I RENAL FUNCTION AND DISORDERS OF WATER AND SODIUM BALANCE

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Overview of Body Fluid Homeostasis

Life takes place in an aqueous solution. Cells, the blood bringing nutrients and oxygen to them, and the interstitial fluid bathing them are all mostly water. Each day, water and salt are lost and replaced. To maintain stability of the internal milieu, body fluids are processed by the kidney, guided by intricate physiologic control systems that regulate fluid volume and composition.

Distribution and Composition of Body Water

Water accounts for approximately half of an adult human’s body weight. Because fat contains little water, individuals with more body fat have less body water. On average, total body water constitutes 60% of lean body weight in young men, 50% in young women and older men, and 45% in older women. Two thirds of body water is intracellular, and the remainder is contained in the extracellular fluid compartment, which includes intravascular (plasma) and interstitial fluid. Small amounts of water are also contained in bone, dense connective tissue, digestive secretions, and cerebrospinal fluid.

Extracellular solutes are predominantly sodium salts (primarily a mixture of NaCl and NaHCO3). Thus, extracellular fluid can be thought of as saltwater. Except for protein (present at a higher concentration in plasma [approximately 1 mmol/L] than in interstitial fluid), the compositions of the intravascular and interstitial subdivisions of the extracellular fluid compartment are similar.

The sodium-potassium adenosine triphosphatase (Na+,K+-ATPase) pump on cell membranes keeps intracellular sodium at low levels. Potassium, the dominant intracellular cation, is electrically balanced, in large part, by anionic charges on impermeant macromolecules. Stability in the number of intracellular anionic charges makes the total solute content of cells much less variable than that of the extracellular fluid.

Osmolality

Extracellular and intracellular fluids contain different types of solutes, but the concentrations of solutes inside and outside of cells are equal. Concentration differences exist only transiently because they create an extremely strong force for water movement across cell membranes. Osmotic pressure moves water rapidly to the fluid compartment with the higher solute concentration until concentrations once again become equal. The osmotic pressure responsible for water movement across cell membranes depends on the total number of solute particles (osmoles) dissolved in solution, a property known as osmolality.

Osmolality is usually expressed as milliosmoles of solute per kilogram of solvent (mOsm/kg), but it can be thought of more simply as the number of millimoles of solute particles per liter of solution. A solute particle’s contribution to osmolality is independent of its charge and molecular size. Ionic substances such as sodium chloride that dissociate in solution contribute more than one osmotically active particle. Sodium salts, glucose, and urea, commonly measured as blood urea nitrogen (BUN), are responsible for most of the solute particles normally present in extracellular fluid. Plasma osmolality can be measured directly with an osmometer or can be estimated with reasonable accuracy from the concentrations of the major extracellular solutes, as follows:

\[ P_{osm} = 2 \times \text{plasma [Na\textsuperscript{+}]} + \frac{[\text{glucose}]}{18} + \frac{\text{BUN}}{2.8} \]

The multiple of 2 reflects the anions accompanying sodium ions, and 18 and 2.8 are the corrections required to convert glucose and urea nitrogen concentration from mg/dl (the units used by most laboratories in the United States) to mmol/L. Exogenous solutes (e.g., ethanol, methanol, ethylene glycol, glycine, mannitol) are measured by osmometers but are not included in the formula shown above. A discrepancy between the measured and the calculated plasma osmolality values (an osmolar gap) is useful clinically as a way to recognize the presence of an exogenous solute.

Fluid Movement between Body Fluid Compartments

The intravascular and interstitial subdivisions of the extracellular fluid compartment are separated by capillary walls that are freely permeable to small extracellular solutes but relatively impermeable to plasma proteins. Protein-free saltwater continuously moves across the capillary endothelial barrier by filtration, driven by a hydrostatic pressure gradient (generated by contractions of the heart), which forces fluid from the capillary into the interstitium, and an oncotic pressure gradient (the consequence of the osmotic force created by intravascular protein), which draws interstitial fluid into capillaries. These so-called Starling forces, which regulate the disposition of fluid within the extracellular compartment, determine how much of the extracellular saltwater is contained in intravascular plasma and how much is in interstitial fluid. The intravascular and interstitial fluid compartments are separated by capillary walls that are freely permeable to small extracellular solutes but relatively impermeable to plasma proteins. Protein-free saltwater continuously moves across the capillary endothelial barrier by filtration, driven by a hydrostatic pressure gradient (generated by contractions of the heart), which forces fluid from the capillary into the interstitium, and an oncotic pressure gradient (the consequence of the osmotic force created by intravascular protein), which draws interstitial fluid into capillaries. These so-called Starling forces, which regulate the disposition of fluid within the extracellular compartment, determine how much of the extracellular saltwater is contained in intravascular plasma and how much is in interstitial fluid. The intravascular and interstitial fluid compartments are separated by capillary walls that are freely permeable to small extracellular solutes but relatively impermeable to plasma proteins. Protein-free saltwater continuously moves across the capillary endothelial barrier by filtration, driven by a hydrostatic pressure gradient (generated by contractions of the heart), which forces fluid from the capillary into the interstitium, and an oncotic pressure gradient (the consequence of the osmotic force created by intravascular protein), which draws interstitial fluid into capillaries. These so-called Starling forces, which regulate the disposition of fluid within the extracellular compartment, determine how much of the extracellular saltwater is contained in intravascular plasma and how much is in interstitial fluid. The intravascular and interstitial fluid compartments are separated by capillary walls that are freely permeable to small extracellular solutes but relatively impermeable to plasma proteins. Protein-free saltwater continuously moves across the capillary endothelial barrier by filtration, driven by a hydrostatic pressure gradient (generated by contractions of the heart), which forces fluid from the capillary into the interstitium, and an oncotic pressure gradient (the consequence of the osmotic force created by intravascular protein), which draws interstitial fluid into capillaries. These so-called Starling forces, which regulate the disposition of fluid within the extracellular compartment, determine how much of the extracellular saltwater is contained in intravascular plasma and how much is in interstitial fluid. The intravascular and interstitial fluid compartments are separated by capillary walls that are freely permeable to small extracellular solutes but relatively impermeable to plasma proteins. Protein-free saltwater continuously moves across the capillary endothelial barrier by filtration, driven by a hydrostatic pressure gradient (generated by contractions of the heart), which forces fluid from the capillary into the interstitium, and an oncotic pressure gradient (the consequence of the osmotic force created by intravascular protein), which draws interstitial fluid into capillaries. These so-called Starling forces, which regulate the disposition of fluid within the extracellular compartment, determine how much of the extracellular saltwater is contained in intravascular plasma and how much is in interstitial fluid.
port (e.g., sodium ions) or because the cell membrane is impermeable to them (e.g., mannitol). Such solutes, which cause both hyperosmolality and hypertonicity, are sometimes called effective osmoles.

**Body Fluid Tonicity and the Plasma Sodium Concentration**

Normally, sodium salts are the major effective osmoles in extracellular fluid, and potassium salts are the major effective solutes in cells. Given that effective osmolality is equal in all fluid compartments, body fluid tonicity can be described by the following equation:

\[
\text{Tonicity} = \frac{2 \times \text{plasma } [\text{Na}^+] + \text{exchangeable K}^+}{\text{total body water}}
\]

Therefore,

\[
\text{Plasma } [\text{Na}^+] = \frac{\text{exchangeable Na}^+ + \text{exchangeable K}^+}{\text{total body water}}
\]

(Only the exchangeable fractions of sodium and potassium are included in the equation, because one third of body sodium is bound to bone and is osmotically inactive.)

Thus, the plasma sodium concentration is, in effect, a measure of the concentration of tonicity of all body fluids. In the absence of an osmolar gap, the plasma sodium concentration is a more valid measure of body fluid tonicity than is plasma osmolality (which includes the ineffective osmole urea). With a few exceptions, most notably hyperglycemia, a low plasma sodium concentration indicates hypotonicity and cell swelling, whereas a high plasma sodium concentration indicates hyperosmolality and cellular dehydration.

**Renal Processing of Body Fluids**

**Glomerular Filtration**

Approximately 170 L of extracellular saltwater containing over 25,000 mmol of sodium are filtered by the glomerulus each day. Although glomerular hydrostatic pressure is considerably higher than the pressure of other capillary beds, the Starling forces that control fluid movement between intravascular and interstitial fluid also drive glomerular filtration. The glomerular filtrate contains the same concentrations of sodium and other solutes as interstitial fluid and is nearly protein free.

**Tubular Reabsorption**

On a conventional diet, all but 2 L of filtered fluid and all but 175 mmol of filtered sodium is reabsorbed by the renal tubules. Regulation of tubular reabsorption of salt and water is the key to renal regulation of body fluid balance.

At the end of the proximal tubule, the remaining filtrate has the same sodium concentration as plasma; as the filtrate passes through downstream tubular segments, it undergoes major changes in composition. In these more distal segments, sodium and water reabsorption are uncoupled; salt can be reabsorbed without water, and water can be reabsorbed without salt. Thus, depending on conditions, the sodium concentration of the final urine can vary from less than 1 mEq/L to nearly 300 mEq/L, and urine osmolality can vary from one sixth (50 mOsm/kg) to four times (1,200 mOsm/kg) that of plasma.

The process of sodium reabsorption is mediated by carriers or channels embedded in the tubular cell’s luminal and basolateral (blood side) membranes. In each nephron segment, sodium reabsorption is powered by the Na⁺,K⁺-ATPase, which is located on the blood side of the tubular cell [see Figure 1]. This sodium pump exports sodium from the cell, lowering the intracellular sodium concentration. The lowered concentration of cellular sodium creates an electrochemical gradient driving sodium from the tubular lumen into the cell. Tubular segments at various regions of the nephron utilize different luminal mechanisms for sodium reabsorption [see Table 1 and Figure 2]. Luminal exchangers, cotransporters, and ion channels along the nephron are subject to physiologic control, and they can be inhibited pharmacologically by specific diuretic agents. Mutations in these transport proteins are responsible for well-defined clinical disorders.

The luminal membrane of the collecting duct is impermeable to water in the absence of arginine vasopressin, an antidiuretic hormone (ADH). Thus, when plasma ADH levels are low, this segment progressively reduces the osmolality and sodium concentration of the final urine and permits the excretion of large volumes (as much as 20 L daily) of dilute urine. In the presence of ADH, water channels—called aquaporins—are inserted in the luminal membrane of the distal tubule and collecting duct. When plasma levels of ADH are high, water is attracted osmotically from the tubular lumen to the hypertonic medullary interstitium, permitting excretion of a small volume (as little as 0.5 L daily) of concentrated urine.

**Regulation of Body Fluid Volumes**

Saltwater (isotonic saline) is confined to the extracellular space. Accumulation of saltwater expands extracellular volume; loss of saltwater causes volume depletion. In either case, changes in saltwater balance do not alter the plasma sodium concentration or cell volume. By contrast, so-called electrolyte-free water, or pure water, is distributed throughout body fluids, affecting both extracellular and intracellular fluid compartments. Because only one third of body water is extracellular, electrolyte-free water has only one third the impact on extracellular...
volume that saltwater has; however, unlike saltwater balance, electrolyte-free water balance has a major impact on the plasma sodium concentration, body fluid tonicity, and cell volume.

Extracellular and intracellular fluid volumes are maintained by separate but interacting control systems [see Table 2]; the extracellular system primarily regulates urinary sodium excretion, whereas the intracellular system regulates the intake and excretion of water. Extracellular fluid volume maintains a proper degree of vascular fullness, a variable that is sensed by atrial stretch receptors and arterial baroreceptors. Intracellular volume is regulated by hypothalamic osmoreceptor cells that swell or shrink in response to changes in plasma tonicity.

