Normal and Abnormal Water Balance: Hyponatremia and Hypernatremia*

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ABSTRACT: This article discusses normal and abnormal water balance in small animals. The terms and concepts central to understanding the maintenance of normal salt and water balance and the manifestations of dysregulation are presented, the physiology of body fluid balance is reviewed, and the concepts of sodium content and sodium concentration are explored. The emphasis of this review is that abnormalities of serum sodium concentration are, in fact, abnormalities of water balance. Thus, hyponatremia reflects too much water relative to sodium in the extracellular fluid, whereas hypernatremia reflects a relative deficit of water.

Several important terms relating to water balance are defined in the box on page 590.

TERMS AND CONCEPTS

Body Fluid Balance

Balance refers to the ratio of the amount of a substance assimilated into the body to the amount that is lost from the body. When this ratio approximates 1:1 (unity), the body is in balance for that substance. Under normal steady-state conditions, on a day-to-day basis, the volume of total body fluid stays the same; this body fluid balance is achieved when fluid intake and losses are equivalent. Total body water comprises two main compartments: intracellular water and extracellular water. The extracellular fluid (ECF) compartment is further divided into interstitial water and plasma water. The relative distribution of body water for a typical dog is shown in Figure 1; however, the percentage of total body water in an individual animal is affected by body fat content.

Salt balance refers to the maintenance of optimal body fluid volume, as shown in Figure 2. It depends primarily on the sodium ion (Na⁺) content of the ECF because Na⁺ is the principal extracellular cation. Although the total solute concentrations in the extracellular and intracellular compartments are equivalent, their compositions differ; within cells, potassium and magnesium ions are the principal cations.
replacing Na\(^+\). These differences in solute composition between intracellular and extracellular space are maintained by active ion transport.\(^2\)

Because Na\(^+\) is the principal extracellular cation, and because the osmolality of body fluids is regulated within a very narrow range,\(^2\) the Na\(^+\) content of the body determines the volume of ECF and total body fluid volume. If sodium ions (always with accompanying anions) are added to the ECF space, the same proportion of water molecules must be added to the ECF space or the osmolality will increase beyond the limits compatible with body function. If an appropriate number of Na\(^+\) are added to the extracellular fluid space, the same proportion of water must be added to the extracellular space or the osmolality will increase beyond the limits compatible with body function.

**Glossary of Important Terms**

**Content**—The total amount of a substance in a given space. The content of a substance such as Na\(^+\) only changes when molecules of that substance are gained or lost from a body space, such as the extracellular fluid space. This term is used in contrast to concentration, which reflects the content of a substance contained within a certain volume of water, typically plasma or urine. Concentrations of electrolytes (e.g., Na\(^+\)) are measured by laboratory investigations. The content of a substance is calculated by multiplying the concentration of the substance by the volume of the fluid space.

**Osmolality**—The concentration of an osmotic solution, especially when measured in osmoles or milliosmoles per 1,000 g of solvent (usually water). Osmolality is a similar term and is often used interchangeably with osmolality when the solvent is water. However, osmolarity refers to the measurement in osmoles or milliosmoles of solute per liter of water—a measurement of osmoles per volume rather than per weight of solvent.

**Osmosis**—The movement of water through a semipermeable membrane (such as a cell membrane) into a solution of higher solute concentration that tends to equalize the concentrations of solute on the two sides of the membrane. Solutions that cause water to move by osmosis are termed osmotic solutions.

**Tonicity**—The osmotic pressure of a solution. The tonicity of a solution (e.g., an intravenous fluid solution, plasma, urine) is only relevant in reference to another physiologic system. For example, intravenous fluids are hypertonic, isotonic, or hypotonic relative to plasma. A patient’s plasma is hypertonic, isotonic, or hypotonic relative to normal plasma. A patient’s urine is hypertonic (hypersthenuria), isotonic (isosthenuria), or hypotonic (hyposthenuria) relative to the patient’s plasma.
with a healthy state. Thus, increasing the number of sodium ions in the ECF (the Na⁺ content) increases the ECF volume. Similarly, if sodium ions are removed from the ECF space, water molecules must leave in proportion, thereby reducing the ECF volume; otherwise, the osmolality of the ECF would decrease below the level allowed in a healthy individual.

The dog shown in Figure 3 has increased total body fluid and ECF volumes due to increased Na⁺ content. Increased Na⁺ content can be the result of increased dietary salt intake or increased renal Na⁺ retention. Conversely, the dog shown in Figure 4 has decreased total body fluid and ECF volumes due to decreased Na⁺ content. This solute deficit can result from gastrointestinal or urinary losses.

**Water balance** (Figure 5) defines the maintenance of optimal body fluid tonicity. Tonicity refers to the osmotic pressure of a solution—its ability to cause water to move across a membrane. Body fluid tonicity is tightly regulated because it determines the volume of the body's cells, which in turn affects cell function. Although ECF and intracellular fluid have very different compositions, they must maintain the same solute concentrations (the same tonicity) so that water can move freely across most cell membranes. Looking at this concept “in reverse,” the water concentrations of the ECF and the intracellular fluid must remain the same. Inequalities of water concentration between body fluid compartments exist only transiently because water immediately and rapidly moves...
Osmolality of body fluids. Glucose and urea make minor contributions, as reflected in the following equation:

\[
\text{Plasma osmolality} = 2(Na^+ \text{ concentration [mEq/L]}) + \left(\frac{\text{glucose concentration [mg/dl]}}{18}\right) + \left(\frac{\text{BUN concentration [mg/dl]}}{2.8}\right)
\]

Osmolality is usually measured by freezing point depression, and the measured value is often higher than the calculated value because equations such as the one presented above do not include all osmotically active particles present in the plasma.

