients with plasma sodium < 125 mEq/L, unless they are symptomatic and have not responded to fluid restriction. The expert panel (23) acknowledged the concern about vaptans and hepatotoxicity. To avoid overcorrection, the panel recommended that vaptans be used alone rather than in conjunction with other treatments for hyponatremia. The panel recommended checking plasma sodium levels every 6–8 hours during initiation of vaptan treatment and not initially restricting fluid intake. Although the panel stated that these drugs could be used as long-term therapy, it noted that such use would probably be limited by high cost and FDA restrictions. Even with these significant concerns, clinicians should consider treatment with vaptans in patients who have not responded to other measures (i.e., plasma sodium < 125 mEq/L and/or persistent symptoms believed to be due to hyponatremia) if the anticipated benefit exceeds the risk.

**When should clinicians consult a nephrologist or endocrinologist for treatment of hyponatremia?**

Clinicians should consult a nephrologist or endocrinologist for guidance when administration of hypertonic saline and/or vaptans is considered. Consultations are also indicated for acute, severe, or symptomatic hyponatremia (plasma sodium < 120 mEq/L) and for help in managing patients with risk factors for ODS, patients who have had overly rapid correction, or those who require long-term therapy for hyponatremia.
Practice Improvement

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

The 2013 US Expert Panel Recommendations (23) and 2014 European Clinical Practice Guidelines (24) are recent guidelines addressing the diagnosis and treatment of hyponatremia. Guidelines from the American College of Cardiology/American Heart Association address the management of all aspects of heart failure, including sodium and water restriction (30) (http://circ.ahajournals.org/content/128/16/1810.full?sid=6716f9b4-016f-4ed6-8a58-d74807c7eeb9).

Guidelines from the European Society of Cardiology address the diagnosis and treatment of heart failure (http://eurheartj.oxfordjournals.org/content/33/14/1787.long).

In the Clinic

Tool Kit

Hyponatremia

NIH MedLine Plus

Clinical Guidelines
www.ese-hormones.org/guidelines/joint.aspx
www.eje-online.org/content/170/3/GI.full

Description and Information
www.mayoclinic.org/diseases-conditions/hyponatremia/basics/definition/CON-20031445?p=1

Patient Resources
www.mayoclinic.org/diseases-conditions/hyponatremia/basics/definition/con-20031445
http://ummm.edu/health/medical/ency/articles/hyponatremia

Patient Resources in Spanish

Treatment... Patients with severe hyponatremia, acute hyponatremia, or moderate to severe symptoms should be hospitalized for diagnosis and treatment. It is important to administer hypertonic saline to rapidly correct plasma sodium levels in patients with acute hyponatremia, even if they are asymptomatic (e.g., exercise-associated hyponatremia), and patients with moderate to severe symptoms (chronic or acute). It is also important to monitor patients closely and not to increase levels > 10 mEq/L within 24 hours or 18 mEq/L within 48 hours. The recommended rates of sodium correction are lower in patients at risk for ODS. Factors that increase risk for this syndrome include an initial plasma sodium level < 105 mEq/L, hypokalemia, alcoholism, malnutrition, and advanced liver disease. Clinicians considering tolvaptan should take into account the FDA recommendation not to exceed 1 month of use.
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 a blood and urine sample 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 a blood and urine sample. He or she may also order further testing, like 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

ACP
American College of Physicians
Leading Internal Medicine, Improving Lives

Medline Plus

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

Downloaded From: http://annals.org/ by a Univ Of Hawaii User on 09/07/2015
Appendix Figure 1. Approach to the diagnosis of hypovolemic hyponatremia.

High Probability of Hypovolemia Based on clinical history and physical examination

<table>
<thead>
<tr>
<th>Variable U\textsubscript{Na}</th>
<th>U\textsubscript{Na} &lt; 30 mEq/L</th>
<th>U\textsubscript{Na} &gt; 30 mEq/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td>Extrarenal losses</td>
<td>Renal losses</td>
</tr>
<tr>
<td>D/C diuretics</td>
<td>Vomiting*, Diarrhea, Pancreatitis, Sweating, Small bowel obstruction</td>
<td>Osmotic diuresis (glucose, urea bicarbonaturia)</td>
</tr>
<tr>
<td>Failure to normalize P\textsubscript{Na}</td>
<td>Salt-losing nephritis, Addison disease, CSW</td>
<td>ACTH-stimulation test</td>
</tr>
<tr>
<td></td>
<td>Administer 0.9% saline</td>
<td>Consistent with Addison disease</td>
</tr>
<tr>
<td></td>
<td>Failure to normalize P\textsubscript{Na}</td>
<td>Treatment: Glucocorticoids and mineralcorticoids</td>
</tr>
<tr>
<td></td>
<td>Normalize P\textsubscript{Na}</td>
<td>Hypovolemia</td>
</tr>
<tr>
<td></td>
<td>Decreasing U\textsubscript{osm}</td>
<td>Salt-depleted SIADH</td>
</tr>
<tr>
<td></td>
<td>No change in U\textsubscript{osm}, U\textsubscript{Na} increases</td>
<td>Hypovolemia</td>
</tr>
</tbody>
</table>

ACTH = adrenocorticotropic hormone; CSW = cerebral salt wasting; D/C = discontinue; SIADH = syndrome of inappropriate antidiuretic hormone secretion.