Control of Extracellular Fluid Volume

In a healthy person, the amount of sodium in the extracellular space can vary considerably, depending on dietary salt intake; however, the extracellular sodium concentration remains almost constant because of physiologic control systems that tightly regulate water intake and excretion. In healthy persons, more salt in the extracellular space means an expanded extracellular fluid volume, and less salt means a smaller extracellular volume; but in either case the extracellular sodium concentration does not change.

Sodium balance and intravascular volume are affected by numerous hormonal and nonhormonal mediators; in addition to aldosterone and angiotensin—the best known mediators of sodium excretion—the sympathetic nervous system, natriuretic peptides, and changes in the renal circulation all play important regulatory roles [see Table 2]. Because of redundancy and overlap in the control system, failure of a single factor does not cause major, sustained abnormalities in intravascular volume. The relative importance of the various mediators that affect urinary sodium excretion is incompletely understood, and it is likely that some sodium regulatory factors remain undiscovered.

Control of Intracellular Fluid Volume

Water balance and cell volume are controlled by a single hormonal mediator, arginine vasopressin [see Tubular Reabsorption, above], which is released into the systemic circulation by the neurohypophysis [see Table 2 and Figure 3]. The hormone activates V2 receptors on the basolateral membrane of principal cells in the renal collecting duct, initiating a cyclic adenosine monophosphate–dependent (cAMP-dependent) process that culminates in the insertion of water channels (aquaporins) into the cells’ luminal membranes.3,4 Modulation of the number of aquaporins controls urine osmolality and the rate of water excretion by the kidney. Vasopressin’s short half-life in the circulation and continuous shuffling of aquaporins between the collecting duct’s cell membrane and cytosol ensure that urinary water excretion responds rapidly to changes in body fluid tonicity.

Vasopressin levels are normally unmeasurable when the plasma sodium concentration falls to 135 mEq/L or lower [see Figure 3]. Low levels of the hormone result in the excretion of large volumes of a maximally dilute urine (50 mOsms/kg). Above a sodium level of 135 mEq/L, plasma vasopressin levels are linearly related to the plasma sodium concentration and increase measurably in response to changes in the plasma sodium concentration of as little as 1 mEq/L. Once the plasma sodium concentration reaches approximately 142 to 144 mEq/L, plasma vasopressin levels are high enough to promote the excretion of maximally concentrated urine (1,200 mOsms/kg). A rising plasma sodium concentration also causes hypothalamic cell volume receptors to relay signals to nearby thirst centers. Mediated by thirst and changes in vasopressin secretion, the plasma sodium concentration is normally prevented from rising above 144 mEq/L or falling below 135 mEq/L.

Under day-to-day conditions, water intake, vasopressin secretion, and urinary free-water excretion primarily respond to changes in the plasma sodium concentration created by variations in electrolyte-free water balance. Unlike sodium excretion, which is affected only by changes in intravascular volume, free-water excretion can be affected by two types of stimuli: intravascular volume and tonicity. Under pathologic conditions, osmotic control of vasopressin secretion and thirst can be overridden by hemodynamic stimuli. The hypothalamic neurons that secrete vasopressin receive neural input from baroreceptors in the great vessels and volume receptors in the atria. When these receptors are stimulated by hypotension or by a major reduction in plasma volume, impulses are carried via cranial nerves IX and X.5 Vasopressin and thirst responses to hypovolemia and hypotension can be regarded as backup systems that serve to maintain arterial blood volume under emergency conditions, sacrificing tonicity to tissue perfusion.

Cell volume regulation in hypotonicity and hypertonicity

Cell volume is determined by the amount and concentration of intracellular solute. Because intracellular and extracellular solute concentrations must be equal, the relation between cell water and extracellular osmolality can be described by the following equation:

\[
\text{Cell water} = \frac{\text{cell solute content}}{\text{extracellular osmolality}}
\]

Table 1

<table>
<thead>
<tr>
<th>Nephron Segment</th>
<th>Glomerular Filtrate Reabsorbed</th>
<th>Mechanism of Luminal Sodium Entry</th>
<th>Physiologic Regulation</th>
<th>Diuretic Site of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal tubule</td>
<td>60%–70%</td>
<td>Na⁺–H⁺ exchange; cotransport with glucose and other organic solutes</td>
<td>Angiotensin II; renal nerves; peritubular Starling forces</td>
<td>Carbonic anhydrase inhibitors (e.g., acetazolamide)</td>
</tr>
<tr>
<td>Loop of Henle</td>
<td>20%–25%</td>
<td>Na⁺–K⁺–2Cl⁻ cotransport</td>
<td>Flow dependent; peritubular Starling forces</td>
<td>Loop diuretics (e.g., furosemide, bumetanide, ethacrynic acid)</td>
</tr>
<tr>
<td>Distal tubule</td>
<td>5%</td>
<td>Na⁺–Cl⁻ cotransport</td>
<td>Flow dependent</td>
<td>Thiazide diuretics</td>
</tr>
<tr>
<td>Collecting tube</td>
<td>4%</td>
<td>Na⁺ channels</td>
<td>Aldosterone; atrial natriuretic factor</td>
<td>Potassium-sparing diuretics (e.g., amiloride, triamterene, spironolactone)</td>
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</tbody>
</table>
Normally, water intake and excretion are modulated to maintain body fluid tonicity within a narrow physiologic range. However, under pathologic conditions, body cells can be exposed to a hypotonic or hypertonic milieu. The first response to osmotic stress is a compensatory adjustment to intracellular electrolytes: loss of potassium in hypotonicity and accumulation of sodium and potassium in hypertonicity. With time, changes in organic solutes dominate the response. Most cells maintain relatively high concentrations of small, osmotically active organic molecules known as organic osmolytes. Organic osmolytes are nonperturbing solutes; unlike sodium and potassium, their intracellular concentrations may vary widely without affecting tertiary protein structure. Cells accumulate organic osmolytes under hypertonic conditions and lose them when confronted with hypotonicity.

The need for cell volume regulation is most imperative in the brain, where the rigid calvaria places sharp limits on the degree of tissue expansion or contraction that can be tolerated. An increase in brain water content of more than about 5% to 10% is incompatible with life. Variations in the intracellular concentration of organic osmolytes provide the brain with an astonishing ability to adapt to chronic osmotic disturbances. However, because changes in the osmolyte content of brain cells require a few days to develop fully, the brain is imperiled by rapid osmotic changes. Thus, acute hyponatremia or hypernatremia may be fatal at plasma sodium concentrations that are well tolerated chronically.

With sustained osmotic disturbances, adaptations that protect against brain swelling and shrinkage also predispose to injury when the osmotic disturbance is suddenly corrected. In chronic hyponatremia, cellular solutes lost in the adaptive phase must be recovered when the plasma sodium concentration returns to normal—a process that may require several days. Unless solute recovery keeps pace with the rising extracellular osmolality, brain cells will become dehydrated. This phenomenon may cause clinical complications [see Complications of Therapy: Myelinolysis and Osmotic Demyelination Syndrome, below]. Similarly, in chronic hypernatremia, accumulated solutes must be shed during correction of the electrolyte disturbance. Cells that have become acclimated to a hypertonic environment lose organic osmolytes slowly because of slow turnover of the efflux mechanism, slow downregulation of hypertotonically stimulated uptake pathways, or both. Thus, when chronic hypernatremia is corrected rapidly, brain cells swell to a greater than normal volume.

**Disorder of Water Excess: Hyponatremia**

Hyponatremia simply means a low plasma sodium concentration. In most cases, hyponatremia is associated with a low plasma osmolality level and body fluids that are too dilute (hypotonic hyponatremia). However, there are exceptions to this rule [see Differential Diagnosis for Hyponatremia, below].

**Pathogenesis of Hyponatremia**

Hyponatremia results from two basic mechanisms, individually or together: (1) massive water intake, exceeding the capacity to excrete electrolyte-free water, or (2) impaired water excretion. Normally, the capacity for water excretion is rather large. In the absence of vasopressin, urine osmolality falls to approximately 50 mOsm/kg. A typical United States diet provides 600 to 900 mOsm of electrolytes and urea that must be excreted each day. At this rate of solute excretion, the volume of maximally dilute urine equals 12 to 18 L. Water intake can occasionally exceed the normal excretory capacity, primarily in psychotic patients who frantically ingest gallons of water over a few hours and in very heavy beer drinkers who ingest large volumes of fluid but take in small amounts of salt and protein. More commonly, hyponatremia occurs in patients with a diminished ability to excrete free water.

**Impaired Water Excretion**

Water excretion is obviously compromised in severe renal failure; oliguric patients become hyponatremic if they are given too much water. However, most cases of hyponatremia occur in patients whose normal kidneys are unable to excrete maximally di-
edema; in the steady state, sodium excretion matches intake.8,12,19,20

um balance, evidence of volume depletion, or tendency to form abnormal thirst mechanisms but have no abnormality in sodium reabsorption. Nonosmotic release of vasopressin and resultant urine. A pathologically low plasma sodium concentration occurs when water is taken in at a time when renal diluting mechanisms are not functioning maximally because either (1) diuretics or tubular transport defects are blocking sodium reabsorption in the renal diluting segments or (2) ADH levels are elevated.

Nonosmotic Release of Vasopressin

Vasopressin is a water-retaining hormone that is released when water is needed. Because hypotonic hyponatremia normally inhibits vasopressin secretion, detectable vasopressin in a patient who is hyponatremic indicates that a nonosmotic stimulus for vasopressin release must be present. Vasopressin action increases the urine osmolality, which can be thought of as a bioassay for the hormone.

Hemodynamic stimuli for vasopressin Hypovolemia, heart failure, and cirrhosis are the most common nonosmotic stimuli for ADH secretion.30–32 The hemodynamic abnormalities that stimulate vasopressin release also promote sodium reabsorption by the renal tubules; thus, these conditions result in both sodium and water retention.

Inappropriate antidiuretic hormone secretion Nonosmotic release of vasopressin without a hemodynamic stimulus to account for it is considered “inappropriate.” Patients with the syndrome of inappropriate antidiuretic hormone secretion (SIADH) retain water because of nonosmotic release of vasopressin and abnormal thirst mechanisms but have no abnormality in sodium balance, evidence of volume depletion, or tendency to form edema; in the steady state, sodium excretion matches intake.30,32,35–37 Because of water retention, SIADH causes mild, subclinical volume expansion. Any additional volume expansion is met by a brisk increase in urinary sodium excretion.

Reset osmostat Reset osmostat is a variant of SIADH, commonly seen in patients with chronic, debilitating illness; it is also a characteristic of normal pregnancy. Patients with this condition are able to dilute their urine normally but at a lower set point than in normal individuals. Such patients are thus mildly hyponatremic, but unlike other patients with SIADH, they are not predisposed to progressive water retention and do not require dietary water restriction or other measures used to treat chronic hyponatremia.38 Reset osmostat can, however, be seen in malignancies, and like other causes of SIADH, it requires a diagnostic evaluation to determine its cause.