The difference between the measured and the calculated values is termed the osmolal gap. In the clinical setting, the term osmolar gap is often used (see the box on page 590 for an explanation of the difference between osmolality and osmolarity). This value should be no higher than 10 mOsm/kg in normal dogs.

Two situations are associated with a significantly elevated osmolal gap: (1) the presence of exogenous solutes (e.g., metabolites of ethylene glycol) in the plasma and (2) a reduced fraction of plasma water resulting from high plasma triglycerides or proteins (e.g., myeloma proteins).

Plasma \(Na^+\) concentration accurately reflects plasma tonicity in normal patients. As stated previously, tonicity is the ability of a solution to move water across a membrane. This movement affects cellular volume. Hyperosmolality results when impermeant solutes are added to the ECF; this promotes cellular dehydration. Hypotonicity results from a decrease in the concentration of impermeant solutes in the ECF and promotes water movement into cells and cell swelling. Hyperosmotic solutions are always hyperosmolar. The reverse is not always true: hyperosmolar solutions are not necessarily hypertonic because ineffective osmoles contribute to osmolality but not tonicity.

As a clinical example, the addition of glucose to a saline solution with the same \(Na^+\) concentration as plasma results in a hyperosmolar solution. However, the solution is not hypertonic when infused into a nondiabetic patient because glucose moves freely into the cells in the presence of insulin. In a diabetic patient, due to the lack of insulin, glucose is not rapidly taken up by the cells. In this case, the glucose molecules are effective osmoles, rendering the solution hypertonic: water

\[\text{Plasma osmolality} = 2(Na^+ \text{ concentration [mEq/L]}) + \left(\frac{\text{glucose concentration [mg/dl]}}{18}\right) + \left(\frac{\text{BUN concentration [mg/dl]}}{2.8}\right)\]

Osmolality Versus Tonicity

The concentration of solutes in a solvent defines a solution’s osmolality. Because cell membranes are permeable to water, and because water will move across a membrane until the solutions on either side of the membrane are isosmolar, the osmolality of plasma reflects the osmolality of total body fluid. When considering how osmolality affects tonicity, it is important to distinguish between permeant and impermeant solutes. Permeant solutes (e.g., urea) move freely across cell membranes and thus do not induce net water movement when they are introduced into a solution; they are termed ineffective osmoles. Impermeant solutes (e.g., \(Na^+\)) do not freely move across cell membranes. Thus, they do induce water movement when introduced into a solution and are termed effective osmoles.

Plasma \(Na^+\) concentration is the key determinant of the osmolality of body fluids. Glucose and urea make minor contributions, as reflected in the following equation:

\[\text{Plasma osmolality} = 2(Na^+ \text{ concentration [mEq/L]}) + \left(\frac{\text{glucose concentration [mg/dl]}}{18}\right) + \left(\frac{\text{BUN concentration [mg/dl]}}{2.8}\right)\]

This equation is a simplification because it does not account for the fact that plasma is only 93% water; that sodium salts are incompletely dissociated in solution; that some anions are polyvalent; or that calcium, magnesium, and potassium salts also contribute. However, these factors cancel out numerically, allowing \(2 \times Na^+\) concentration to be used as an estimate of the osmotic effect of the plasma ions.

Figure 6. The hypertonic hyponatremia that occurs in unregulated diabetes mellitus is an example of translocation hyponatremia. The baseline influence of intracellular and extracellular osmoles on water movement remains (thick red arrows), but the presence of an additional impermeant solute (▲) in the ECF drives water translocation from the intracellular to extracellular space (thin red arrows) to maintain an equal concentration of water across the cell membrane. Thus the proportion of water molecules relative to \(Na^+\) in the ECF is increased, resulting in hyponatremia (illustrated by a 2:1 ratio of water to \(Na^+\)). The dog has a decreased intracellular fluid volume (shrunken cell and brain) and a correspondingly increased ECF volume. Because fluid has moved between compartments, the dog’s body weight is unchanged.
moves out of the cells into the ECF, the ECF Na\(^+\) concentration declines, and so-called hypertonic hyponatremia is observed (Figure 6). When hyperglycemia develops slowly, idiogenic osmoles are generated within the cells; this helps to increase intracellular water content and mitigate the decrease in cell volume.

### Osmoregulation

The term osmoregulation refers to the control of body fluid tonicity. Because cell membranes are permeable to water, cells are in osmotic equilibrium with the fluid that surrounds them. Therefore, by stabilizing body fluid tonicity, osmoregulation controls cell volume. Hypothalamic cells called osmoreceptors sense changes in their own volume in response to an osmotic gradient between themselves and plasma.

### Content Versus Concentration

Separate mechanisms regulate Na\(^+\) content and Na\(^+\) concentration (Table 1). The Na\(^+\) content of the body is regulated by mechanisms that control the renal excretion of Na\(^+\), which can vary more than 500-fold, depending on Na\(^+\) intake and physiologic need. These mechanisms operate in response to body fluid volume, not plasma Na\(^+\) concentration. The kidneys have evolved mechanisms to conserve salt; however, the homeostatic mechanisms that control Na\(^+\) content are poorly understood. Although species differences may exist, many animals have evolved a salt appetite to increase Na\(^+\) intake in salt-deficient states.