* If patient is vomiting, U\textsubscript{Cl} should be low.
† Volume-depleted elderly patients can have urinary sodium > 30 mEq/L but FE\textsubscript{Na} < 0.5%.
Appendix Figure 2. **Approach to the diagnosis of euvolemic hyponatremia.**

- **Clinical Euvolemia**
  - $U_{\text{Na}} < 20$ mEq/L
  - Variable $U_{\text{Na}}$
  - $>20$ mEq/L

- **D/C diuretics**
  - $P_{\text{Na}}$ normalizes
  - Not SIADH

- **Probable hypovolemia**
  - $P_{\text{Na}}$ decreases or no change
  - SIADH
  - Administer additional saline
  - Decreasing $U_{\text{osm}}$
  - Hypovolemia

- **Probable euvolemia**
  - $P_{\text{Na}}$ increases
  - Decreased $U_{\text{Na}}$
  - Administer additional saline
  - No change in $U_{\text{osm}}$
  - No change in $U_{\text{Na}}$
  - Salt-depleted SIADH

- **Unsure diagnosis after ruling out cortisol deficiency, hypothyroidism**

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D/C = discontinue; SIADH = syndrome of inappropriate antidiuretic hormone secretion.

* Severe hypothyroidism = urinary sodium < 20 mEq/L.
† If plasma sodium < 120 mEq/L, consult endocrinologist or nephrologist for guidance.

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

- **Hypervolemia**
  - $U_{\text{Na}} < 30$ mEq/L
    - Heart failure
    - Liver disease
    - Nephrotic syndrome
  - $U_{\text{Na}} > 30$ mEq/L
    - Chronic kidney disease†
      - Diuretic use in:
        - Heart failure
        - Liver disease
        - Nephrotic syndrome

---

* If patient is receiving diuretics, urinary sodium can be >30 mEq/L.
† Patients with chronic kidney disease can also be euvolemic.
### Appendix Table. Drug and Nondrug Treatment for Hyponatremia

<table>
<thead>
<tr>
<th>Drug or Drug Class</th>
<th>Dosing</th>
<th>Side Effects</th>
<th>Precautions</th>
<th>Clinical Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium chloride tablets</td>
<td>5–15 g daily</td>
<td>Hypernatremia, fluid overload</td>
<td></td>
<td>SIADH common when combined with furosemide</td>
</tr>
<tr>
<td>Furosemide (Lasix)</td>
<td>20–80 mg daily</td>
<td>Orthostatic hypotension, hyperuricemia, azotemia, ototoxicity, impaired glucose tolerance, pancreatitis</td>
<td>Water and electrolyte depletion; caution with sulfonamide hypersensitivity, CKD, hepatic impairment*</td>
<td>Combined with sodium supplementation in SIADH, CHF, and liver disease with ascites</td>
</tr>
<tr>
<td>Urea</td>
<td>15–30 g daily</td>
<td>Too rapid an increase in serum sodium, poor palatability, azotemia at higher doses</td>
<td>Monitor serum sodium levels</td>
<td>SIADH</td>
</tr>
<tr>
<td>Demeclocycline (Declomycin)</td>
<td>600-1200 mg total daily dose, dosed 3 to 4 times daily</td>
<td>CNS side effects, nausea, vomiting, diarrhea, photosensitivity, azotemia, acute renal failure, hematologic effects with long-term therapy</td>
<td>Avoid with pregnancy; caution with hepatic disease, CKD; do not administer within 4 hours of drugs containing divalent or trivalent cations; administer 1 h before or 2 h after meals</td>
<td>SIADH</td>
</tr>
<tr>
<td>Tolvaptan (Samsca)</td>
<td>15 mg daily, then 30 mg daily; maximum 60 mg daily</td>
<td>Xerostomia, asthenia, hyperglycaemia, anorexia, hepatic disease, constipation, thirst, polyuria, polydipsia, dehydration, orthostatic hypotension, neurologic sequelae when correction of serum sodium exceeds the suggested rate</td>
<td>Initiate and reinitiate in a hospital and monitor serum sodium levels; avoid if CrCl*</td>
<td>Can be useful in SIADH and CHF if benefit exceeds risk</td>
</tr>
</tbody>
</table>

CHF = congestive heart failure; CKD = chronic kidney disease; CNS = central nervous system; CrCl = creatinine clearance; CYP = cytochrome P450 isoenzyme; P-gp = P-glycoprotein; SCr = serum creatinine; SIADH = syndrome of inappropriate antidiuretic hormone secretion.  
* Black box warning.