Urinary Electrolyte Losses: Desalination and Hyponatremia

If the urine is concentrated, urinary sodium and potassium losses can contribute to the pathogenesis of hyponatremia. The plasma sodium concentration can be reduced either by loss of sodium or potassium or by water gain. However, to lower the plasma sodium concentration, electrolytes must be lost in urine that has a higher electrolyte concentration than plasma. The combination of high vasopressin levels (which concentrate the

<table>
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<tr>
<th>Regulated variable</th>
<th>Clinical indicator</th>
<th>Sensors</th>
<th>Mediators</th>
<th>Affected variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extracellular volume</td>
<td>Blood pressure</td>
<td>Baroreceptors, atrial volume receptors</td>
<td>Renin-angiotensin-aldosterone system, Sympathetic nervous system, Atrial natriuretic peptide, Starling forces in peritubular capillaries</td>
<td>Urinary sodium excretion</td>
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<td>Vascular fullness</td>
<td>Edema</td>
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<tr>
<th>Table 2  Control of Body Fluid Volumes</th>
<th>Saltwater Balance</th>
<th>Electrolyte-Free Water Balance</th>
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<td></td>
<td>Regulated variable</td>
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<tr>
<td></td>
<td>Cell volume</td>
<td>Plasma sodium concentration</td>
</tr>
<tr>
<td></td>
<td>Arterial filling</td>
<td>Blood pressure</td>
</tr>
</tbody>
</table>

Figure 3 Graph depicts the normal relation between plasma vasopressin levels and urine osmolality (black line) and the plasma sodium concentration (blue line). Plasma vasopressin levels change within minutes in response to changes in plasma sodium, and urine osmolality changes within minutes in response to changes in vasopressin levels. When hydration reduces the plasma sodium level below 135 mEq/L, plasma vasopressin becomes undetectable and the urine becomes maximally dilute (osmolality, 50 mOsm/kg). Between sodium concentrations of 135 and 142 mEq/L, vasopressin levels are linearly related to the plasma sodium, causing nearly a 100 mOsm/kg increase in urine osmolality for every 0.5 mEq/L increase in sodium concentration. Above a plasma sodium concentration of 142 mEq/L, the urine is maximally concentrated; increased water intake, mediated by thirst, then becomes the major defense against progressive hyponatremia.

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urine) and a high rate of sodium and potassium excretion can yield hypertonic urine capable of generating free water, which in essence desalinates the plasma.23

**DIFFERENTIAL DIAGNOSIS FOR HYponatREMIA**

Several conditions can lower the plasma sodium concentration without causing hypotonicity and are referred to as nonhypotonic hyponatremia [see Table 3]. The diagnostic and therapeutic approach to these conditions differs fundamentally from the approach to hypotonic hyponatremia. Thus, it is important that nonhypotonic hyponatremia be excluded whenever a low plasma sodium concentration is encountered.

**Hyperglycemic Hyponatremia**

Hyperglycemia lowers the plasma sodium concentration; in the absence of insulin, glucose is an effective osmole that holds water in the extracellular space, diluting extracellular sodium. A variety of correction factors have been offered to quantify this effect.24 However, a precise correction factor is probably unobtainable because in practice, hyperglycemia develops, in part, from the ingestion of glucose with water and resolves, in part, from the urinary excretion of glucose with water.25 As a rough estimate, the serum sodium concentration decreases 2 mEq/L for every 100 mg/dl increase in blood glucose.

Exogenous solutes such as mannitol and maltose (a sugar contained in intravenous immunoglobulin preparations) are confined to the extracellular space and have an effect on the plasma sodium concentration similar to that of hyperglycemia. When the clinical setting suggests that these solutes might be responsible for hyponatremia, their presence can be confirmed by measuring the plasma osmolality and comparing it with the calculated value to identify an osmolar gap [see Osmolality, above].22

### Postprostatectomy Syndrome and Hysteroscopic Hyponatremia

Irrigants containing mannitol, sorbitol, or glycine are used for endoscopic transurethral and intrauterine procedures [see Table 3].28 Occasionally, several liters of irrigant may be absorbed systemically, reducing the plasma sodium in a matter of minutes. Immediately after surgery, the serum sodium concentration is much lower than would be anticipated, because the electrolyte-free solution is initially confined to the extracellular space. Glycine, the most commonly used irrigant in the United States, is metabolized to ammonia and eventually to urea and glucose. Hyperammonemia may be responsible for most of the symptoms in patients with postprostatectomy syndrome and hysteroscopic hyponatremia, and glycine itself has direct neuroinhibitory effects and may cause hypotension, bradycardia, and visual disturbances.

**Pseudohyponatremia**

High plasma concentrations of lipid or protein cause mild nonhypotonic hyponatremia because of an artifact of laboratory measurement [see Table 3].21,25 With extremely high concentrations of triglycerides (enough to give serum a milky appearance), hypercholesterolemia with lipoprotein X from obstructive or cholestatic jaundice, or very high serum protein levels (from multiple myeloma or Waldenstrom macroglobulinemia), plasma water may constitute a smaller fraction of the plasma sample than normal, which can result in an underestimate of the “true” sodium concentration. The plasma osmolality and the sodium concentration in plasma water (as measured in an undiluted sample by a sodium-sensitive electrode) are unaffected. There are no symptoms, and no therapy is required.

### ACUTE HYponatREMIA (WATER INTOXICATION)

The term water intoxication was coined in the early 1920s to describe a neurologic syndrome that develops when large volumes of water are retained within a relatively short period of time (<48 hours). The syndrome is often referred to as acute hyponatremia.22,26

**Etiology**

Acute hyponatremia develops when water intake is high and electrolyte-free water excretion is impaired. Potentially, hyponatremia can develop rapidly in any patient predisposed to water...

### Table 3 Causes of Nonhypotonic Hyponatremia

<table>
<thead>
<tr>
<th>Condition</th>
<th>Plasma Osmolality</th>
<th>Pathogenesis</th>
<th>Therapeutic Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperglycemia</td>
<td>High</td>
<td>Extracellular glucose osmotically draws water into the ECF, diluting extracellular sodium</td>
<td>During treatment of hyperglycemia, anticipate 3 mEq/L increase in serum sodium for every 200 mg/dl reduction in blood sugar</td>
</tr>
<tr>
<td>Intravenous hypertonic mannitol therapy</td>
<td>High</td>
<td>Water shift from ICF to ECF as with hyperglycemia</td>
<td>Mannitol is rapidly excreted when renal function is normal</td>
</tr>
<tr>
<td>Intravenous γ-globulin therapy</td>
<td>High</td>
<td>Maltose present in solution acts like mannitol</td>
<td>Measure plasma osmolality when hyponatremia is suspected</td>
</tr>
<tr>
<td>Irritant absorption (prostatectomy or intrauterine surgery)</td>
<td>Normal or low (when hypotonic irritants are used)</td>
<td>Absorbed solute—mannitol, sorbitol, or glycine (most common)—initially confined to ECF, causing severe hyponatremia but little change in plasma osmolality</td>
<td>Mannitol is rapidly excreted; sorbitol is metabolized, causing late-onset hypotonic hyponatremia; glycine is neurotoxic and causes transient blindness and is metabolized to ammonia, causing encephalopathy; consider hemodialysis</td>
</tr>
<tr>
<td>Pseudohyponatremia (severe hyperlipidemia, multiple myeloma, macroglobulinemia)</td>
<td>Normal</td>
<td>Laboratory artifact; plasma water constitutes a smaller fraction of the plasma sample, causing a more serious underestimate of the true sodium concentration</td>
<td>Suspect when serum is lactescent; compare measured plasma osmolality with calculated osmolality or measure plasma sodium with direct-reading sodium electrode</td>
</tr>
</tbody>
</table>

ECF—extracellular fluid ICF—intracellular fluid


**Table 4  Causes and Treatment of Acute Hyponatremia**

<table>
<thead>
<tr>
<th>Causes</th>
<th>Pathogenesis</th>
<th>Effect of Treatment</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative stress*</td>
<td>Vasopressin is secreted in response to surgical stress for 2 or more days; free water from hypotonic I.V. fluids is retained and sodium and potassium are excreted in urine at high concentrations</td>
<td>Normal saline ineffective for correction—administered sodium is excreted in concentrated urine, “desalinating” isotonic fluid and causing water retention</td>
<td>Avoid hypotonic fluid (e.g., D5W, 0.45% saline) and excessive volumes of isotonic fluid (lactated Ringer solution or 0.9% saline) after surgery; treat symptomatic hyponatremia with 3% saline and furosemide</td>
</tr>
<tr>
<td>Oxytocin</td>
<td>Used in obstetrics to induce labor; direct antidiuretic effect of drug mimics SIADH; free water from I.V. fluids retained</td>
<td>Urine becomes dilute when oxytocin is discontinued</td>
<td>Avoid administration of oxytocin in or with hypotonic fluids; treat hyponatremia by discontinuing drug</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Drug has antidiuretic effect that persists for as long as 12 hours; patients are encouraged to drink large volumes of water to prevent chemically induced cystitis</td>
<td>Normal saline ineffective for correction as in other causes of persistent SIADH</td>
<td>Treat symptomatic hyponatremia with 3% saline and furosemide</td>
</tr>
<tr>
<td>Psychotic self-induced water intoxication</td>
<td>Extreme polydipsia (&gt; 1 L/hr) common in patients with severe psychosis; retained water causes hyponatremia by late afternoon or evening, and water diuresis restores normonatremia by morning</td>
<td>Normal ability to dilute urine in most patients so hyponatremia self-correction when water intake stops; some patients have vasopressin release (often transient) from stress, smoking, or medications (e.g., carbamazepine)</td>
<td>Monitor diurnal weight in institutionalized patients for early detection; avoid antidiuretic medications; treat hyponatremia with water restriction; use hypertonic saline and furosemide for occasional patient with SIADH</td>
</tr>
<tr>
<td>Marathon running</td>
<td>Extracellular volume depletion caused by saltwater losses from sweating and possibly stress are nonosmotic stimuli for vasopressin secretion; large volumes of sugar water consumed during race are retained</td>
<td>Isotonic saline restores ability to dilute urine</td>
<td>3% saline without furosemide for seizures; isotonic saline and water restriction for more moderate symptoms</td>
</tr>
<tr>
<td>Ecstasy (methyleneoxymethamphetamine [MDMA]) use</td>
<td>Excessive fluid intake and inappropriate antidiuretic hormone secretion, induced by MDMA, is implicated</td>
<td>Isotonic saline ineffective; self-correction typical but may be delayed</td>
<td>Hypertonic saline for severe symptoms</td>
</tr>
</tbody>
</table>

*Excluding irrigant absorption syndromes (see Table 3). D5W—5% dextrose in water SIADH—syndrome of inappropriate antidiuretic hormone

retention who takes in a large volume of water in a short period of time. However, this is likely to occur in a limited number of settings [see Table 4], and such instances account for most cases of severe symptomatic hyponatremia and for most of the recorded fatalities.

**Postoperative hyponatremia** Vasopressin is released immediately after surgical procedures in what appears to be a stress response [see Table 4]. Particularly during the first 24 hours, the concentration of urinary cations (sodium plus potassium) may greatly exceed the plasma sodium concentration. As a result, even isotonic fluids may be “desalinated” and can lower the plasma sodium concentration. Thus, all hypotonic fluids and excessive amounts of isotonic fluids should be avoided after surgery. As noted, endoscopic prostatectomy and intrathecal procedures can cause hyponatremia if the irrigant used in the procedures is absorbed systemically. The management of irrigant absorption syndromes differs from that of other causes of postoperative hyponatremia [see Postprostatectomy Syndrome and Hysteroscopic Hyponatremia, above].

**Oxytocin infusions** Oxytocin, which is used in obstetrics to induce labor, has a direct antidiuretic effect. If the drug is administered in 5% dextrose in water (D5W), which was formerly a common practice, symptomatic hyponatremia may emerge after the infusion of less than 3 L of fluid [see Table 4]. Termination of the infusion permits a water diuresis and correction of hyponatremia; however, the syndrome is best avoided by using isotonic saline as a vehicle for the drug.