Regulation of Na\(^+\) content is generally a slow process compared with regulation of Na\(^+\) concentration. While excess water intake stimulates the osmoregulatory mechanisms and is dealt with very rapidly, many hours pass before excessive sodium intake (e.g., infusion of isotonic saline) is corrected by increased renal Na\(^+\) excretion. When dietary Na\(^+\) intake is increased, it takes several days to reach a new steady state of neutral Na\(^+\) balance.

Na\(^+\) excretion is influenced by several regulatory factors, and mechanisms for Na\(^+\) retention are generally better developed than are those for Na\(^+\) excretion. It can be extremely difficult to sort out the roles of the many sensors and mediators involved (Table 1) and understand the relative importance of the various regulatory systems.

In contrast, plasma Na\(^+\) concentration is regulated by osmoregulatory control mechanisms. Changes in plasma osmolality (pOsm) sensed by the hypothalamic osmoregulatory cells alter the secretion of vasopressin (antidiuretic hormone [ADH]). ADH is the primary regulator of renal water excretion. Its primary function is to increase the water permeability of the luminal membrane of the renal collecting duct through the insertion of water channels called aquaporins. Water is reabsorbed through these channels in the collecting ducts along the concentration gradient established in the renal medullary interstitium.

#### Table 1. Mechanisms That Sense and Regulate Na\(^+\) Content and Na\(^+\) Concentration*  

<table>
<thead>
<tr>
<th>Type of Regulation</th>
<th>Signal</th>
<th>Sensors</th>
<th>Effectors</th>
<th>Mechanism Effected</th>
<th>Regulation Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na(^+) concentration; osmoregulation (water balance)</td>
<td>Plasma osmolality</td>
<td>Hypothalamic osmoreceptor</td>
<td>• Vasopressin</td>
<td>• Urine osmolality (urine concentration)</td>
<td>• Rapid • Precise</td>
</tr>
<tr>
<td>Na(^+) content; volume regulation (salt balance)</td>
<td>Effective plasma volume&lt;sup&gt;b&lt;/sup&gt;</td>
<td>• Carotid sinus</td>
<td>• Renin–angiotensin–aldosterone system</td>
<td>Urine Na(^+) excretion</td>
<td>• Slow • Dominant in deficiency</td>
</tr>
</tbody>
</table>

<sup>a</sup>Adapted from Rose BD: Clinical Physiology of Acid-Base and Electrolyte Disorders, ed 3. New York, Raven, 1992, pp 2837–2872.

<sup>b</sup>Effective plasma volume is a phrase used to describe salt-retaining states. It is not a measurable quantity, and the concept lacks a precise definition. It refers to the fullness of the vascular volume and is the portion of the vascular volume that is being sensed by the mechanisms that regulate body fluid volume. An inadequate effective circulating volume is inferred when salt-retaining mechanisms are activated.
strongly affect the thirst mechanism. This is why patients that are deficient in ADH (those with central diabetes insipidus) cannot conserve water through renal mechanisms but can maintain a normal pOsm if they have access to water.

Hypotension and hypovolemia also stimulate ADH release. ADH release is not as sensitive to hemodynamic stimuli as it is to changes in pOsm; however, when the hemodynamic stimulus is sufficiently strong, the ADH response will be of greater magnitude, and volume will be preserved at the expense of decreased osmolality.

The kidneys have a primary role in water balance through their concentrating and diluting functions. The details of these complex hormonally regulated processes are beyond the scope of this article but are summarized here and in Figure 7. The osmolality of the glomerular filtrate as it enters the proximal tubule is identical to that of plasma. In this segment of the tubule, the bulk of the urinary solutes (e.g., Na⁺ and other electrolytes, amino acids, glucose) and water is reabsorbed isosmotically. As the filtrate traverses the descending limb of the loop of Henle, water diffuses from the tubule lumen to the hypertonic medullary interstitium. The tubular fluid then becomes progressively more dilute as it travels through the ascending limb of the loop of Henle. This diluting process occurs because active Na⁺ reabsorption is unaccompanied by water in this segment. The fluid is hypoosmotic to plasma on its arrival in the distal tubule. ADH stimulates reabsorption of sodium chloride in the ascending limb and thus facilitates generation of the renal medullary solute gradient necessary for urinary concentration.

Hormonal action on the collecting ducts determines the final concentration of urine produced. In a state of antidiuresis, ADH increases water permeability and augments aldosterone-stimulated Na⁺ reabsorption, thereby promoting water movement from the tubule lumen to the interstitium for reclamation. In a state of water diuresis, when ADH is not present, the collecting duct remains impermeable to water, and dilute urine is produced. Also, in the distal collecting duct, urea permeability is relatively high and is increased in the presence of ADH; thus, urea moves back into the renal medullary interstitium for maintenance of the medullary gradient.

The ability of the kidneys to maintain a normal water balance through creation of hypertonic or hypotonic urine can be disrupted in many ways (Table 2). Disorders that affect renal concentrating ability are discussed in more detail in the companion article on p. 612.

**CONCEPTS OF WATER BALANCE IN CLINICAL SITUATIONS**

**Dehydration**

Dehydration can have several different meanings, which may lead to confusion and therapeutic error. One definition is based on clinical findings when hydration tests such as skin turgor, mucous membrane moisture, pulse rate, and capillary refill time are conducted. Typically, when a clinician considers the issue of whether a patient is clinically dehydrated, he or she is referring to physical examination findings that assess interstitial and plasma fluid volume status. These findings reflect the patient’s low ECF volume and negative sodium balance.

