REVIEW

BENJAMIN J. FREDA, DO
Department of Nephrology and Hypertension, The Cleveland Clinic Foundation

MICHAEL B. DAVIDSON, DO
Department of Internal Medicine, The Cleveland Clinic Foundation

PHILLIP M. HALL, MD
Staff Consultant, Department of Nephrology and Hypertension, The Cleveland Clinic Foundation

Evaluation of hyponatremia: A little physiology goes a long way

ABSTRACT

Hyponatremia is common in hospitalized patients. By taking a careful and logical approach, one can promptly recognize the causative factor or factors in nearly all cases. Most cases of hyponatremia are due to impaired renal water excretion, and recognizing the cause and pathophysiologic process makes it possible to provide focused individualized care and avoid mistreatment.

KEY POINTS

In evaluating hyponatremia, the clinician should determine the chronicity or acuity of the hyponatremia, confirm that the patient has true plasma hypo-osmolality, determine the extracellular fluid volume status, assess laboratory tests and urine sodium values, and assess any exogenous free water intake.

In heart failure and hepatic cirrhosis, effective circulating blood volume is low, triggering release of antidiuretic hormone and water retention regardless of plasma osmolality.

If hyponatremia is severe (plasma sodium < 120 mmol/L), quickly examine the patient for signs or symptoms of acute neurologic changes (seizures, altered mental status, or focal neurologic signs) that may signal the need for immediate therapy with hypertonic intravenous saline and furosemide.

Plasma glucose should be measured in all cases of hyponatremia, and the plasma sodium concentration should be corrected for hyperglycemia.

HYPONATREMIA (a low plasma sodium concentration) is among the most common laboratory abnormalities that physicians encounter, yet its causes are among the more complex in medicine.

In a study of more than 2,800 hospitalized patients, 15% had plasma sodium concentrations below the lower end of the reference range of 134 mmol/L.[1] Almost 5% had levels less than 125 mmol/L.

In some instances, hyponatremia represents a true medical emergency, requiring immediate intervention to prevent cerebral edema. More commonly, hyponatremia may reflect the severity of a causative underlying illness and be a marker of morbidity and mortality. For example, the plasma sodium concentration is a powerful predictor of severity of heart failure[2] and mortality in hepatic cirrhosis.[3]

This paper reviews the pathophysiology and diagnostic evaluation of hyponatremia. Armed with a sound understanding of body fluid physiology, clinicians should be proficient in treating this common disorder and avoid the potentially lethal complications of mistreatment.

A LITTLE PHYSIOLOGY

The plasma sodium concentration is the main determinant of plasma osmolality and therefore of the total water balance among the body's fluid compartments. Perturbations of plasma sodium concentration reflect an underlying disorder involving water homeostasis.

The challenge for the physician is to understand the disorder that is causing the hyponatremia. The mechanism, etiology, man-

Most body water is within cells

Although the water content of humans depends on several factors such as age, gender, and amount of adipose tissue, *total body water* can be estimated as 60% of body weight in men and 50% of body weight in women. Older persons and those with more adipose tissue have less lean muscle mass and therefore less overall body water than determined from the above estimate.

The total body water is divided between the intracellular space (40% of body weight) and extracellular space (20% of body weight). Roughly one third of the extracellular volume is intravascular (plasma volume) and two thirds is interstitial. Of the total plasma volume (approximately 4.6 L in a 70-kg man), 85% is in the venous circulation and 15% is in the arterial circulation.

Thus, a 70-kg person has an arterial volume of roughly 700 cc.[4] As we will discuss, this seemingly small volume is perhaps the most critical determinant of the "fullness" of the body's circulation that is critical to the regulation of the body's sodium and fluid levels.

agement, and complications of hyponatremia are more easily understood if one considers the physiology of water regulation by the kidney and neuroendocrine axis.

Hyponatremia is most commonly due to decreased renal clearance of water

Hyponatremia can occur when there is either sodium loss or, more commonly, water retention.

Total body water = 60% of body weight (men) or 50% (women)

Movement of water from cells to the blood can also result in hyponatremia by increasing the amount of plasma water relative to plasma sodium (see **Most body water is within cells,** on this page).

Total body water can increase as a result of increased intake or decreased renal clearance. Hyponatremia due to increased water intake happens rarely in patients with normal renal function because one would have to drink more than 20 L/day to overcome the kidneys' capacity to excrete free water.

Thus, in almost all cases of hyponatremia, the problem lies in an impaired ability of the kidneys to excrete free water due to the action of antidiuretic hormone (ADH, vasopressin). ADH plays a central role in most cases of renal-mediated water retention. ADH activity may be increased appropriately (eg, in hypovolemia) or inappropriately (eg, in cancer or a drug effect).

How the kidneys regulate water balance

The fluid that is filtered from the glomerulus has the same concentration of electrolytes as the plasma. For electrolyte-free water to be excreted, this ultrafiltrate must be delivered to the diluting segment of the kidney. This requires an adequate glomerular filtration rate and an intact thick ascending limb of the loop of Henle. In the loop of Henle, salt is reabsorbed from the ultrafiltrate back into the plasma without water. What remains is a relatively dilute (hypotonic) fluid that proceeds into the distal nephron.

This dilute fluid, made up mostly of water, will be excreted in the urine if it is not reabsorbed in the collecting ducts. The reabsorption of water depends on the presence and activity of ADH.