**Cyclophosphamide infusion** Intravenous cyclophosphamide impairs water excretion by an unknown mechanism. The antidiuretic effect of the drug begins 4 to 12 hours after injection and persists for as long as 12 hours. Patients receiving cyclophosphamide are particularly susceptible to hyponatremia because they are encouraged to drink large volumes of water to prevent chemically induced cystitis [see Table 4].

**Psychotic self-induced water intoxication** Extreme polydipsia is relatively common in patients with psychiatric illnesses, particularly schizophrenia, and it may lead to symptomatic hyponatremia [see Table 4]. Daily intake of 10 to 15 L has been documented, and much of the intake may take place over a few hours. Many patients become hyponatremic in the late afternoon and evening; however, water diuresis typically restores normonatremia by the following morning. Occasionally, individuals drink enough water to produce seizures. By monitoring diurnal changes in body weight, water intoxication can be recognized before the onset of severe neurologic symptoms. Transient release of vasopressin (most commonly provoked by nau-
Water intoxication during exercise

Hyponatremia is disturbingly common in nonelite marathon runners; it is associated with slow finishing times and with excessive consumption of fluids while running, as evidenced by substantial weight gain. Severe symptomatic hyponatremia has mostly been reported after participation in marathons or ultramarathons, but symptomatic hyponatremia may also occur after recreational running and military fitness training.

Water intoxication from the drug ecstasy

During the 1990s, 3,4-methylenedioxymethamphetamine (MDMA, or ecstasy) gained widespread popularity as a recreational drug taken at dances. When malignant hyperthermia was recognized as a complication associated with this drug, MDMA users were advised in underground magazines and the lay press to drink plenty of fluids. Subsequently, acute water intoxication emerged as a potentially lethal complication of the drug [see Table 4]. Excessive fluid intake and SIADH, induced by MDMA, have been implicated.

Diagnosis

Symptoms of water intoxication include headaches, weakness, nervousness, and vomiting, progressing to disorientation, delirium, tremulousness, and ultimately convulsions and coma. The pupils are often dilated, and bilateral Babinski signs may be present. On occasion, patients may present with hemiparesis, mimicking a cerebrovascular accident. The syndrome reflects cerebral edema, which can lead to herniation of the brain and death. Clinical findings may emerge explosively. Complaints of headache and mild confusion may be followed within hours by respiratory arrest and, in some cases, neurogenic pulmonary edema. For reasons that remain obscure, almost all reported fatalities from acute postoperative hyponatremia have been in women (usually of childbearing age) and young children. Fatal cases of acute hyponatremia from other etiologies have been recorded in men and women.

Acute hyponatremia should be suspected in any patient who has unexplained neurologic symptoms, especially in psychiatric patients, marathon runners, users of ecstasy, and patients receiving hypotonic fluids intravenously (e.g., after surgery). Serum electrolyte levels should be obtained immediately. In the proper setting, a tentative diagnosis of water intoxication is advisable when symptoms develop in a patient whose serum sodium concentration is lower than 130 mEq/L (provided that causes of nonhypotonic hyponatremia have been excluded). Although severe neurologic symptoms do not usually appear until the sodium level has fallen below 120 mEq/L, some patients (particularly young women and children) may be unusually susceptible to brain edema when they become acutely hyponatremic; in rare cases, fatalities have been reported at plasma sodium concentrations between 120 and 128 mEq/L.

Elderly patients can tolerate acute hyponatremia better than the young, because brain atrophy affords more room for brain cell swelling. The same water load per kilogram of body weight can cause a much more severe degree of acute hyponatremia when water is ingested rapidly, especially if the person has a much smaller muscle mass (the reservoir for a water load that limits brain cell swelling). When the serum sodium concentration is falling rapidly, the arterial sodium concentration (to which the brain responds) may be lower than the venous sodium concentration (which is measured in most clinical electrolyte assays).

Computed tomography demonstrates cerebral edema in severe cases of water intoxication, and it rules out other potential explanations for neurologic findings. However, when symptoms are severe, therapy should not be delayed while imaging studies are being obtained.

Treatment

Free-water intake should be stopped immediately whenever water intoxication is suspected. Hypertonic saline is the treatment of choice for water-intoxicated patients who cannot autoregulate their electrolyte disturbance, including patients with neurogenic pulmonary edema. Each 1 ml of 3% saline contains 0.5 mEq of sodium. Because there are approximately 0.5 L of body water for every 1 kg of body weight, 1 ml of 3% saline per 1 kg of body weight can be expected to increase the plasma sodium concentration by 1 mEq/L. For patients with severe neurologic symptoms, an infusion of 3% saline at 1 to 2 ml/kg/hr will increase the plasma sodium concentration by approximately 1 to 2 mEq/L/hr, a rate that is considered appropriate for initial therapy. Hypertonic saline is best infused in 100 ml containers to avoid inadvertently giving an excessive dose. Concurrent administration of a loop diuretic (furosemide, bumetanide, or torsemide) is advisable. The diuretic prevents volume overload and, by blocking sodium reabsorption in the loop of Henle, impedes the formation of concentrated urine.

The goal of therapy in acute hyponatremia is to decrease the severity of cerebral edema and to stop seizures. A 4 to 6 mEq/L increase in plasma sodium concentration is usually sufficient to accomplish these goals. Thus, the plasma sodium concentration should be monitored frequently during therapy, and emergency treatment with hypertonic saline should be stopped after 2 to 3 hours. Once initial therapy with high-dose hypertonic saline has been completed, more conservative measures should be substituted to gradually return the plasma sodium concentration to normal. To avoid complications from excessive correction of hyponatremia, the plasma sodium concentration should not be intentionally increased by more than 12 mEq/L during the first day of therapy or by more than 6 mEq/L/day thereafter.

Chronic hyponatremia

The distinction between acute and chronic hyponatremia is somewhat arbitrary. Commonly, hyponatremia is considered chronic when it has evolved over the course of 48 hours or more. Although the precise duration of an electrolyte disturbance cannot be known when it develops outside the hospital (except for psychotic water drinkers, marathon runners, and users of ecstasy), outpatients can be assumed to have chronic hyponatremia. Prolonged hyponatremia cannot occur unless there is a sustained defect in water excretion. Except for patients with renal failure, virtually all chronically hyponatremic patients have some abnormality in vasopressin secretion.

Etiology

Advanced renal failure

A low glomerular filtration rate limits the ability to excrete electrolyte-free water. Many patients with advanced renal failure excrete urine that has the same osmolality as plasma regardless of physiologic conditions (fixed
isosthenuria). In acute oliguric renal failure, the ability to excrete free water is virtually nil; administration of hypotonic fluids must be scrupulously avoided to avoid hyponatremia.

Diuretics Thiazide diuretics are commonly the sole cause or a major contributing factor of hyponatremia requiring hospital admission.18,19 For unknown reasons, severe hyponatremia caused by thiazides affects elderly women much more often than other groups. By blocking the reabsorption of sodium and chloride in the distal tubule, thiazides and metolazone prevent the generation of maximally dilute urine.9 Because sodium reabsorption in the ascending limb of the loop of Henle is left unaffected by these agents, they permit excretion of maximally concentrated, hypertonic urine and can lead to simultaneous retention of water and depletion of sodium and potassium. Extraordinarily severe hyponatremia can result from thiazides, with plasma sodium levels as low as 100 mEq/L. Vasopressin levels are usually elevated in patients who present with thiazide-induced hyponatremia, sometimes because of diuretic-induced volume depletion but more often because of the stress of minor intercurrent illnesses. Patients with thiazide-induced hyponatremia do not usually appear clinically volume depleted, presumably because retained water partially sustains extracellular fluid volume. Patients who have become hyponatremic on thiazides should not be given these agents again; recurrent episodes of severe hyponatremia are common.

Hyponatremia Hypovolemic hyponatremia is most often associated with gastrointestinal fluid losses caused by vomiting, diarrhea, or laxative abuse. Surprisingly, particularly in alcoholics, patients who continue to drink while vomiting repeatedly can still absorb enough ingested water to become hyponatremic. Electrolyte losses in the vomitus, combined with urinary sodium and potassium losses that result from metabolic alkalosis, lower the plasma sodium concentration.

Beer potomania Patients who subsist on beer (a practice known as beer potomania) are susceptible to hyponatremia because of their low rates of solute excretion (beer contains little protein or electrolyte). Reduced delivery of the glomerular filtrate to distal diluting sites limits the amount of water that can be excreted. Nonosmotic stimuli to vasopressin secretion caused by nausea or gastrointestinal fluid losses or by treatment with thiazide diuretics are often contributing factors.15

Edematous conditions Any disease that can cause edema also predisposes to water retention and hyponatremia. The same hemodynamic factors that promote sodium retention are nonosmotic stimuli for vasopressin release.6,10,11 Elevated vasopressin levels have been reported in hyponatremic patients with congestive heart failure, cirrhosis, and nephrotic syndrome. In heart failure, hyponatremia is associated with a low cardiac output and a poor prognosis.

SIADH Nonosmotic release of vasopressin that has no hemodynamic explanation is termed inappropriate [see Table 5].12,13 A number of tumors (most commonly small cell carcinoma of the lung) ectopically synthesize and secrete vasopressin.20 Unexplained, persistent hyponatremia should be considered a marker for an underlying malignancy.

SIADH may also complicate the course of a wide variety of conditions in which there is damage to or inflammation of the central nervous system.21 In patients with subarachnoid hemorrhage, natriuretic peptides released by the brain may directly promote urinary sodium loss, regardless of extracellular volume (cerebral salt wasting).22,23 Urinary salt losses combined with vasopressin-induced water retention are responsible for hyponatremia. SIADH is a common complication of chest infection. Antidiuretic activity has been demonstrated by bioassay in patients with tuberculous lung tissue, and tuberculosis causes SIADH.11 In pneumonia, vasopressin levels are increased during the acute phase of the disease and return to baseline within a few days. Isolated glucocorticoid deficiency caused by anterior pituitary dysfunction also causes hyponatremia; patients with hypopituitaryism develop SIADH but, unlike patients with Addison disease, have normal levels of mineralocorticoid and do not become hypovolemic or hyperkalemic. Hyponatremia caused by glucocorticoid deficiency promptly resolves when cortisol is replaced. Hypothyroidism also causes SIADH; hyponatremia gradually resolves when thyroid hormone replacement is given.26

A number of therapeutic agents can induce SIADH.15-18 Nonsteroidal anti-inflammatory drugs (NSAIDs) decrease water excretion because they inhibit formation of prostaglandin E2.