However, another definition of dehydration is a decrease in intracellular water (i.e., dehydrated cells). This reflects a high plasma tonicity and a problem of negative water balance. Yet another definition is a decrease in...
total body water, which also reflects a negative sodium balance, provided the pOsm is normal. Therefore, rather than using the imprecise term dehydration, clinicians are better served by thinking about body fluid status in terms of the body's compartments and the overall sodium balance and water balance. Thus, patients with decreased skin turgor and membrane moisture or acute loss of body weight reflecting fluid loss are best described as having ECF volume depletion. Patients with a high pOsm (hypertonicity) and intracellular fluid losses are best described as having free water deficits. Some patients may have both. These distinctions determine therapeutic decisions: is the patient lacking Na\(^+\), water, or both?

**Plasma Sodium Ion Concentration**

Clinicians should become familiar not only with the published laboratory reference ranges for plasma Na\(^+\) concentration but also with the mean and variance in their own population of patients. The amount of deviation in the pOsm that ordinarily alters ADH and thirst in an individual animal is smaller than normal laboratory ranges (e.g., a 1% to 2% increase in osmolality is sufficient to induce thirst). In other words, laboratory

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**Table 2. Clinical Situations That Disrupt the Renal Mediation of Normal Water Balance**

<table>
<thead>
<tr>
<th>Prerequisites for Creation of Dilute Urine</th>
<th>Clinical Situation That Disrupts This Portion of the Mechanism</th>
<th>Prerequisites for Creation of Concentrated Urine</th>
<th>Clinical Situation That Disrupts This Portion of the Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>A sufficient number of nephrons to provide the glomerular filtration rate (GFR) necessary for the delivery of ultrafiltrate to the thick ascending loop of H nele, distal convoluted tubule, and collecting duct</td>
<td>Decreased functional renal mass, as in chronic renal failure</td>
<td>A sufficient number of nephrons to provide the GFR necessary for delivery of ultrafiltrate to the thick ascending loop of H nele, distal convoluted tubule, and collecting duct</td>
<td>Decreased functional renal mass, as in chronic renal failure</td>
</tr>
<tr>
<td>Sufficient delivery of sodium to the diluting segments of the nephron (thick ascending loop of H nele, distal convoluted tubule)</td>
<td>• Hypovolemia &lt;br&gt; • Very low solute diets</td>
<td>Sufficient delivery of sodium to the ascending loop of H nele and distal convoluted tubule and urea to the distal collecting duct for countercurrent multiplication</td>
<td>Low blood urea nitrogen concentration such as with an ultralow protein diet or hepatic failure</td>
</tr>
<tr>
<td>Optimal active transport of Na(^+) out of the ascending loop of H nele coupled with impermeability to water for generation of a maximal hypotonic fluid in the diluting segments of the nephron</td>
<td>• Osmotic diuresis &lt;br&gt; • Loop and thiazide diuretics</td>
<td>Generation and preservation of a maximal renal corticomedullary gradient</td>
<td>• Osmotic diuresis &lt;br&gt; • Water diuresis &lt;br&gt; • Loop diuretics</td>
</tr>
<tr>
<td>Maintenance of water impermeability in the collecting ducts determined by the absence of ADH (or other antidiuretic substances)</td>
<td>• Syndrome of inappropriate ADH secretion (SIADH) &lt;br&gt; • Desmopressin therapy</td>
<td>A collecting duct permeable to water through the action of ADH (or other antidiuretic substances) and functional vasopressin (V2) receptors, their second messengers and aquaporins</td>
<td>• Lack of ADH (central diabetes insipidus) &lt;br&gt; • Primary nephrogenic diabetes insipidus, including heritable abnormalities in V2 receptors or aquaporins &lt;br&gt; • Diuretics that interfere with second messengers of the V2 receptors, such as caffeine &lt;br&gt; • Hypercalcemia &lt;br&gt; • Obstructive and postobstructive diuresis</td>
</tr>
</tbody>
</table>

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\(b\) Free water is used as a contraction of the terms solute-free water or electrolyte-free water.
reference ranges are often wider than differences that are important for clinical decision making. For example, a patient may normally have a plasma Na⁺ concentration of 145 mEq/L. If water losses are ongoing and the plasma Na⁺ concentration begins to increase, ADH and thirst will be fully stimulated before the plasma Na⁺ concentration reaches 150 mEq/L, which may still be well within the laboratory's reported reference range. Such a change in plasma Na⁺ concentration for a patient that is receiving intravenous fluid therapy and unable to drink would warrant a change in the free water prescription. By the time the plasma Na⁺ concentration increases beyond the reference range, even by 1 mEq/L, it may be clinically significant and abnormal for that animal. Similarly, trends in plasma Na⁺ concentration can be very significant in patients being monitored over

**Clinical Questions and Answers**

**Question:** My patient's plasma Na⁺ concentration is only mildly outside the laboratory's reference range. I don't include such minor abnormalities in serum enzymes on the problem list. Why is this analyte different?

**Answer:** Any abnormalities in plasma Na⁺ concentration warrant clinical attention, even if the Na⁺ concentration is only 1 or 2 mEq/L outside the normal reference range. The body tightly regulates plasma Na⁺ concentration (as well as the plasma concentration of the other electrolytes), so any deviations in plasma Na⁺ concentration suggest a water balance disorder.