ADH secretion is directly tied to osmolality

In a healthy patient, the ADH level is sensitive to both the plasma osmolality (determined primarily by the plasma sodium concentration) and the volume status.

As the volume of plasma water increases, the sodium concentration decreases, and thus so does the plasma osmolality. This decrease is sensed by osmoreceptors in the hypothalamus that regulate ADH secretion. These cells are sensitive to changes in plasma osmolality of as little as 1% above or below normal values, and they respond to decreased osmolality by signalling the pituitary to inhibit ADH release.

In the absence of ADH, normally functioning kidneys excrete more electrolyte-free water, restoring plasma osmolality and the plasma sodium concentration to normal levels. At a plasma osmolality of less than 275 mOsm/kg H_2O, ADH secretion ceases.[5] Conversely, as osmolality increases, ADH

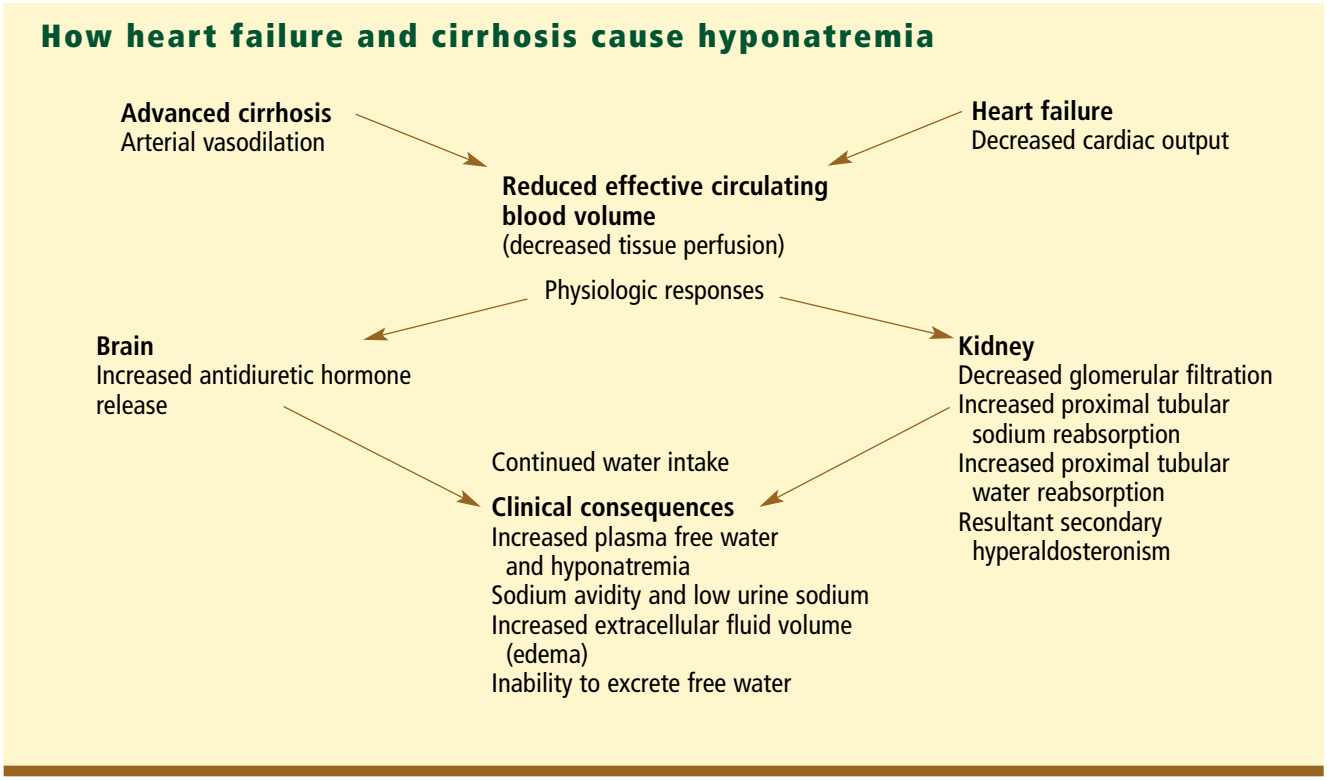

FIGURE 1

secretion increases. In a normal kidney, this results in the reabsorption of free water and the reduction of osmolality.

Decreased effective circulating volume: Why patients retain water in heart failure and hepatic cirrhosis

In some diseases, the normal mechanisms of water homeostasis go awry, leading the kidney to reabsorb water even though the patient appears fluid-overloaded. As a result of water retention, the plasma osmolality decreases, and hyponatremia ensues.

Patients with heart failure or hepatic cirrhosis may continue to retain sodium and water, even though they may have a clinically apparent excess of extracellular fluid volume (ie, edema or ascites).

Diminished cardiac output (in heart failure) and peripheral vasodilation (in hepatic cirrhosis) cause baroreceptors in the renal afferent arterioles and the carotid sinus to sense decreased pressure and therefore decreased "circulatory fullness." Circulatory fullness is a combination of cardiac output, intravascular blood volume, and arterial vascular tone, which is sensed by carotid and afferent arteriolar baroreceptors. In an attempt to restore perfusion pressure to the tissues of the body, these baroreceptors signal the posterior pituitary to release ADH, resulting in free water reabsorption and hyponatremia, even if the plasma is already dilute.[6] The volume of extracellular fluid needed to maintain perfusion pressure and avoid stimulation of ADH release has been called the *effective circulating blood volume*.[6]

Other mechanisms resulting in water and sodium retention in patients with edematous states are outlined in FIGURE 1.