Table 5 Causes of the Syndrome of Inappropriate Antidiuretic Hormone

<table>
<thead>
<tr>
<th>Category</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumors</td>
<td>Bronchogenic (small cell)</td>
</tr>
<tr>
<td></td>
<td>Pancreatic</td>
</tr>
<tr>
<td></td>
<td>Duodenal</td>
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<tr>
<td></td>
<td>Urethral</td>
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<tr>
<td></td>
<td>Nasopharyngeal</td>
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<tr>
<td></td>
<td>Leukemia</td>
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<tr>
<td></td>
<td>Hodgkin disease</td>
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<tr>
<td></td>
<td>Thymoma</td>
</tr>
<tr>
<td>Neurologic disorders</td>
<td>Psychosis</td>
</tr>
<tr>
<td></td>
<td>Trauma</td>
</tr>
<tr>
<td></td>
<td>Neoplasms (primary and metastatic)</td>
</tr>
<tr>
<td></td>
<td>Vascular (hemorrhage, infection, and vasculitis)</td>
</tr>
<tr>
<td></td>
<td>Infection (meningitis, brain abscess, and encephalitis)</td>
</tr>
<tr>
<td></td>
<td>Miscellaneous (Guillain-Barré syndrome, multiple sclerosis, hydrocephalus, Shy-Drager syndrome)</td>
</tr>
<tr>
<td>Pulmonary disorders</td>
<td>Infectious (bacterial, viral, and fungal pneumonia and tuberculosis)</td>
</tr>
<tr>
<td></td>
<td>Functional (asthma, acute respiratory failure, and mechanical ventilation)</td>
</tr>
<tr>
<td>Endocrine diseases</td>
<td>Glucocorticoid deficiency (hypopituitarism)</td>
</tr>
<tr>
<td></td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Drugs</td>
<td>Antidiuretic hormones (vasopressin, DDAVP, and oxytocin)</td>
</tr>
<tr>
<td></td>
<td>Psychotropic agents (tricyclic antidepressants, serotonin reuptake inhibitors, monoamine oxidase inhibitors, and carbamazepine)</td>
</tr>
<tr>
<td></td>
<td>Ecstasy (MDMA)</td>
</tr>
<tr>
<td></td>
<td>Antineoplastic agents (cyclophosphamide, vincristine, and vinblastine)</td>
</tr>
<tr>
<td></td>
<td>Nonsteroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td></td>
<td>Diabetic agents (chlorpropamide and tolbutamide)</td>
</tr>
<tr>
<td></td>
<td>Miscellaneous (bromocriptine and nicotine)</td>
</tr>
<tr>
<td>Other causes</td>
<td>Postoperative stress</td>
</tr>
<tr>
<td></td>
<td>Alcohol withdrawal</td>
</tr>
<tr>
<td></td>
<td>AIDS</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
</tr>
</tbody>
</table>

DDAVP—1-desamino-8-arginine vasopressin

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which modulates vasopressin action. Rare cases of hyponatremia solely attributable to NSAIDs have been reported, but these commonly used agents may exacerbate other causes of hyponatremia.

**Hyponatremia in AIDS** Hyponatremia is an extremely common finding in AIDS patients. Many AIDS patients have features of SIADH associated with opportunistic infections that cause pneumonia and meningitis. Others have clinical signs of volume depletion without low urine sodium values, a finding that may indicate coexistent renal disease or adrenal insufficiency. Hyponatremia often occurs when antibiotics are administered in hypotonic intravenous solutions.

**Diagnosis**

Hyponatremia should be approached in a systematic fashion. First, the various disorders that can lower the plasma sodium concentration without causing hypotonicity should be excluded [see Differential Diagnosis for Hyponatremia, above]. Once it has been established that hypotonic hyponatremia is present, the mechanism for impaired water excretion is identified (hypovolemia versus an edematous condition versus SIADH), and the differential diagnosis that applies to that mechanism is considered. The most challenging goals of the diagnostic process are to determine whether chronic SIADH is present and, if it is, to define the specific disease responsible for the syndrome.

**Clinical manifestations** Because cerebral edema is usually not severe, the symptoms of chronic hyponatremia are much more subtle, vague, and nonspecific than those of acute water intoxication; indeed, patients with chronic hyponatremia are often asymptomatic at sodium levels that may be lethal to a patient with acute water intoxication. As the plasma sodium concentration falls below 115 to 120 mEq/L, patients often experience anorexia, nausea, vomiting, muscle weakness, and muscle cramps. They may be irritable and show personality changes, becoming uncooperative, confused, hostile, or simply slow to respond. At plasma sodium concentrations below 110 mEq/L, gait disturbances, falling, stupor, tremulousness, and, more rarely, seizures may occur.

Chronic hyponatremia itself is rarely, if ever, fatal. However, chronically hyponatremic patients may develop life-threatening acute hyponatremia if they rapidly drink water or are infused with a large volume of hypotonic fluid. Because hyponatremia can be a marker for severe underlying illness, hospitalized patients with hyponatremia often have a high mortality, dying with but not of chronic hyponatremia. There is little evidence that chronic hyponatremia itself leads to permanent sequelae, even when the plasma sodium concentration falls below 105 mEq/L. However, patients with prolonged, severe hyponatremia are susceptible to iatrogenic injury if their electrolyte disturbance is corrected too rapidly [see Treatment, below].

**History and physical examination** The history in patients with chronic hyponatremia should include information about diet, fluid intake, gastrointestinal fluid losses, and use of diuretics, antidepressants, or other antidiuretic drugs. During the physical examination, physicians should look for clinical signs of volume depletion or an edematous condition. Evidence of volume depletion may not always be definitive, however. For example, vomiting may be a symptom rather than the cause of hyponatremia; extreme hyponatremia may occasionally impair baroreceptor reflexes, causing postural hypotension and a false impression of volume depletion; and retained water may mask underlying volume depletion. When the distinction between hyponatremia caused by hypovolemia and hyponatremia caused by SIADH is not obvious, laboratory clues may helpful.

**Laboratory tests** Measurement of the urinary sodium concentration, chloride concentration, or both is often the most helpful test. Water retention caused by hypovolemia or by an edematous condition is usually associated with a urinary sodium concentration lower than 20 mEq/L in a spot sample. Hypovolemia caused by upper gastrointestinal fluid losses is an important exception. Loss of gastric fluid causes a metabolic alkalosis that may increase urinary sodium excretion despite volume depletion; the diagnosis can be made by measuring the urine chloride concentration, which is reduced in this condition. In SIADH, urinary sodium matches intake; because the urine is usually concentrated, the urinary sodium concentration exceeds 40 mEq/L unless dietary sodium intake is very low. Measurements of the BUN and serum uric acid complement these measurements. When a hemodynamic abnormality is responsible for hyponatremia, the kidney is underperfused, urea and uric acid clearances are diminished, and the BUN and serum uric acid levels are usually elevated. Conversely, SIADH is a volume-expanded state, and BUN and uric acid levels are usually low. Uric acid is a more reliable indicator of volume status than the BUN, because the latter value is affected by dietary protein intake as well as renal clearance.

Assessment of acid-base and potassium balance may provide helpful clues to the diagnosis. The serum potassium and bicarbonate levels are normal in SIADH. Hypokalemia and metabolic acidosis suggest diuretic therapy or vomiting, which can be surreptitious. Hyperkalemia and metabolic acidosis suggest the possibility of adrenal insufficiency. Hypokalemia and acidosis can result from diarrhea, and their presence may raise the possibility of surreptitious laxative abuse.

**Withdrawal of hyponatremic drugs** When a patient is taking a drug that can cause hyponatremia, it is important to exclude another underlying cause of hyponatremia before attributing the electrolyte disturbance to the medication. For example, thiazide diuretics can exacerbate hyponatremia caused by SIADH. The best way to confirm a diagnosis of drug-induced hyponatremia is to eliminate the offending agent and be sure that water excretion returns to normal when the patient is off the drug. Full resolution of hyponatremia and full recovery of diluting function may be delayed for a week or two in patients with thiazide-induced hyponatremia. During repair of sodium and potassium deficits, transient resetting of the osmostat is common and should not necessarily prompt an extensive search for an underlying cause.

**Response to therapy** On occasion, evidence regarding the cause of hyponatremia can be equivocal. In such cases, the patient’s response to isotonic saline (or a generous oral salt intake and the passage of time) is the best clue to the diagnosis. Patients with subclinical edematous conditions will retain the administered sodium, developing clinically obvious edema. Volume-depleted patients initially retain the administered sodium, but as soon as hypovolemia is corrected, the urine becomes dilute, the rate of urinary sodium excretion increases to match intake, and hyponatremia improves as water is excreted in the urine. Uri-
nary sodium excretion promptly increases in patients with SIADH, but the urine remains concentrated and hyponatremia persists. Isotonic saline should be given with extreme caution to patients with very low plasma sodium concentrations; in SIADH, saline can exacerbate hyponatremia, whereas in volume depletion, hyponatremia may correct too rapidly.

Identifying a specific cause for SIADH  SIADH is a mechanism for developing hyponatremia, not a diagnosis. In all patients with SIADH, a specific etiology for inappropriate vasopressin secretion should be sought. When hyponatremia develops during hospitalization, the cause is sometimes obvious (e.g., pneumonia, meningitis, or acute respiratory failure) and no further testing is indicated. In a patient with clinical features of SIADH but no obvious cause for it, a more extensive evaluation is indicated. The workup should include a careful search for malignancy and central nervous system pathology and an endocrine evaluation to exclude hypothyroidism and hypopituitarism. Sometimes, no cause for SIADH is found, especially in elderly patients and patients with psychiatric disorders, mental retardation, or alcoholism. Careful follow-up is important, because malignancies may become clinically apparent after several years in so-called idiopathic SIADH.

Treatment

Patients with very low plasma sodium concentrations usually have some neurologic symptoms, and they are at risk of sustaining injuries from falls. However, unlike acute water intoxication, chronic hyponatremia poses little risk of an explosive onset of seizures or a fatal outcome, provided that water is withheld and the plasma sodium concentration is not allowed to fall any further. On the other hand, patients with chronic hyponatremia are at considerable risk for neurologic injury caused by overaggressive correction. Thus, there are four major goals in managing chronic hyponatremia: (1) prevention of a progressive decrease in plasma sodium concentration; (2) amelioration of hyponatremic symptoms by promptly but carefully increasing the plasma sodium concentration; (3) avoidance of excessive correction; and (4) gradual restoration and maintenance of a normal plasma sodium concentration.

Free-water restriction should be instituted in all patients until the plasma sodium concentration has begun to increase. Intravenous fluids should be at least isotonic, and oral fluid intake should be limited to 500 to 1,000 ml/day, depending on the severity of the electrolyte disturbance. In patients with reversible defects in water excretion, limitations on free-water intake should be lifted once the plasma sodium concentration has begun to increase.

Attempts to calculate the dose of sodium chloride needed to correct hyponatremia are doomed to failure. The increase in plasma sodium concentration depends on the amounts of administered sodium and potassium that the body retains, as well as on the amount of electrolyte-free water that is eliminated in the urine. Indeed, in some cases, the plasma sodium concentration will return to normal solely because of a water diuresis, with no sodium given.

The measures required to increase the plasma sodium concentration, along with the likelihood of inadvertent rapid correction, vary depending on the cause of hyponatremia. For therapeutic purposes, the causes can be divided into reversible and persistent defects in water excretion.

Reversible defects in water excretion  Hyponatremia corrects easily when the cause of defective water excretion can be eliminated by volume expansion, by withdrawal of a therapeutic agent, or by treatment of an underlying illness [see Table 4]. In patients with reversible defects in water excretion, avoiding excessive correction may become a major challenge.

Hyponatremia results readily to 0.9% sodium chloride because the sodium concentration of isotonic saline is higher than the cation concentration of the excreted urine. Once the volume deficit is repaired and the hemodynamic stimulus to vasopressin secretion is removed, the urine becomes dilute and a water diuresis may rapidly return the plasma sodium concentration to normal. Similarly, patients with diuretic-induced hyponatremia are extremely susceptible to rapid correction; restoration of the renal diluting mechanism when the diuretic is discontinued and replacement of sodium and potassium deficits contribute to the increase in plasma sodium concentration.