**Question:** Can I begin therapy for hyponatremia pending diagnostics?

**Answer:** Empirical treatment for hyponatremia depends primarily on the mechanism. Thus the patient's volume status must be assessed to determine appropriate fluid therapy.

**Question:** Why don't animals with central diabetes insipidus have hypernatremia?

**Answer:** ADH is not necessary to maintain a normal pOsm. Even patients with complete central diabetes insipidus can have a normal pOsm, provided they are able to drink. However, it is important to realize that their obligate urinary water losses are exceptionally high. Life-threatening hypernatremia can ensue in a matter of a few hours in these patients, which can lead to the clinical description of “water hunger” (extreme water-seeking behavior, even after short periods of deprivation) in these patients.
A prolonged period, such as cats receiving subcutaneous fluids for chronic renal failure. If such a cat were to have a plasma Na\(^+\) concentration of 150 to 152 mEq/L consistently for several months, followed by an upward trend of 153, 155, and 156 mEq/L over the next few months, the increase may be very significant for that cat, despite the value consistently remaining within the laboratory’s reported reference range for cats.

When clinicians are dealing with laboratory values in which minor changes can be clinically meaningful, the “noise” of day-to-day measuring variance can cloud interpretation. This makes it even more important for each clinician to become familiar with the assay from his or her specific laboratory. Generally speaking, any deviation of plasma Na\(^+\) concentration should be noted. When it is unexpected, the first course of action may be verification of repeatability. However, small deviations in plasma Na\(^+\) concentration should not be dismissed and omitted from the problem list because the osmoregulatory system controls the pOsm within such a narrow range in healthy animals.

**HYponatREMIA**

**Diagnostic Approach**

The plasma Na\(^+\) concentration does not measure the total Na\(^+\) content in the ECF and, therefore, does not reflect the volume of ECF or total body fluid. The plasma Na\(^+\) concentration merely reflects the amount of water relative to the Na\(^+\) content, which is determined by the osmoregulatory system. Thus hyponatremia is a disorder of water balance because the amount of water is increased relative to the amount of Na\(^+\) in the ECF. The Na\(^+\) content of the ECF (and, therefore, the body), and thus the total body fluid volume, can be normal, increased, or decreased in hyponatremia. Further localization of hyponatremia by mechanism is shown in Figure 8.

Hyponatremia is usually associated with hypoosmolality. Exceptions are so-called pseudohyponatremia and translocational hyponatremia secondary to exogenous...
osmoles, in which a large concentration of alternative osmoles is present (Figure 6).

Pseudohyponatremia results from an in vitro artifact observed when measuring serum Na\(^+\) concentration by flame photometry in the presence of elevated plasma lipids or proteins. In these situations, the measured Na\(^+\) concentration is lower than the true Na\(^+\) concentration. Although newer ion-selective electrodes have largely eliminated this problem in undiluted samples, the term persists as a way to distinguish this in vitro phenomenon from clinically significant hyponatremia.

Translocational hyponatremia may be divided into two categories: (1) conditions in which the measured and calculated serum osmolalities are the same (hyperglycemia); and (2) conditions in which there is an osmolar gap: some osmoles are clearly present and are measured but have not been identified. Unidentified osmoles may include mannitol, glycine, and alcohols such as ethanol and ethylene glycol. Only impermeant solutes (e.g., glucose in the absence of insulin, mannitol, glycine) will lead to water translocation from inside to outside cells and cause hyponatremia (Figure 6).

In diagnosing true hypoosmolar hyponatremia, two principal pathophysiologic mechanisms must be considered. The first is impaired renal excretion of free water, or impaired diluting ability. In this situation, the animal cannot excrete maximally dilute urine (urine osmolality [uOsm] <100 mOsm/L). Several disease states and conditions can be associated with impaired renal diluting capacity and free water excretion. Most common is hypovolemia, which can reflect either absolute volume depletion caused by gastrointestinal, transepidermal, or renal losses or high-volume edematous states associated with reduced effective plasma volume. When absolute or effective plasma volume is decreased, the ensuing reduced renal perfusion limits the quantity of glomerular filtrate reaching the diluting segment of the kidneys. In volume depletion, Na\(^+\) conservation in the proximal nephron is enhanced and less Na\(^+\) reaches the thick ascending limb of the loop of Henle. ADH may also be released in response to volume depletion, overriding the effect of the hypotonicity and compounding the defect in water excretion.

Impaired diluting ability is also a feature of advanced renal failure in which the ability to excrete water is approximately 20% of that of a normal, healthy kidney. It is a common misconception that renal azotemia is ruled out by the finding of hyposthenuria. In early and moderate renal failure, the kidneys retain some tubular function and, therefore, meaningful diluting capacity.

Urinary water excretion is also impaired when ADH remains elevated in the presence of plasma hypoosmolality, as in hypovolemia. Figure 9 shows hypovolemic hyponatremia.

The serum sodium concentration does not reflect the total amount of sodium in the extracellular fluid.
tion. SIADH, although well described in humans, is rarely reported in dogs or cats. In humans, SIADH may be associated with the following conditions: (1) ectopic production of ADH by certain neoplasms; (2) administration of exogenous ADH or oxytocin; (3) enhanced hypothalamic ADH secretion due to neuropsychiatric disorders, drugs, or pulmonary disease; or (4) drug-related potentiation of ADH effects.