Thus, the presence of hyponatremia may indicate that underlying heart failure or cirrhosis is severe enough to limit tissue perfusion as sensed by the kidney and carotid baroreceptors.

Hyponatremia is usually due to impaired clearance of water

ADH secretion can be independent of osmolality

Although the prime regulator of ADH secretion is osmolality, there are also "osmolality-independent" stimulants of ADH secretion. These include:

TABLE 1

Initial evaluation of hyponatremia

Examine the patient for signs of acute neurologic changes
Confirm that the blood draw was accurate (verify result)
Clinically determine his or her extracellular fluid volume status
Rule out hyperglycemia
Determine rate of development of hyponatremia (hours to weeks)
Review all recent and current intravenous fluid orders
Review all intravenous medications for free water content (eg, antibiotics mixed with dextrose and water)
Review all medications (especially use of diuretics)
Confirm true hypo-osmolality (see text and TABLE 3)
Review and order appropriate laboratory tests (see TABLE 2)

- **Hypovolemia** (as described above). Hypovolemia decreases the osmotic threshold at which ADH is secreted: during hypovolemia, ADH secretion will persist even if plasma osmolality is less than 275 mOsm/kg H_2O.
- **Postoperative nausea, pain, and stress** may also stimulate ADH secretion.
- **Many neoplasms** and pulmonary and central nervous system disease processes can be powerful stimulants of ADH secretion or even produce ectopic ADH.
- **Drugs** that stimulate ADH secretion include but are not limited to selective serotonin reuptake inhibitors, haloperidol, vincristine, cyclophosphamide, and carbamazepine. Nonsteroidal anti-inflammatory drugs can also contribute to hyponatremia by reducing renal prostaglandins, which normally act to antagonize the free-water reabsorption mediated by ADH.[5]

Sodium and glucose act as effective osmoles; urea does not

Water can also move in and out of cells

In addition to changes in total body water and sodium, we need to consider movement of water and electrolytes between fluid compartments. Key to understanding this movement is the concept of effective and ineffective osmoles.

Water moves between body fluid compartments primarily as a result of osmotic forces. A solute that induces movement of water between fluid compartments is an "effective" osmole. An "ineffective" osmole can readily cross from one fluid compartment to another, thereby limiting its ability to incite movement of water.

Sodium, which resides primarily in the extracellular fluid due to the action of the sodium-potassium ATPase pump, is an effective osmole—it tends to hold water in the extracellular fluid. Similarly, potassium acts as the major intracellular effective osmole, acting to hold water within the cell.

In contrast, urea is an ineffective osmole because it readily crosses cell membranes and has similar concentrations in the intracellular and extracellular fluid. Thus, although it contributes to measured plasma osmolality as a measured solute, it does not generate an osmotic force to move water between fluid compartments.

Hyperglycemia can cause hyponatremia

Glucose acts as an effective osmole in hyperglycemic states by inducing water movement from the intracellular to the extracellular fluid space. Plasma water is increased and hyponatremia develops as a result of dilution of plasma sodium. Plasma osmolality is actually increased in severe cases of hyperglycemia, owing to large amounts of glucose in the plasma. Therefore, the patient is generally not at risk for the morbidity (eg, cerebral edema) associated with truly hypo-osmolar hyponatremia.

Although the effect of hyperglycemia on plasma sodium levels is dependent on additional factors (eg, water loss via a glucose-mediated osmotic diuresis), normalization of glucose levels generally leads to resolution of hyponatremia.

Hypokalemia can contribute to hyponatremia

Large losses of total body potassium, as in prolonged vomiting or diarrhea, resulting in severe hypokalemia, will cause potassium to migrate from the cells to the plasma. This can affect the plasma sodium concentration because sodium will then move into cells to maintain electroneutrality. In this way, hypokalemia can in itself cause a relative hyponatremia as sodium concentration in the plasma decreases while the concentration in the cells increases.

Thus, one must consider the effect of correcting any concomitant hypokalemia on the