Intravenous saline should be discontinued once clinically apparent hypovolemia has been corrected and the plasma sodium concentration has begun to increase. Saline should be given cautiously, if at all, to hypokalemic patients who require potassium replacement. During repair of a potassium deficit, potassium enters cells, displacing sodium, which then returns to the extracellular fluid; administered potassium is therefore as effective as sodium in raising the plasma sodium concentration. Diuretic-induced hyponatremia does not usually necessitate use of intravenous saline; for most patients, an adequate diet, replacement of potassium deficits, and discontinuance of thiazide diuretics are sufficient. In severely hyponatremic patients, the plasma sodium concentration should be monitored every 6 to 8 hours for the first 2 to 3 days of therapy. If it appears that a water diuresis is going to increase the plasma sodium by more than the desired amount, replacement of fluid losses with oral water or D5W may become necessary.

Persistent defects in water excretion: SIADH  Patients with SIADH tend to be resistant to rapid changes in plasma sodium concentration (unless the cause of SIADH is short-lived). Water restriction is the cornerstone of therapy, but if used alone, water restriction often leads to an extremely slow resolution of hyponatremia. Isotonic saline is ineffective and may even be counterproductive. Furosemide and other loop diuretics are often useful therapeutic adjuncts because by blocking sodium reabsorption in the ascending limb of the loop of Henle, they interfere with the renal-concentrating mechanism, partially blocking the effect of vasopressin. Loop diuretics can be combined with oral salt or a slow infusion (approximately 15 ml/hr) of 3% saline. Oral and intravenous urea have been used extensively to treat SIADH in some parts of Europe, but experience with this agent in the United States is very limited. Demecevycin, a tetracycline that blocks the effect of vasopressin on the collecting duct, is another therapeutic option in chronic SIADH; however, its expense and long duration of action limit its effectiveness. Several orally active vasopressin receptor blockers have been developed and are currently in clinical trials.

Persistent defects in water excretion: edematous conditions and renal failure  Saline should rarely, if ever, be given to correct hyponatremia in edematous patients or patients with renal failure (except for those with prerenal azotemia). Because it has no effect on water excretion, 1 L of 0.9% saline will increase the plasma sodium concentration by only 1 mEq/L. In addition,
saline exacerbates edema and ascites in patients with cirrhosis and may cause pulmonary edema in patients with heart failure or renal failure.

Although thiazide diuretics are contraindicated, loop diuretics are the mainstay of treatment of hyponatremia for patients with edematous conditions because they increase free-water excretion and improve hyponatremia, particularly when dietary salt intake is increased. There is a natural inclination to discontinue loop diuretics when severely edematous patients develop hyponatremia. The usual problem, however, is oliguria and diuretic resistance rather than overdiuresis; the proper response is to increase the dose of loop diuretics and restrict water intake. The combination of a loop diuretic and an angiotensin-convert-
ing enzyme (ACE) inhibitor is particularly effective in patients with heart failure. The beneficial effect of an ACE inhibitor can be explained by reduced thirst and vasopressin secretion attributable to angiotensin II and by a direct effect on the hydro-osmotic effect of vasopressin, mediated by prostaglandins.11

Hyponatremia in edematous conditions is mediated by vasopressin. Clinical trials have shown that vasopressin receptor antagonists can be effective in managing patients with hypona-
tremia and edema.46,47

Treatment of hyponatremic seizures A small percentage of chronically hyponatremic patients with very low plasma sodium concentrations present with seizures. Regardless of the suspected duration or cause of the electrolyte disturbance, active seizures may be resistant to anticonvulsants alone and should be treated with hypertonic saline. The therapeutic approach is similar to that used for patients with acute water intoxication, except that even more vigilance is required to prevent an excessive increase in plasma sodium concentration once emergency measures have been discontinued.12

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Complications of Therapy: Myelinolysis and Osmotic Demyelination Syndrome

Excessive correction of chronic hyponatremia may be complicated by neurologic injury.10,46 Typically, the patient’s hyponatremic symptoms improve as the plasma sodium concentration increases, but after a delay of one to several days, new findings emerge. The patient may become confused and may exhibit psychotic or catatonic behavior, pathologic crying, or a movement disorder. Swallowing dysfunction, progressive unresponsiveness, and a spastic quadripareisis may develop. In severe cases, locked-in syndrome occurs—that is, the patient is awake but unable to move or respond. The stereotypical pattern of delayed neurologic deterioration after rapid correction of hyponatremia has been named the osmotic demyelination syndrome, because these clinical features are associated with brain lesions (myelinolysis) characterized by disruption of myelin and sparing of neurons and axons.46,49 Lesions, which are best identified by magnetic resonance imaging, are typically found in the center of the basal pons (central pontine myelinolysis), but histologically similar lesions may also occur in a symmetrical distribution in extrapontine areas of the brain where there is a close admixture of gray and white matter. The osmotic demyelination syndrome has been reproduced in animal studies; these experiments have shown that the disorder is a complication of rapid correction of hyponatremia rather than the electrolyte disturbance itself. Observational studies in severely hyponatremic patients suggest that this therapeutic complication can be avoided if correction rates are maintained below 10 to 12 mEq/L/day and 18 mEq/L/48 hr. It should be emphasized that these values are limits and not goals. Because large increases in the serum sodium concentration are seldom required to relieve hyponatremic symptoms and because unintentional excessive correction is common, the goal of therapy should be to increase serum sodium concentration by 8 mEq/L/day or less.12

Disorder of Water Deficiency: Hypernatremia

PATHOGENESIS

Persistent hypernatremia results from one of two basic mechanisms: water is lost and not adequately replaced or, less commonly, too much salt is taken in without enough water [see Table 6].13,51-53 In either case, electrolyte-free water is needed to return the plasma sodium concentration to normal. Because thirst is the primary defense against hypertonicity, persistent hypernatremia indicates a defect in water intake. A maximally concentrated urine minimizes but does not prevent water losses. Insensible water losses from the skin and lungs are unavoidable, and urea excretion obligates some urinary losses. Maintenance of a normal serum sodium concentration (135 to 142 mEq/L) requires that daily water losses be replaced.

Most hyponatremic patients are too sick, too young, or too old to obtain water themselves or ask for it.13,53 Sometimes, the thirst sensation itself is impaired, so that the patient has no desire to drink when the plasma sodium concentration increases above the normal range. Inadequate water intake by itself will lead to hypernatremia. When impaired intake is coupled with excessive water losses, severe hypernatremia results.

ETIOLOGY

Electrolyte-free water can be lost as pure water, with no accompanying electrolyte, or it can be lost in hypotonic fluids,
which have lower electrolyte concentrations than plasma. Hypotonic losses can be thought of as mixtures of isotonic fluid and free water. Pure-water and hypotonic fluid losses, the most common causes of hypernatremia, are typically associated with a contracted extracellular fluid volume. However, this is not always the case. When hypernatremia is caused by a rapid intake of salt (acute salt poisoning), the extracellular volume expands because of water drawn from the intracellular space. In critically ill patients, extracellular volume expansion with edema often coexists with hypernatremia; the finding reflects free-water losses in patients who become edematous after fluid resuscitation for shock or underlying conditions such as congestive heart failure, renal disease, and hepatic cirrhosis.

**Pure-Water Losses**

When pure-water losses are responsible for hypernatremia, each body-fluid compartment loses an equal percentage of its volume. Plasma constitutes only one twelfth of total body water (one quarter of extracellular fluid volume), and plasma volume is defended by oncotic pressure, which increases with water loss. Thus, plasma volume contracts by less than 83 ml for each 1 L of water lost; clinical signs of hypovolemia are unusual unless the water deficit is extremely large.

**Insensible water losses** Water is constantly lost by evaporation from the skin and lungs and must be replaced to avoid dehydration. Daily insensible water losses, normally about 0.5 L, can be increased severalfold by high environmental temperature, fever, or hypermetabolic states such as thyrotoxicosis.

**Increased urea excretion** Although urea is an ineffective osmole that freely crosses most cell membranes, urinary urea excretion can play an important role in water balance. High rates of urea excretion caused by very high protein diets, catabolism, or recovery from renal failure oblige increased rates of water loss. When the urine solute is composed almost exclusively of urea, the urine becomes an electrolyte-free water solution, regardless of its osmolality.

**Diabetes insipidus** Because sodium excretion is unaffected in diabetes insipidus (see below), the excess fluid lost in the urine is pure water. As long as water is available and the patient is able to drink, hypernatremia does not occur. Without water replacement, however, hypernatremia develops within a few hours.

**Hypotonic Losses**

Hypernatremia caused by hypotonic fluid loss is associated with extracellular volume depletion.

**Sweat** Sweat is a hypotonic solution containing water, sodium, potassium, and chloride. Sweat glands respond to aldosterone by lowering the sodium concentration and increasing the potassium concentration of their secretions.

**Gastric fluid losses** Fluid lost by vomiting or nasogastric suction is hypotonic to plasma. Without adequate water replacement, large gastric fluid losses can cause hypernatremia.

**Osmotic cathartics** Fecal losses of water contain electrolytes at a concentration comparable to that of plasma, except when osmotic cathartics such as sorbitol or lactulose are given. These cathartic agents osmotically attract electrolyte-free water to the intestinal lumen, leading to hypotonic fluid losses. Oral sorbitol is a nonabsorbable solute, given with sodium polystyrene sulfonate (Kayexalate) to treat hyperkalemia or with charcoal to treat poisoning; the sorbitol osmotically attracts electrolyte-free water into the intestinal lumen, where it is eliminated in the stool. Similarly, lactulose, which is used to treat hepatic encephalopathy, can promote large electrolyte-free water losses, causing a high incidence of hypernatremia unless the lost water is replaced.

**Osmotic diuretics and glycosuria** Glucose in the extracellular fluid acts as an effective osmole that attracts water to the extracellular fluid, dehydrating cells and lowering the plasma sodium concentration. Excretion of glucose in the urine acts as an osmotic diuretic that can provoke the loss of several liters of hypotonic fluid. Electrolyte-free water losses induced by glycosuria raise the plasma sodium concentration, offsetting the hypernatremic effect of the high blood glucose levels. Intravenous hypertonic mannitol has a similar effect on body fluids.

**Acute Salt Poisoning**

Water losses increase the serum sodium concentration over hours or days. The oral ingestion of large amounts of salt without water—1 tbsp of salt contains nearly 350 mEq of NaCl, enough to increase the plasma sodium concentration by 8 mEq/L—or the intravenous infusion of hypertonic salt solutions can increase the plasma sodium concentration much more rapidly (i.e., cause acute salt poisoning).

**DIAGNOSIS**

**Clinical Manifestations**

An acute onset of hypernatremia (seen almost exclusively in acute salt poisoning) causes the brain to shrink, leading to vascular injury and intracranial bleeding. Patients present with seizures, coma, hyperventilation, hyperreflexia, hypertonia, and high fever. Acutely hypernatremic patients with plasma sodium levels above 170 mEq/L often die.

Given time to adapt, brain cells protect their volume by accumulating organic osmoles, preventing the hemorrhages caused by acute hypernatremia. Thus, the clinical manifestations of chronic hypernatremia are less dramatic than those seen in acute salt poisoning, ranging from lethargy to coma, depending on the severity of the electrolyte disturbance.

The clinical signs of pure-water loss and acute salt poisoning are primarily neurologic. Hypotonic fluid losses may be associated with signs and symptoms of extracellular fluid volume depletion in addition to symptoms related to hypernatremia.