Certain diuretics, such as loop diuretics and thiazides, impair renal water excretion because they decrease Na\(^+\) transport in the diluting segment of the nephron. Decreased renal diluting ability is also reported with highly reduced dietary solute intake. This is unlike other causes of decreased free water excretory capacity because the uOsm is less than 100 mOsm/L. In humans, this occurs with the practice of beer potomania—a syndrome in which individuals consume large quantities of beer (which is hypoosmolar) but an inadequate amount of food, leading to insufficient dietary solute and impaired ability to excrete free water. This would be a highly unexpected mechanism in dogs or cats.

The second principal mechanism for the development of hypoosmolar hyponatremia is when water intake exceeds maximal renal excretory capacity. This is a far less common cause of hyponatremia than is impaired renal water excretion. Normally, renal diluting capacity is adequate to keep pace even with ardent drinkers. Thus most primary polydipsias do not result in overt hyponatremia. In humans, hyponatremia may occur with polydipsia accompanying psychosis. Perhaps analogous in dogs is so-called psychogenic polydipsia, in which nervous or hyperactive dogs respond to the stress of confinement or boredom by drinking obsessively. Such dogs usually have hypostenuria and mild hyponatremia, although they may remain within a laboratory’s published range. Often, removing these patients from their routine, such as through overnight hospitalization with free access to water, will disrupt the unwanted behavior and demonstrate the polydipsia as primary by revealing a concentrated urine specific gravity when the abnormal drinking routine is interrupted.

Because the kidneys are ordinarily highly efficient in excreting water, patients with primary polydipsia are more likely to have overt hyponatremia when impaired renal water excretion is concurrently present. Thus it is clinically important to assess patients with primary polydipsia and hyponatremia for concurrent renal diluting defects such as SIADH or abnormally regulated ADH secretion.

**Clinical Approach**

For the clinician, distinguishing between the physical causes of hyponatremia relies heavily on a complete history and an analysis of the patient’s other problems. The first question that should come to mind when assessing any patient with hyponatremia is, “Why is there too much water?” Evaluation of a blood sample for lipemia and assessment of the plasma protein concentration can rapidly rule out pseudohyponatremia. Translocational hyponatremia is easily ruled out by assessment of the serum glucose concentration and the absence of a history of administration of an exogenous solute, such as mannitol. The clinician is then left to distinguish primary polydipsia exceeding renal excretory capacity from impaired diluting capacity (impaired water excretion), although the two may exist simultaneously. The history is often illuminating in cases of true psychogenic polydipsia, such as a “high-strung,” bored dog. Other primary polydipsias rarely cause overt hyponatremia in the presence of normal renal diluting capacity.

The patient should be carefully assessed for ECF volume depletion. Some animals can sustain a loss of 5% body weight from ECF volume depletion without detectable clinical signs. Because clinical estimates of body fluid deficits can be inaccurate, the patient history should be carefully scrutinized for clues to suggest gastrointestinal or urinary fluid loss.

For more difficult cases, key laboratory evaluations include pOsm, uOsm, and urine Na\(^+\) concentration. uOsm can be used to help distinguish impaired water excretion from polydipsia. Hyponatremic animals with a uOsm greater than 100 mOsm/L have impaired water excretion.
A decreased pOsm with a uOsm less than 100 mOsm/L suggests primary polydipsia (when polyuria is present) or low solute intake (in which case, a recognizable increase in urine volume may be notably absent). Decreased solute intake is rare in the veterinary setting; therefore, a low uOsm typically suggests primary polydipsia.

A low urinary Na\(^+\) concentration (<20 mEq/L in human patients) suggests hypovolemia as the cause of hyponatremia. Veterinary patients with SIADH, diuretic-induced hyponatremia, mineralocorticoid deficiency, or renal failure should have a urine Na\(^+\) concentration greater than 20 mEq/L.\(^{11}\)

The clinical signs of hyponatremia arise from the effects on the central nervous system. Reduction of the plasma Na\(^+\) concentration drives water from the ECF into cells. Clinical signs—lethargy, confusion, nausea, vomiting, seizures, and coma—result from cerebral edema. The development of signs depends on the magnitude of hyponatremia and the rate at which it developed; the signs of chronic hyponatremia are generally more subtle and nonspecific than those of acute hyponatremia.\(^{13}\)

Although severe hyponatremia can lead to neurologic signs, too rapid a rate of correction of this disorder can also lead to brain disease, termed myelinolysis. Clinical signs may include weakness, obtundation, ataxia, paresis, and coma, and death may result. Myelinolysis has been well documented in humans, dogs, rats, and rabbits as a result of rapid correction of chronic (>48 hr duration) hyponatremia.\(^{21-23}\) Some canine patients have survived the development of myelinolysis with supportive care.\(^{22-24}\) The pathogenesis of myelinolysis is complex and incompletely understood, but it appears that the lower the rate of correction of chronic hyponatremia, the lower the risk of myelinolysis. It has, therefore, been recommended that chronic hyponatremia should be corrected as slowly as possible, with an upper rate limit of no more than 10 mEq/L during any 24-hour period.\(^{21}\)