TABLE 2

Laboratory assessment of hyponatremia

TEST	DEFINITION AND NORMAL VALUE	COMMENTS
Serum osmolality	Measured value: amount of solute in serum water (275–290 mOsm/kg H_2O) Calculated value: (2 × serum sodium concentration) + (serum glucose concentration / 18) + (blood urea concentration / 2.8)	Low value (< 275 mOsm/kg H_2O) confirms true hypo-osmolality Osmolal gap < 10 rules out pseudo-hyponatremia or unmeasured solutes such as mannitol, glycine, or sorbitol Measured serum osmolality is not affected by increased protein or lipids
Urine osmolality	Amount of solute in urine No "normal" value; depends on fluid and solute intake, kidney function, and water balance Range is 50–1,200 mOsm/kg H_2O, but is more narrow in older patients and renal impairment Estimate = 35 × last two digits of urine specific gravity	Appropriate response to hyponatremia is production of maximally dilute urine (< 100 mOsm/kg H_2O) Urine osmolality has limited value because nearly all patients with hyponatremia do not make maximally dilute urine except in psychogenic polydipsia or reset osmostat
Urine sodium	Spot value from fresh urine Usually < 20 (mEq/L) in low effective circulating blood volume states Usually > 20–40 in euvolemic patients without decreased effective circulating blood volume	See TABLE 5 for caveats in interpreting urine sodium
Plasma glucose	Serum sodium will decrease 1.6–2.4 mmol/L for every 100 mg/dL increase in glucose over 100 mg/dL	*Mandatory* to measure plasma glucose in all cases of hyponatremia
Tests of thyroid and adrenal function	Thyroid-stimulating hormone (TSH), Free thyroxine (T4) adrenocorticotropic hormone (ACTH), ACTH stimulation test	Useful: • When there is a clinical suspicion of thyroid or adrenal hypofunction • To establish a diagnosis of SIADH* (document normal thyroid and adrenal function) • When careful evaluation does not provide clear etiology
Serum uric acid and blood urea nitrogen (BUN) levels	Usual values: refer to individual laboratory reference range	Helpful in differentiating euvolemic SIADH from hypovolemic causes of hyponatremia Low uric acid and BUN levels are more compatible with euvolemia and SIADH

*SIADH = syndrome of inappropriate antidiuretic hormone secretion

As plasma osmolality decreases, so does ADH secretion, and the kidneys should excrete more water

overall rate of correction of hyponatremia. In practical terms, this means that giving normal saline with added potassium to a patient with hyponatremia and hypokalemia will have a greater effect on increasing the plasma sodium level than giving normal saline by itself.

INITIAL EVALUATION: IS IT REAL? IS IT SERIOUS?

TABLE 1 lists the clinical information necessary to initially evaluate a patient with hyponatremia.

TABLE 3

How to calculate plasma osmolality and the osmolal gap

1 Measure osmolality directly by laboratory assessment

2 Calculate plasma osmolality:

(2 × plasma sodium concentration) + (plasma glucose concentration / 18)
+ (blood urea nitrogen concentration / 2.8)

3 Calculate osmolal gap:

Measured value – calculated value*

*An osmolal gap > 10 mOsm/kg H_2O suggests a nonsodium effective osmole (mannitol, glycine, or sorbitol) or pseudohyponatremia (severe hyperlipidemia or hyperproteinemia); it may also be seen with ineffective osmoles (eg, ethanol, methanol, ethylene glycol). However, these latter substances do not cause water shifts or hyponatremia.

Thiazide diuretics are more likely to induce hyponatremia than are loop diuretics

Is it real? With any laboratory abnormality, the clinician must be careful to exclude errors in collecting the blood sample. This is especially relevant when an extremely low sodium level is reported in a patient who is clinically well. In such cases the sodium level should be rechecked and verified to be collected from a vein that is not being simultaneously infused with a hypotonic intravenous fluid. In patients with signs or symptoms consistent with hyponatremia, the laboratory value should be taken as accurate until proven otherwise.

How quickly did the hyponatremia develop? This information is important, as it will dictate the risk for neurologic morbidity (cerebral edema) and how quickly the plasma sodium concentration must be corrected. As will be discussed in a subsequent paper in this journal dealing with the treatment of hyponatremia, overly rapid correction may lead to neuronal damage and central pontine myelinolysis.

Are there neurologic signs or symptoms? Patients with severe hyponatremia (< 120 mmol/L) should be examined expeditiously for signs of acute neurologic changes (seizures, altered mental status, focal neurologic signs) that may signal the need for immediate therapy with hypertonic intravenous saline and furosemide.

What medications is the patient receiving? All medications should be reviewed, with careful attention to diuretics (especially thiazide-type) or medications associated with inappropriate ADH release (see above; **Drugs**). All recent and current intravenous fluid orders should also be reviewed, and intravenous medications (eg, antibiotics, cardiovascular drips) should be scrutinized for their free water content, as many antibiotics are reconstituted in dextrose and free water.

Are additional laboratory tests needed? TABLE 2 lists laboratory tests that are useful during the evaluation of hyponatremia. As discussed below, the clinician should be able to explain the hyponatremia on the basis of the clinical history, medications, extracellular fluid volume status, and directed investigations into the presence of comorbid disease or diseases that predispose to hyponatremia.

Specific laboratory tests are useful in cases in which the etiology is still unclear after careful, logical, clinical evaluation. Also, additional laboratory tests may be necessary when it is difficult to clinically assess extracellular fluid volume.

Rule out hyperglycemia

An important early step is to rule out hyperglycemia, and every patient with hyponatremia should have his or her plasma glucose measured. For every 100 mg/dL increase in plasma glucose, the plasma sodium concentration will decrease by roughly 1.6 mEq/L, although a recent report[7] suggests that the correction factor should be closer to 2.4.

Calculate the osmolal gap to confirm true plasma hypo-osmolality

In a few uncommon situations, hyponatremia does not reflect true underlying plasma hypo-

osmolality. These cases of hyponatremia are usually related to the presence of effective osmoles other than sodium in the plasma or extreme states of hyperproteinemia or hyperlipidemia.