**Recognition of Water Deficit**

The plasma or serum sodium concentration can be used to determine how much water is needed to restore normotonicity; it seriously underestimates the magnitude of the water deficit in diabetic patients with hyperglycemic dehydration [see Diabetic Dehydration, below]. In patients without severe hyperglycemia, the percentage increase in the serum sodium concentration approximates the percentage decrease in total body water, as stated more precisely in the following equation:

\[
\text{Water deficit} = \text{normal body water (1 - serum [Na⁺]/140)}
\]

The value for body water is based on the patient’s usual body weight (often an estimate), age, and sex.
The calculated water deficit is the amount of water that will return the serum sodium concentration to normal. It reveals nothing about the volume status of the extracellular fluid. Extracellular fluid volume deficits (or surfeits) must be estimated from the history and physical examination, not from the serum sodium concentration.

TREATMENT

Correction of severe extracellular volume depletion takes precedence over correction of hypervolemia. When the patient is hypotensive, initial therapy should include a rapid infusion of isotonic saline to quickly achieve hemodynamic stability. In hemodynamically stable patients, pure-water losses should be replaced with pure water, and isotonic saline is not required. Edematous patients with hypervolemia can be given diuretics along with electrolyte-free water to replace urinary electrolyte-free water losses; the net effect is reduction of the extracellular volume surfeit and restoration of normotonicity and cell volume.

Electrolyte-free water can be given intravenously as D5W to patients who are unable to drink. Dextrose solutions cannot be infused more rapidly than approximately 500 ml/hr. Faster infusions provide more glucose than can be metabolized and therefore cause hyperglycemia, glycosuria, and urinary water losses, which are counterproductive to the correction of hypertonicity. Water replacement should not be based on formulas alone; the serum sodium concentration and urine output should be monitored frequently so that the fluid prescription can be adjusted appropriately.

Rate of Correction

In the vast majority of cases, the onset of hypertonicity is slow enough for brain adaptations to minimize cerebral dehydration. Organic osmolytes that accumulate in the adaptation to hypernatremia are slow to leave the cell during rehydration. If hypernatremia is corrected too rapidly, cerebral edema results. To be safe, the serum sodium concentration should be reduced by no more than 10 to 12 mEq/L/day. To achieve the desired rate of correction, electrolyte-free water intake should exceed free-water losses by no more than 2 L daily.

Acute salt poisoning causes devastating brain injury that is largely irreversible. In rare cases when acute salt poisoning can be rapidly diagnosed (e.g., in a case of inadvertent intravenous infusion of hypertonic saline during therapeutic abortion), an effort to prevent a neurologic catastrophe can be made with rapid infusions of electrolyte-free water along with a loop diuretic before the results of the serum electrolyte measurements are known.

Diabetic Dehydration

Hypertonicity associated with diabetes mellitus is a complex disorder. The osmotic diuresis induced by glycosuria results in both saltwater and electrolyte-free water losses; the accumulation of glucose in the extracellular fluid adds impermeant solute, which contributes to hypertonicity and neurologic symptoms. Severely dehydrated hyperglycemic patients may not appear hypovolemic at first, because the high glucose concentration in the extracellular fluid osmotically attracts water from cells, masking the loss of saltwater. With correction of hyperglycemia, marked hypovolemia may emerge. Initial treatment should include 1 to 2 L of isotonic saline in anticipation of this complication, even in patients who are initially normotensive. With volume expansion, excess glucose will be excreted in the urine, creating an ongoing requirement for both saline and electrolyte-free water. An infusion of 0.45% saline at a rate that exceeds urine output will serve to replace the electrolyte-free water deficit and remaining saltwater deficits. The serum sodium concentration, blood glucose level, and urine output should be monitored carefully so that fluid replacement can be tailored to the patient’s needs.

Rapid correction of hypertonicity should be avoided in severely hyperglycemic patients because of the risk of cerebral edema. This problem is of particular concern in young children with diabetic ketoacidosis. For this reason, in young patients, the serum sodium concentration should be allowed to increase as the blood glucose level falls (i.e., 0.5 mmol/L increase in serum sodium for every 18 mg/dl decrease in plasma glucose), maintaining a near-constant effective osmolality, especially in the first 12 to 16 hours. In children, hypotonic fluids should probably be avoided during the first day of therapy.

Patients with oliguric renal failure do not become dehydrated when they become severely hyperglycemic. Such patients often experience hypertension or congestive heart failure because of fluid shifts from cells to the extracellular fluid. Even after adjusting for the effect of hyperglycemia, the serum sodium concentration is often low. Insulin is the only required treatment; neither isotonic saline nor 0.45% saline is indicated.

Disorder of Water Conservation: Diabetes Insipidus

PATHOGENESIS

Diabetes insipidus (DI) may be neurogenic or nephrogenic. Neurogenic DI is caused by deficient secretion of vasopressin; nephrogenic DI results from the kidney’s unresponsiveness to normally secreted hormone. In both disorders, patients present with polyuria (loosely defined as the passage of excessive volumes of urine—generally more than 3 to 4 L daily) and polydipsia (excessive thirst). Most patients with polyuria do not become hypernatremic, because thirst maintains electrolyte-free water balance. The causes and treatment of neurogenic, or central, DI are discussed elsewhere. Defective responsiveness to vasopressin (nephrogenic DI) may be inherited as an X-linked trait, caused by a mutation in the gene encoding the V2 vasopressin receptor, or as an autosomal recessive trait caused by a mutation in the gene encoding the vasopressin-responsive water channel (aquaporin 2). Acquired nephrogenic DI may be caused by lithium or demeclocycline therapy, hypokalemia, or hypercalcemia; or it may complicate a number of renal diseases. Vasopressin-resistant DI may emerge during the late stage of pregnancy as a result of vasopressinase released by the placenta; many affected patients have underlying, subclinical partial neurogenic or nephrogenic DI that has been exacerbated by increased catabolism of circulating vasopressin.

DIAGNOSIS

Clinical Manifestations

Patients with DI complain of polyuria, nocturia (the need to urinate during the night), and polydipsia. The only significant physical findings or laboratory abnormalities are those of the underlying cause.

Laboratory Tests

A diagnosis of DI can be made if the urine osmolality is less
Pathogenesis

Excess fluid collects in the interstitial space in response to Starling forces, which govern the movement of extracellular fluid into and out of the vasculature. Edema occurs when there is increased capillary blood pressure, decreased plasma oncotic pressure, increased capillary permeability to protein, or obstruction to lymph flow.

Disorder of Saltwater Excess: Edematous States

Edema, a swelling of the soft tissues that can be indented or pitted by the examiner’s fingers, is the clinical manifestation of an expanded interstitial fluid volume. To be detected clinically, interstitial volume must increase by at least 2.5 to 3 L, nearly equaling the total amount of fluid in the intravascular space. Thus, generalized edema requires an increase in the total amount of saltwater in the extracellular space, and it implies retention of dietary or infused sodium, with an impaired ability to excrete saltwater.

Etiology

**Primary Renal Sodium Retention: Edema Caused by Renal Disease**

**Nephrotic syndrome** The nephrotic syndrome is characterized by heavy urinary protein losses (in excess of 3 g/day), hypoalbuminemia, and edema. The syndrome, which can be seen in a variety of glomerular diseases, is caused by increased permeability of the glomerular capillary to protein. Traditionally, edema in the nephrotic syndrome has been ascribed to decreased plasma oncotic pressure. This no longer appears to be the sole explanation. Correction of hypoalbuminemia by infusing albumin does not consistently improve the edema, and in steroid-responsive cases, edema may resolve before hypoalbuminemia improves. Thus, in most patients, primary sodium retention by the kidney, independent of an underfilled vasculature, plays a major contributing role.

**Nephritic edema** Glomerular diseases characterized by proliferation of mesangial cells (e.g., diffuse proliferative glomerulonephritis and membranoproliferative glomerulonephritis) often cause primary sodium retention that is not associated with heavy proteinuria or hypoalbuminemia (the nephritic syndrome). Patients with nephritic edema are typically hypertensive and may present with congestive heart failure because of an overexpanded vascular volume.

**Secondary Renal Sodium Retention: Edema Caused by Extrarenal Disease**

In congestive heart failure and hepatic cirrhosis, the body responds as if it were volume depleted. Despite an expanded interstitial fluid volume, as well as increased total body sodium content, the kidney avidly retains salt and water. The normal renal response to a high salt intake is lost, and progressive salt retention occurs. In these conditions, volume-regulatory mechanisms are responding to reduced fullness of the arterial portion of the vascular system, which normally contains about 15% of the total blood volume.

**Congestive heart failure** Advanced stages of the many disorders that affect the pericardium, myocardium, or heart valves can produce congestive heart failure, a disorder characterized by renal sodium retention and interstitial edema in systemic or pulmonary capillary beds. Arterial receptors are activated when cardiac output falls (low-output heart failure) or when cardiac output is not high enough to compensate for decreased peripheral resistance (high-output failure).

**Cirrhosis** Patients with severe liver disease may exhibit profound salt retention, often excreting less than 10 mEq of sodium in the urine each day. Scarring of the hepatic parenchyma increases resistance to blood flow in the post sinusoidal venules, resulting in high sinusoidal pressures and venous hypertension throughout the portal system. Portal hypertension and hypalbuminemia promote the formation of ascites. In addition, cirrho-
Idiopathic edema  Idiopathic edema is a benign disorder of young, menstruating women who have no cardiac, hepatic, or renal disease. Fluid retention often begins premenstrually and then becomes persistent. Depression and neurotic symptoms are commonly present, and affected patients are often weight conscious and markedly concerned about even minor degrees of edema. Some patients episodically fast for days at a time and then accumulate edema on refeeding. In many others, diuretics play an important role in the pathogenesis of idiopathic edema. Long-term diuretic or cathartic use leads to persistent hypovolemia and chronic activation of sodium-retaining mechanisms, which include hypertrophy of the nephron segments distal to the site of action of the diuretic. When the diuretic is stopped, marked sodium retention occurs because the sodium-retaining forces cannot be shut off rapidly. The patient thus becomes convinced of the need for diuretics, and the cycle continues.

Diagnosis

The symptoms and laboratory findings associated with edematous conditions depend on the underlying cause. Dyspnea on exertion and orthopnea provoked by pulmonary interstitial edema are prominent features in patients with left ventricular failure or nephritic edema, but these symptoms are usually absent when edema is caused by right heart failure, nephrotic syndrome, or cirrhosis. Mild peripheral edema develops in the dependent portions of the anatomy and is usually asymptomatic. Although more severe edema, which can extend to the thighs and buttocks, may be uncomfortable, it is usually harmless. A large volume of ascites not only causes discomfort but also may elevate the diaphragm, causing shortness of breath; may promote reflux of gastric fluid, causing bleeding from esophageal varices; or may become infected spontaneously.

The diagnosis of edema should be approached systematically; the physician should look for evidence of heart, renal, or liver disease. A diagnosis can usually be made from the history and physical examination, urinalysis, liver function tests, and chest x-ray. More puzzling cases may require echocardiography or, rarely, right heart catheterization. Plasma levels of B-type natriuretic peptide (BNP) are increased in patients with heart failure. Used in conjunction with other clinical information, rapid-measurement BNP is useful in establishing or excluding the diagnosis of congestive heart failure in patients who present with acute dyspnea.

Treatment

Dietary salt restriction is important for patients with edema, but this measure alone is impractical or insufficient when urinary sodium excretion is reduced to very low levels. Thus, most edematous patients whose underlying condition cannot be reversed require treatment with diuretics. Salt restriction and diuretics are adjunctive treatments for heart failure. Therapy is also directed at improving cardiac performance by using digoxin and vasodilators to reduce afterload. Recombinant human BNP (nesiritide) has become available for the treatment of acute decompensated heart failure. The agent reduces pulmonary capillary wedge pressure and systemic vascular resistance, improves cardiac performance, and has a diuretic effect, in part because of its effect on sodium reabsorption in the distal nephron.