**Treatment**

Regardless of the cause of hyponatremia, moderation in therapy is key. The serum Na\(^+\) concentration should be measured frequently and therapy adjusted to ensure that chronic hyponatremia is not corrected by more than 10 mEq/L/day.\(^4\) Although there are no rules for how frequently to monitor (and frequency may decrease as severely affected patients improve), we recommend using a central venous catheter to allow monitoring as often as every 3 to 4 hours initially.
Patients with hypovolemia (negative sodium balance) require restoration of the ECF Na\(^+\) content; this will return control of ADH secretion and thirst to osmotic factors, and the kidneys will excrete the excess free water once the diluting defect resulting from the hypovolemia is corrected. Thus patients with hypovolemia can initially be treated safely with isotonic (or very mildly hypertonic for that patient) fluid replacement. In a hyponatremic patient, a fluid that is truly isotonic would, in fact, be of lower osmolality than a fluid that is isotonic for a normal patient. Thus typical balanced electrolyte solutions used in hyponatremic patients are actually mildly hypertonic for those individuals. Fluids that are hypotonic to the patient should always be avoided, as should hypertonic saline, unless death from hypovolemic shock is imminent. However, even if isotonic fluids are used, as indicated above, solute-free water will be excreted once hypovolemia is corrected, and this alone could lead to rapid correction of hyponatremia; thus, serial monitoring of serum Na\(^+\) concentration is essential in these patients. It is also important to remember that hypovolemia is a result of fluid losses exceeding intake, so a provision must be made in the fluid therapy prescription to meet these ongoing losses, in addition to restoring deficits, until the underlying disease (e.g., Addison’s disease, primary gastrointestinal disease) can be resolved with appropriate specific therapy.

Patients with translocational hyponatremia may have different fluid needs, depending on the osmole involved. The most common clinical scenario is unregulated diabetes mellitus, in which hypovolemia is often present and needs to be corrected. Subsequent initiation of insulin therapy lowers plasma glucose levels and returns the excess ECF water to its intracellular location.

Patients with edema or ascites have excess ECF Na\(^+\) and an even greater excess of ECF water. Therapy is more challenging because these patients have a decreased effective plasma volume and renal mechanisms for retention of Na\(^+\) are stimulated. Correction of hyponatremia generally requires restriction of water intake to below the level of urine output. This can be very difficult because thirst is stimulated. Therapy for the primary underlying disorder is required; therefore, therapy before diagnostics is generally not indicated.

Patients with hyponatremia secondary to water intoxication are rare in veterinary medicine; however, these patients may have clinical signs related to hypotonicity. Treatment generally consists of water restriction and careful monitoring.

HYPERNATREMIA

Hyponatremia is also a disorder of water balance. It reflects a state of too little water relative to Na\(^+\) content in the ECF. The Na\(^+\) content of the body can be normal, increased, or decreased. Similar to hyponatremia, in patients with hypernatremia, the plasma Na\(^+\) concentration does not provide a measurement of an animal’s volume status. The first question a clinician should ask after detecting hypernatremia is, “Why is there too little water?”

Many cases of hypernatremia develop while patients are hospitalized, and the diagnosis involves analysis of the patient’s fluid intake and losses. The presence or absence of hypovolemia helps to distinguish pure water losses from hypotonic fluid losses. uOsm can help to distinguish the cause of hypernatremia. In patients with extrarenal hypotonic losses, such as those with severe diarrhea, the renal salt-conserving mechanisms should be maximally stimulated to preserve ECF volume. The urine of these patients has a low Na\(^+\) concentration and a low water content due to high ADH, but the uOsm is high because other solutes are present. Patients with a very low uOsm (<150 mmol/L) in a setting of hypertonicity and polyuria have diabetes insipidus, which may be central or nephrogenic.

Diagnostic Approach

Impaired water intake leading to a water deficit, as shown in Figure 10, is one cause of hypernatremia. In dogs, pOsm increases of as little as 1% stimulate thirst. These deviations are normally rapidly corrected by water ingestion; thus, sustained hypertonicity implies a defect in thirst sensation, restricted access to water, or a physical inability to drink.

Primary hypodipsia is a condition of diminished or absent thirst that results in hypernatremia. Thirst is the ultimate defense against hypernatremia. If an animal does not drink, hypernatremia will develop due to normal insensible water losses. Hypodipsia is usually associated with identifiable hypothalamic disease. If ADH production is intact, renal water conservation will miti-
gate the hypernatremia, provided the defect in the thirst mechanism is not severe.

Essential hypernatremia is a similar condition in which the osmostat in the hypothalamus is reset and a greater degree of hypertonicity is required to trigger the thirst and ADH responses. A number of case reports have proposed this syndrome in a cat and several dogs; miniature schnauzers appear to be overrepresented in some case series.

Salt toxicity resulting from ingestion of salt or administration of hypertonic fluids is rare in veterinary medicine. Nonetheless, it is an issue of too little water relative to salt, as opposed to a problem of too much salt. These patients typically do not have significant clinical signs related to extracellular volume overload unless cardiac disease is present, leading to intolerance of an acutely expanded ECF volume. Hypernatremia associated with salt ingestion should be mild and transient, provided water intake is not impaired. In cases of salt poisoning, or when hypertonic saline is given without free water, neurologic signs consequent to rapid decreases in brain cell volume include lethargy, irritability, weakness, behavior changes, hyperreflexia, disorientation, ataxia, seizures, and coma. These signs result from water translocation to the hypertonic ECF and the associated rupture of cerebral vessels and may be sufficiently severe and rapid in onset to impair the thirst response that would ordinarily protect the animal.

Inadequate free water intake in the presence of excess water loss (Figures 11 and 12) accounts for most cases of hypernatremia. In humans, geriatric patients are particularly at risk due to decreased thirst. The same risk may apply to geriatric animals and would be increased in the presence of declining renal concentrating ability. Water intake is often impaired in very sick, hospitalized patients due to debility, sedation, or other problems that impair the ability to drink. Long-term use of intravenous or subcutaneous fluids that are isotonic and do not provide sufficient free water will also lead to hypernatremia in patients that do not drink. This is particularly true if renal water-conserving mechanisms are impaired.