Therefore, it is necessary to calculate the *osmolal gap* by subtracting the calculated plasma osmolality from the measured laboratory value (TABLE 3). If the osmolal gap is more than 10 mOsm/kg H_2O, the clinician should suspect that other effective osmoles are present in the plasma (see below).

Sodium-free irrigation fluids such as glycine or mannitol, used during transurethral resection of the prostate or hysteroscopic endometrial surgery, can be systemically absorbed in large amounts, leading to severe hyponatremia.[8] In these cases the measured plasma osmolality is normal but the osmolal gap is large, reflecting the mannitol or glycine in the blood.

Although the exact mechanism is not completely understood, mannitol and glycine are thought to have an osmotic effect, drawing water from the cells into the extracellular fluid (plasma). There is also a dilutional component later in the postoperative course as glycine shifts into the cells, leaving sodium-free water behind in the extracellular fluid.

Very high protein or lipid levels (usually triglycerides with lactescent serum) can cause the plasma sodium concentration to appear falsely low if it is measured by older flow photometry methods. These methods measure the concentration of sodium in the whole plasma (including both solid and liquid phases), in which the amount of sodium in the sample of whole plasma is diluted by the elevated levels of protein and lipid. In this situation, called *pseudohyponatremia*, serum osmolality is normal as measured using direct ion-specific electrodes. The calculated plasma osmolality will be low, and there will be an elevated osmolal gap.[9]

Newer methods measure the concentration of sodium in serum water independent of the solid phase of plasma, using ion-specific electrodes,[10] and the problem of pseudohyponatremia is much rarer now.

Urine osmolality offers little diagnostic aid

Even though the urine osmolality is routinely evaluated, it offers very little in narrowing the differential diagnosis of hyponatremia.

Almost all cases of hyponatremia are associated with an improperly concentrated urine (> 100 mOsm/kg H_2O). Less common causes of hyponatremia that are associated with appropriately dilute urine (urine osmolality < 100 mOsm/kg) include psychogenic polydipsia, in which patients drink excessive amounts of water, and a reset osmostat.

Although it is necessary to demonstrate that the urine is inappropriately concentrated to diagnose the syndrome of inappropriate antidiuretic hormone secretion (SIADH; see below), there is no "diagnostic" correlation between the osmolality of the urine and serum in this disorder.

TABLE 4

Causes of hyponatremia based on extracellular fluid volume status

Hypovolemic
- Gastrointestinal solute loss (diarrhea, emesis)
- Third-spacing (ileus, pancreatitis)
- Diuretic use
- Addison disease
- Salt-wasting nephritis

Euvolemic
- Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
- Diuretic use
- Glucocorticoid deficiency
- Hypothyroidism
- Beer-drinker's potomania, psychogenic polydipsia
- Reset osmostat

Hypervolemic with decreased effective circulating blood volume
- Decompensated heart failure
- Advanced liver cirrhosis
- Renal failure with or without nephrosis

It is mandatory to measure plasma glucose in all cases of hyponatremia

NEXT, EVALUATE THE VOLUME STATUS

Once hyponatremia is verified and true hypo-osmolality is confirmed, the critical next step is to determine the patient's extracellular fluid volume status. True hypo-osmolar hyponatremia can be associated with euvolemia, hypervolemia, or hypovolemia.

While the exact cause of the hyponatremia may not be immediately apparent (see TABLE 4

TABLE 5

Caveats in interpreting spot urinary sodium levels

SETTING	EFFECT ON URINE SODIUM	COMMENTS
Diuretics	Increase	Urine sodium may be falsely elevated by diuretic action, but may still be low if there is severe concomitant hypovolemia
Osmotic diuresis	Increase	Solute diuresis (eg, glucosuria) obligates sodium and water loss even in the setting of hypovolemia
Chronic kidney disease, tubulointerstitial disease	Increase	Sodium handling is altered due to renal disease, and urine sodium may be elevated even in the presence of hypovolemia
Bicarbonaturia	Increase	Bicarbonate loss obligates sodium loss to balance negative charge in urine (eg, proximal renal tubular acidosis and emesis-induced metabolic alkalosis)

for major causes), assessing the extracellular fluid volume is critical in determining the proper initial treatment (ie, fluid restriction vs resuscitation with isotonic saline).

In true hyponatremia, determine if fluid volume is high, normal, or low

Careful evaluation of the history (diarrhea, vomiting, thirst, and polyuria), nursing records (daily weights, intake and output), and physical examination (orthostasis, neck veins, peripheral edema, and ascites) should be adequate to determine the patient's extracellular fluid volume status.

Peripheral edema or ascites indicates elevated total body sodium and therefore elevated extracellular fluid volume. On the other hand, patients with circulatory compromise (orthostatic changes or supine hypotension and tachycardia) and no edema have low extracellular fluid volume. Other patients may have hypovolemia not detectable by initial examination or may be truly euvolemic.

Although it is usually easy to determine if a patient is hypervolemic, it may be harder to differentiate euvolemia from subtle hypovolemic states.[11] Other data such as urine sodium, serum uric acid, and blood urea nitrogen (BUN) levels and response to isotonic intravenous saline may be helpful in these cases (see **If the extracellular fluid volume is normal,** below).

If the extracellular fluid volume is elevated

Most hospitalized patients with hyponatremia and increased extracellular fluid volume have either **decompensated heart failure** or **advanced hepatic cirrhosis**.