Ascitic fluid is a separate compartment of the extracellular fluid compartment that is much more difficult to mobilize than peripheral edema. Thus, cirrhotic patients who have ascites but no peripheral edema are susceptible to intravascular volume depletion when they are treated with diuretics; weight loss should thus be limited to 0.5 kg daily. Repeated large-volume paracenteses combined with intravenous albumin is a safe and effective alternative to diuretics that avoids intravascular volume depletion. The subsequent administration of diuretics prevents accumulation of ascitic fluid.

Use of Diuretics

Diuretics increase saltwater excretion by impairing tubular reabsorption of the sodium filtered by the glomerulus. The diuretic effect is dose-dependent; the maximum response is determined by the diuretic's site of action within the nephron, the filtered load of sodium, and the amount of sodium reabsorbed by nephron segments unaffected by the diuretic.

Mechanism of action  All diuretics except spironolactone are specific inhibitors of luminal transporters and must gain access to the tubular fluid to block sodium reabsorption. Because diuretic agents are highly protein bound, they are not readily filtered at the glomerulus; instead, they are actively transported into the urine by the organic acid (in the case of agents such as acetazolamide, thiazides, and loop diuretics) or organic base (in the case of agents such as amiloride and triamterene) via secretory pumps in the proximal tubule. A dose-response curve links the amount of drug reaching the urine to the amount of sodium excretion that is elicited [see Figure 4]. Spironolactone binds to the cytosolic receptor for aldosterone, and its diuretic action, unlike that of other diuretics, does not depend on secretion into the tubular lumen.

The most potent agents are those that block sodium transport in the loop of Henle. At high doses, loop diuretics almost totally block sodium reabsorption in this nephron segment, causing about 20% of the filtered load of sodium to be excreted in the urine; at low glomerular filtration rates, the same percentage of filtered sodium is excreted, but the total amount is reduced. Conditions such as volume depletion, heart failure, and cirrhosis, which cause avid sodium reabsorption in the proximal and distal tubules, blunt the maximum response to the diuretic. Because gastrointestinal absorption of diuretics is often delayed in edematous conditions (presumably because of bowel edema), higher oral doses must be used to achieve adequate blood levels. In renal disease and cirrhosis, organic anions such as hippurate and bile acids compete with the diuretic for secretion into the proximal tubule; thus, higher plasma levels may be required to achieve adequate drug levels in the urine. Similarly, severe hypoalbuminemia can diminish drug secretion into the tubular lumen, because albumin binding of most diuretics maximizes the rate of diuretic delivery to the organic anion secretory pump in the proximal tubule. Reduced renal blood flow also limits delivery of drug to the tubular lumen. Some patients with advanced cirrhosis who are resistant to furosemide respond to spironolactone, a generally weak diuretic whose effectiveness does not depend on tubular secretion.

Agents that act in the proximal tubule, loop of Henle, or distal tubule cause potassium wasting and hypokalemia because they...
increase delivery of tubular fluid to the cortical collecting tubule, where potassium secretion is flow dependent. Potassium-sparing diuretics, which act in the cortical collecting tubule, cause hyperkalemia because sodium reabsorption at this site favors potassium secretion. The carbonic anhydrase inhibitor acetazolamide causes metabolic acidosis, as do the potassium-sparing diuretics. Thiazides and loop diuretics cause metabolic alkalosis because of increased distal delivery of sodium to sites where sodium reabsorption stimulates hydrogen ion secretion.

**Clinical strategies** Diuretic doses should be adjusted to achieve explicit therapeutic goals. Outpatient therapy is usually designed to produce a gradual loss of fluid, with the dose being increased until a desired target weight is reached. The patient should be instructed to keep a daily log that records weight and diuretic dose. Patients are instructed to stop the diuretic if their weight falls too low, resuming at a lower dose when enough saltwater has been retained to restore the target weight.

Inpatient diuretic management should also employ the target-weight concept, but dose adjustments can be made more often and more aggressively, particularly at the start of therapy. It is important to rapidly define the dose that can deliver enough drug to the tubular lumen to reach the steep portion of the dose-response curve. Once an effective dose is defined, larger doses of diuretic provide little benefit. If a greater response is needed, the effective dose should be repeated several times during the day, or alternatively, a continuous infusion can be given to maintain effective urinary drug levels. Continuous infusion of loop diuretics induces a slightly larger natriuretic response than does bolus administration and is associated with a shorter hospital stay in patients with advanced heart failure.

**Diuretic resistance** Resistance to high doses of loop diuretics may be overcome by administering loop diuretics in combination with a thiazide or metolazone. Acetazolamide may be used along with or in place of a thiazide or metolazone. This strategy blocks sodium reabsorption at several sites along the nephron, avoiding resistance caused by increased sodium reabsorption proximal or distal to the loop of Henle. Careful monitoring is extremely important, because these combinations can be extremely potent, causing large potassium and sodium losses.

**Diuretic complications** All diuretic agents may cause volume depletion and azotemia, but these complications are most likely to occur with loop diuretics. Hypokalemic alkalosis, hyperglycemia, and hyperuricemia (sometimes with clinical gout) are common dose-dependent complications of both thiazides and loop diuretics. Thiazides decrease calcium excretion and may cause hypercalcemia in patients with underlying conditions that increase gastrointestinal calcium absorption (e.g., sarcoidosis) or bone reabsorption (e.g., hyperparathyroidism). Thiazides are also much more likely to cause hyponatremia than other agents and should be avoided in patients who habitually drink large amounts of fluid. Potassium-sparing agents (e.g., triamterene, amiloride, and spironolactone) may cause hyperkalemia; these agents should generally not be given with potassium supplements, and they should be used with caution in patients with renal insufficiency (particularly diabetic nephropathy) and patients taking ACE inhibitors or angiotensin receptor blockers. Loop diuretics can predispose to hearing loss, particularly when high doses are administered by bolus injection to patients receiving other ototoxic drugs. Hearing loss from ethacrynic acid is more likely to be permanent.

**Disorder of Saltwater Deficiency: Volume Depletion**

**PATHOGENESIS**

Volume depletion occurs when saltwater is lost from the extracellular fluid at a rate that exceeds intake. Saltwater can be lost from the gastrointestinal tract, kidney, or skin, or it can result from extravascular sequestration (third-space losses) in the abdominal cavity or in traumatized tissues.

Underfilling of the arterial circulation triggers a cascade of physiologic responses that preserve blood flow to vital organs. Volume receptors and baroreceptors activate the sympathetic nervous system and the renin-angiotensin-aldosterone system. Except when renal salt wasting is the cause, these responses reduce urinary sodium excretion so that nearly all ingested salt is retained. Volume-depleted persons also become thirsty; ingested water is retained because vasopressin, released in response to volume depletion, concentrates the urine, decreasing water excretion. The plasma sodium concentration can be high, normal, or low in volume-depleted persons, depending on electrolyte-free water intake and excretion. Vasocostriction maintains the systemic blood pressure and also reduces renal blood flow. Initially, efferent arteriolar resistance, mediated by angiotensin II, predominates, sustaining intraglomerular pressure and the
glomerular filtration rate; in more severe hypovolemia, renal blood flow is further reduced and glomerular filtration falls.

**Etiology**

Because renal sodium conservation can reduce urinary sodium losses to less than 10 mmol/day, volume depletion is unlikely to occur from decreased intake alone. The small bowel and colon are the most common sources of isotonic fluid loss. Spectacular amounts of isotonic saltwater can be lost in diarrhea. For example, rice-water stool losses in cholera can reach 20 L/day, causing death within a few hours without fluid replacement. Small bowel obstruction causes pooling of several liters of saltwater within the bowel lumen. Fluid may also be sequestered in the abdominal cavity in patients with pancreatitis or peritonitis. Sequestration of fluid in the soft tissues may also complicate crush injuries with rhabdomyolysis or burns.

Renal salt wasting can cause volume depletion, but only a few disorders can cause enough renal salt loss to be clinically apparent. Diuretics and osmotic diuresis caused by glycosuria are the most frequent causes of renal salt wasting. Transient renal salt wasting may occur in the recovery phases of acute tubular necrosis or obstructive uropathy, and it can also occur in toxic nephropathies. Renal salt wasting also occurs in adrenal insufficiency.

**Diagnosis**

**Clinical Manifestations**

Minor degrees of volume depletion (less than 10% of plasma volume, equivalent to the loss of one unit of blood) cause an increase in heart rate and may also be associated with complaints of fatigue, thirst, or muscle cramps. With modest hypovolemia, arteriolar vasoconstriction is sufficient to maintain the blood pressure when the patient is recumbent. However, dizziness and hypotension emerge on standing or during physical exertion. Severe fluid losses cause hypotension in recumbency and, ultimately, signs of tissue ischemia and shock (e.g., cool, clammy extremities, decreased urine output, lethargy, and confusion). Irreversible tissue injury may occur if this condition is allowed to continue.

Loss of weight within a short period is the most reliable sign of volume depletion. Physical findings include a low jugular venous pulse rate and orthostatic changes in blood pressure and heart rate. However, because postural hypotension can occur in up to 30% of normovolemic persons older than 65 years, these changes must be interpreted with caution. Decreased skin turgor and dry mucous membranes are generally unreliable findings in volume-depleted adults; these signs can be absent in severe hypovolemia, and they can be present (particularly in mouth breathers and the elderly) when the patient is actually volume overloaded. The presence of edema makes true volume depletion unlikely.

**Laboratory Tests**

Laboratory findings are related to the decreased volume of intravascular saltwater and to decreased renal perfusion. The hemocrit increases in proportion to the contraction of plasma volume, and the serum albumin may be increased as well. Urinary sodium is usually less than 20 mEq/L except in metabolic alkalosis (in which the urine chloride is low) or when renal sodium wasting is the cause of the condition. Renal blood flow is reduced, but unless the patient is frankly hypotensive, the glomerular filtration rate is maintained by vasoconstriction of the efferent glomerular arteriole. Thus, except in severe volume depletion, the serum creatinine changes very little. Unlike creatinine, urea is reabsorbed from the glomerular filtrate. Thus, in volume depletion (prerenal azotemia), the BUN is increased disproportionately to the increase in creatinine. Azotemia may be blunted in patients with a poor dietary-protein intake and may be exacerbated in patients who are catabolic, bleeding, or receiving steroid therapy.

**Treatment**

Patients with mild volume depletion can be treated by increasing their dietary intake of salt, relying on normal thirst mechanisms to provide the appropriate amount of water. For most patients, the familiar (but misguided) order to drink fluids should be replaced with an order to salt one’s food. Even severe volume depletion can be treated with oral solutions containing electrolytes, sugar, and amino acids. Glucose and amino acids promote intestinal absorption of sodium through cotransport mechanisms similar to those found in the proximal tubule of the kidney. Rice-based oral replacement solutions have been a major advance in the treatment of diarrhea in developing countries. Intravenous fluids are necessary when fluids cannot be taken orally. If the patient is hypotensive, isotonic saline should be given as rapidly as possible until tissue perfusion is adequate. Colloid-containing solutions have no proven advantage over crystallloids. There is no accurate way to estimate the total fluid deficit in hypovolemia other than continued clinical observation of the patient’s response to therapy.

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The author has no commercial relationships with manufacturers of products or providers of services discussed in this chapter.

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