Therapy
For all patients, ECF volume deficits must be replaced.
The fluid therapy plan for hypernatremic patients must include a provision for maintenance and replacement of ongoing losses in addition to restoration of the free water deficit. Patients with mild hypernatremia that have been restricted from water and are normal neurologically will correct their own deficits when water is provided, and they do not require fluid therapy support. Therapeutic correction of more severe hypernatremia when the patient is sick requires replacement of the calculated water deficit with fluid therapy. Data from the patient history about the time course over which the hypernatremia likely developed are particularly important.

The volume of the deficit can be estimated using the following equation⁴⁴:

\[
\text{Free water deficit} = 0.6 \times \text{body weight (kg)} \times \left(\frac{\text{plasma Na}^+ + 148}{148} - 1\right)
\]

Water can be replaced either enterally (orally or by gastric tube) or intravenously with hypotonic saline or 5% dextrose in water.

Hypernatremia that is known to have developed acutely (over no more than 24 to 36 hr⁴⁴) can be corrected relatively rapidly. This may be observed in patients with acute water deprivation, especially in hot environments where respiratory water losses for thermoregulation are very high. Therapy requires rapid correction of both the free water and the ECF Na⁺ content deficits. This acute time course is also likely in rare cases when hypernatremia results from solute administration (e.g., hypertonic fluid administration). These patients require both water administration and solute removal (with loop diuretics).

In contrast, patients with more chronic hypernatremia adapt by increasing intracellular solutes in the brain to protect against the adverse effects of intracellular dehydration. The initial response of the brain to hypernatremia is to accumulate intracellular electrolytes, but this can impair brain function. So, with time, the brain accumulates organic solutes (idiogenic osmoles) such as amino acids, trimethylamines, and myoinositol.⁴⁵,⁵,35 Although these adaptations diminish the effects of the ECF hypertonicity, they put the patient at risk for cere-

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**Figure 12.** Increased free water losses may result from pure water loss or hypotonic fluid loss.
bral edema if the hypernatremia is corrected too quickly. When these brain adaptations have taken place, hypernatremia must be corrected more slowly. No ideal, universally safe rate of correction has been established for dogs and cats in which neurologic signs of hypernatremia are present; however, based on recommendations in human medicine, a rate of no more than 0.5 to 1 mEq/L/hr can serve as a guideline until the signs resolve. In human medicine, a rate of correction of no more than 0.5 mEq/L/hr has been recommended. Once neurologic signs have resolved, the rate can be adjusted to provide the remainder of the correction over the next 48 hours. Deterioration of the neurologic status with correction of hypernatremia suggests cerebral edema and too rapid a rate of correction. When the time course over which hypernatremia developed is unknown, clinicians should err on the side of slow, steady correction.

REFERENCES

**ARTICLE #1 CE TEST**

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1. **Effective osmoles**
   a. move freely across cellular membranes and thus do not induce net water movement across cell membranes.
   b. affect a solution’s tonicity.
   c. include urea and ethanol.
   d. are subtracted from ineffective osmoles to determine the osmolar gap.

2. **A patient with increased plasma Na⁺ content has**
   a. hypervolemic hypernatremia.
   b. hypovolemic hypernatremia.
   c. hypovolemia.
   d. hypervolemia.

3. **A patient with hypernatremia has**
   a. a salt balance disorder.
   b. a water balance disorder.
   c. too high a plasma Na⁺ content.
   d. expanded intracellular volume.

4. **Patients with congestive heart failure, edema, and hypernatremia have**
   a. impaired renal diluting capacity due to hypovolemia.
   b. impaired renal diluting capacity due to decreased effective plasma volume.
   c. renal salt wasting.
   d. primary polydipsia.

5. **Which of the following values indicates only primary polydipsia?**
   a. uOsm = 50 mOsm/L  
   b. uOsm = 310 mOsm/L  
   c. pOsm = 330 mOsm/L  
   d. pOsm = 360 mOsm/L

6. **A 5% dextrose solution given intravenously to a nondiabetic patient with a normal plasma Na⁺ concentration is**
   a. hypoosmolar but hypertonic.
   b. hypertonic and hyperosmolar.
   c. used for provision of free water.
   d. used to expand the ECF volume.

7. **A patient presenting with hypernatremia within 2 hours of ingesting a rock salt driveway deicer should have its hypernatremia corrected**
   a. as rapidly as possible by provision of intravenous and/or enteral free water.
   b. over 24 to 48 hours by provision of enteral free water.
   c. over 24 to 48 hours by provision of intravenous free water.
   d. as rapidly as possible for the first 35% of the calculated free water deficit and then over 24 to 48 hours.

8. **The osmolality of the ultrafiltrate as it enters the renal proximal tubule is**
   a. the same as that of plasma.
   b. much higher than that of plasma.
   c. much lower than that of plasma.
   d. unpredictable.

9. **Which of the following does not impair renal diluting ability?**
   a. thiazide diuretics
   b. central diabetes insipidus
   c. markedly reduced dietary solute intake
   d. Addison’s disease

10. **Myelinolysis**
    a. is caused by translocational hyponatremia.
    b. is the delayed effect of incomplete correction of chronic hypernatremia.
    c. can result from rapid correction of chronic hyponatremia.
    d. is rare, provided glucocorticoids are given before any correction of the plasma Na⁺ concentration.