Although edema or ascites always indicate elevated total body sodium, and therefore elevated extracellular fluid volume, total body water is elevated to an even greater degree in these patients due to reduced effective circulating volume.

In the absence of diuretic use or other variables affecting renal handling of sodium (TABLE 5), patients with hyponatremia, expanded extracellular fluid volume, and reduced effective circulating blood volume are profoundly "sodium-avid" (their kidneys will retain sodium). This will be manifested by a low urine sodium level (< 10–20 mEq/L).

A urine sodium level greater than 20 mEq/L in a patient with expanded extracellular fluid volume and no recent diuretic use is consistent with adequate effective circulating volume.

TABLE 5 reviews important caveats that may affect interpretation of urinary sodium values in patients with hyponatremia.

Severe renal impairment. The hallmark of renal impairment is reduced functional nephron mass and impaired glomerular filtration. Smaller volumes of fluid are filtered, and if water intake exceeds the amount that can be filtered, water will be retained and hyponatremia will develop. An acute worsening of

renal function may also impair free water excretion independent of changes in water intake.

Patients with nephrotic syndrome may develop hyponatremia regardless of the presence or degree of renal impairment. Loss of plasma oncotic pressure due to hypoalbuminemia favors a shift of fluid from the plasma into the interstitial compartment. This reduces the effective circulating blood volume and triggers ADH release. However, this mechanism may not apply in all patients with nephrotic syndrome who develop hyponatremia.[12]

If the extracellular fluid volume is low

Nonedematous patients with hyponatremia and signs of extracellular fluid volume contraction are losing sodium and water and replacing it with hypotonic fluids. Solute loss and resulting extracellular fluid volume contraction stimulate ADH release.

The sodium loss is nearly always hypotonic or isotonic to plasma; therefore, the development of hyponatremia is usually caused by replacement of the fluid losses with intravenous or oral free water.

Measure urine sodium to determine the source of sodium loss

The evaluation of patients with hyponatremia and decreased extracellular fluid volume begins by determining the source of sodium loss.

Sodium loss usually occurs via the gastrointestinal tract or kidney. Common causes include diarrhea and emesis. Third-spacing of fluid and sodium, seen in pancreatitis, burns, rhabdomyolysis, or ileus, may also lead to sodium loss and contracted extracellular fluid volume.

The cause of sodium loss may not always be clinically obvious, however. In these cases, it is critical to measure urine sodium in a spot sample to evaluate the renal response (or contribution) to extracellular fluid volume contraction.

If urine sodium is low. Urine sodium should be low (< 20 mEq/L) if extrarenal factors (ie, gastrointestinal losses or third-spacing) account for solute loss. However, as outlined in **TABLE 5**, renal sodium handling may be dysfunctional in patients with chronic kidney disease or tubulointerstitial disease. In these circumstances the kidney may not be able to avidly retain sodium even in hypovolemic states.

If urine sodium is high or normal in patients with clinically suspected extracellular fluid volume contraction, then the patient is either taking diuretics or the kidney is wasting sodium.

Diuretic use is the most common cause of hypovolemic hyponatremia, which in most cases occurs within the first 2 weeks of therapy.[13] A combination of hypokalemia, contracted extracellular fluid volume, and impaired urinary dilution contribute to its occurrence. Clinicians must be careful to interpret the urine sodium excretion in the context of the timing of the last diuretic dose.

Patients with hyponatremia who are taking diuretics can also present with hypervolemia or euvolemia, depending on sodium intake and other underlying diseases (eg, heart failure).

Thiazide diuretics are more likely to induce hyponatremia than are loop diuretics because they impair both diluting and concentrating mechanisms in the kidney. As a result of tubular sodium loss from the distal nephron, thiazide diuretics preserve the medullary osmotic gradient; therefore, free water can still be reabsorbed in the presence of ADH.

Acting at a more proximal location, loop diuretics decrease the medullary osmotic gradient and therefore impair free water reabsorption (urinary concentration) and urinary dilution.

Other causes. Salt-wasting nephritis is associated with several uncommon renal disorders, including renal cystic diseases, analgesic nephropathy, obstructive uropathy, and chronic pyelonephritis.[14]

These states are associated with the inability to conserve sodium even in the presence of hypovolemia, most often when renal impairment is severe (glomerular filtration rate < 10–15 mL/minute). In patients with adrenal insufficiency due to Addison disease (mineralocorticoid and glucocorticoid deficiency), there is sodium wasting due to aldosterone deficiency.

Edema or ascites indicates elevated total body sodium

When sodium intake cannot keep up with sodium loss (eg, during diarrhea), hypovolemia develops in the face of elevated continuing renal sodium loss (ie, Addisonian crisis). Renal salt loss and hypovolemia-induced stimulation of ADH cause the hyponatremia.[4]

If the extracellular fluid volume is normal

The causes of hyponatremia associated with clinical euvolemia include the syndrome of inappropriate antidiuretic hormone secretion (SIADH), hypocortisolism, diuretic use, beer-drinker's potomania, psychogenic polydipsia, and hypothyroidism. Diuretic use and SIADH contribute the majority of cases. In making the diagnosis of SIADH, euvolemia must be demonstrated (see below).

In patients with hyponatremia who appear euvolemic, the challenge is to rule out hypovolemia that is not revealed by clinical examination. The clinical suspicion of euvolemia should be confirmed by appropriate laboratory assessment with random urine sodium, BUN, and serum uric acid measurements.

Confirm euvolemia by measuring urine sodium, BUN, and serum uric acid

Clinical euvolemia with elevated urine sodium. If a spot urine sodium measurement is not low and there are no conditions that may affect the interpretation of urine sodium values (TABLE 5), the patient is likely truly euvolemic.

Clinical euvolemia with low urine sodium. In patients who appear euvolemic, urine sodium may be low if:

- There was recent extracellular fluid volume loss that was replaced by hypotonic fluids, or
- Dietary solute intake is very low but water intake is adequate (eg, in beer-drinker's potomania, as detailed below), or
- It is early in the course of hypovolemia when clinical signs (eg, tachycardia, orthostatic changes) are lagging behind the onset of sodium retention by the kidney.

In these situations, repeat measurement is advised.

If there is uncertainty about the patient's volume status

If there is uncertainty about the patient's extracellular fluid volume status after initial examination and urine sodium measurement:

Monitor response to isotonic saline. In cases in which it is still unclear if the patient is euvolemic or hypovolemic (equivocal examination and urine sodium), the clinician can monitor the renal response to isotonic intravenous fluids (1–2 L of 0.9% saline over 24–48 hours).

If the patient is truly hypovolemic, the plasma sodium level should increase as fluid resuscitation corrects the hypovolemia and decreases nonosmotic ADH release, resulting in excretion of free water.

On the other hand, euvolemic patients would be expected to excrete relatively more of the sodium load from the intravenous saline than patients with hypovolemia. An increase in the fractional excretion of sodium of more than 0.5% after isotonic saline infusion has been proposed to distinguish truly euvolemic patients (ie, those with SIADH) from patients with hypovolemia.[15]

Serum uric acid and BUN can also be used to distinguish between euvolemic and hypovolemic hyponatremia.

Patients with normal or slightly expanded extracellular fluid volume are more likely to have low levels of serum uric acid and nonelevated BUN. The converse is true in cases of hypovolemia in which uric acid is normal and BUN is elevated due to decreased renal perfusion. In euvolemic patients with SIADH, serum uric acid is often low due to increased urate excretion.[16]

SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION

In patients with hyponatremia, euvolemia, and true hypo-osmolality, the continued release of ADH is inappropriate. However, release can continue in SIADH. Most cases of SIADH are associated with tumors, pulmonary and central nervous system disease, or various drugs, although the cause is not always evident when hyponatremia is detected.[17]

While most cases of SIADH appear to be associated with abnormal and inappropriate levels of ADH (relative to plasma osmolality), 10% to 20% of patients do not have measurable levels of the hormone in their serum, despite continued renal free water reabsorption.[18]

TABLE 6

Diagnostic criteria for the syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Essential criteria

True plasma hypo-osmolality (< 275 mOsm/kg H_2O)
Inappropriate urinary response to hypo-osmolality (urine osmolality > 100 mOsm/kg H_2O)
Euvolemia; no edema, ascites, or signs of hypovolemia
Elevated urine sodium(> 30 mEq/L) during normal sodium and water intake
No other causes of euvolemic hyponatremia (hypothyroidism, diuretic use, hypocortisolism)

Supplemental criteria

Unable to excrete > 80% of a water load (20 cc/kg) in 4 hours and/or failure to achieve urine osmolality < 100 mOsm/kg H_2O
No significant increase in serum sodium after volume expansion, but improvement with fluid restriction

MODIFIED FROM VERBALIS JG. THE SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION AND OTHER HYPO-OSMOLAR DISORDERS. IN: SCHRIER RW, EDITOR. DISEASES OF THE KIDNEY AND URINARY TRACT, 7TH ED. PHILADELPHIA; LIPPINCOTT WILLIAMS & WILKINS, 2001: 2511–2548.

Diagnosis of SIADH

SIADH is a diagnosis of exclusion. As with other cases of hyponatremia, true plasma hypo-osmolality must be confirmed. There must also be failure to excrete a maximally dilute urine and documentation of euvolemia. As discussed previously, the latter can sometimes prove difficult. In these cases we recommend measuring serum uric acid and BUN and testing the response to isotonic saline to rule out hypovolemia. The diagnostic criteria for SIADH are listed in TABLE 6.[18]

During the course of chronic hyponatremia due to SIADH, a steady state is achieved in which urinary sodium excretion typically matches dietary sodium intake, resulting in a urine sodium of around 40 mEq/L.[5] In this case, the persistence of hyponatremia depends on continued water intake, as patients will often become normonatremic on proper water restriction.

However, if a patient with SIADH becomes hypovolemic, urine sodium may fall to levels below 20 mEq/L, confusing the clinical picture. Furthermore, in patients with euvolemia and SIADH, serum uric acid levels and BUN are commonly reduced.

Other causes of euvolemic hyponatremia

Patients with **psychogenic polydipsia** ingest massive amounts of water (typically 20–30 L/day) and overcome the renal capacity for free water excretion. They have true plasma hypo-osmolality, but most importantly, they also make an appropriately dilute urine (< 100 mOsm/kg H_2O). They can appear euvolemic or volume-expanded, depending on solute intake and other comorbidities.

Beer-drinker's potomania refers to the development of hyponatremia from water intake (in this case in the form of beer) that is disproportionate to a severely reduced dietary sodium intake.[19] At reduced levels of solute intake, there is a decrease in the ability of the nephron to excrete free water. As most adults ingest approximately 1,000 mOsm of solute per day and can dilute their urine to 50 mOsm/kg H_2O, the kidney can excrete around 20 L (1,000/50) of free water per day.

If dietary solute intake is severely reduced to 300 mOsm/day and the resulting maximum capacity for renal dilution is 50 mOsm/kg H_2O, any water intake from beer over 6 L will result in free water retention and hyponatremia.

Hypothyroidism can also impair free water excretion. Although the mechanisms are not fully understood, giving thyroid hormone can correct the low plasma sodium concentration.[20]

Pure glucocorticoid deficiency due to adrenocorticotropic hormone deficiency or anterior hypopituitarism can cause hyponatremia in the presence of preserved mineralocorticoid function. These patients are usually euvolemic. Cortisol replacement suppresses ADH release from the hypothalamus and promotes free water release at the level of the kidney.[21]

SIADH is a diagnosis of exclusion

REFERENCES

1. **Gill G, Leese G.** Hyponatremia: biochemical and clinical perspectives. Postgrad Med J 1998; 74:516–523.
2. **Lee WH, Packer M.** Prognostic importance of serum sodium concentration and its modification by converting-enzyme inhibition in patients with severe chronic heart failure. Circulation 1986; 73: 257–267.
3. **Gines P, Arroyo V, Rodes J.** Complications of cirrhosis: ascites, hyponatremia, hepatorenal syndrome, and spontaneous bacterial peritonitis. In: Bacon BR, Di Bisceglie AM, editors. Liver Disease: Diagnosis and Management, 1st ed. Philadelphia; Churchill Livingstone, 2000:238–250.
4. **Berl T, Schrier RW.** Disorders of water metabolism. In: Schrier RW, editor. Renal and Electrolyte Disorders, 6th ed. Philadelphia; Lippincott Williams & Wilkins, 2003:1–63.
5. **Rose BD, Post TW.** Clinical Physiology of Acid-Base and Electrolyte Disorders, 5th ed. New York; McGraw-Hill, 2001:696–745.
6. **Schrier RW.** Body fluid volume regulation in health and disease: a unifying hypothesis. Ann Intern Med 1990; 113:155–159.
7. **Hillier TA, Abbott RD, Barrett EJ.** Hyponatremia: evaluating the correction factor for hyperglycemia. Am J Med 1999; 106:399–403.
8. **Agarwal R, Emmett M.** The post-transurethral resection of prostate syndrome: therapeutic proposals. Am J Kidney Dis 1994; 24:108–111.
9. **Oster JR, Singer I.** Hyponatremia, hyposmolality, and hypotonicity: tables and fables. Arch Intern Med 1999; 159:333–336.
10. **James TJ.** Ion-selective electrodes. Postgrad Med J 1999; 75:254.
11. **Chung HM, Kluge R, Schrier RW, Anderson RJ.** Clinical assessment of extracellular fluid volume in hyponatremia. Am J Med 1987; 83:905–908.
12. **Dorhout Mees EJ, Geers AB, Koomans HA.** Blood volume and sodium retention in the nephrotic syndrome: a controversial pathophysiological concept. Nephron 1984; 36:201–211.
13. **Sonnenblick M, Friedlander Y, Rosin AJ.** Diuretic-induced severe hyponatremia. Review and analysis of 129 reported patients. Chest 1993; 103:601–606.
14. **Uribarri J, Oh MS, Carroll HJ.** Salt-losing nephropathy. Clinical presentation and mechanisms. Am J Nephrol 1983; 3:193–198.
15. **Milionis HJ, Liamis GL, Elisaf MS.** The hyponatremic patient: a systematic approach to laboratory diagnosis. CMAJ 2002; 166:1056–1062.
16. **Maesaka JK.** An expanded view of SIADH, hyponatremia and hypouricemia. Clin Nephrol 1996; 46:79–83.
17. **Verbalis JG.** The syndrome of inappropriate antidiuretic hormone secretion and other hypo-osmolar disorders. In: Schrier RW, editor. Diseases of the Kidney and Urinary Tract, 7th ed. Philadelphia; Lippincott Williams & Wilkins, 2001: 2511–2548.
18. **Zerbe R, Stropes L, Robertson G.** Vasopressin function in the syndrome of inappropriate antidiuresis. Annu Rev Med 1980; 31:315–327.
19. **Thaler SM, Teitelbaum I, Berl T.** "Beer potomania" in non-beer drinkers: effect of low dietary solute intake. Am J Kidney Dis 1998; 31:1028–1031.
20. **Hanna FW, Scanlon MF.** Hyponatremia, hypothyroidism, and role of arginine-vasopressin. Lancet 1997; 350:755–756.
21. **Linas SL, Berl T, Robertson GL, Aisenbrey GA, Schrier RW, Anderson RJ.** Role of vasopressin in the impaired water excretion of glucocorticoid deficiency. Kidney Int 1980; 18:58–67.

ADDRESS: *Phillip M. Hall, MD, Department of Nephrology and Hypertension, The Cleveland Clinic Foundation, A51, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail hallp@ccf.org.*