Diseases of Water Metabolism

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The maintenance of the tonicity of body fluids within a very narrow physiologic range is made possible by homeostatic mechanisms that control the intake and excretion of water. Critical to this process are the osmoreceptors in the hypothalamus that control the secretion of antidiuretic hormone (ADH) in response to changes in tonicity. In turn, ADH governs the excretion of water by its end-organ effect on the various segments of the renal collecting system. The unique anatomic and physiologic arrangement of the nephrons brings about either urinary concentration or dilution, depending on prevailing physiologic needs. In the first section of this chapter, the physiology of urine formation and water balance is described.

The kidney plays a pivotal role in the maintenance of normal water homeostasis, as it conserves water in states of water deprivation, and excretes water in states of water excess. When water homeostasis is deranged, alterations in serum sodium ensue. Disorders of urine dilution cause hyponatremia. The pathogenesis, causes, and management strategies are described in the second part of this chapter.

When any of the components of the urinary concentration mechanism is disrupted, hypernatremia may ensue, which is universally characterized by a hyperosmolar state. In the third section of this chapter, the pathogenesis, causes, and clinical settings for hypernatremia and management strategies are described.

CHAPTER 1

Physiology of the Renal Diluting and Concentrating Mechanisms

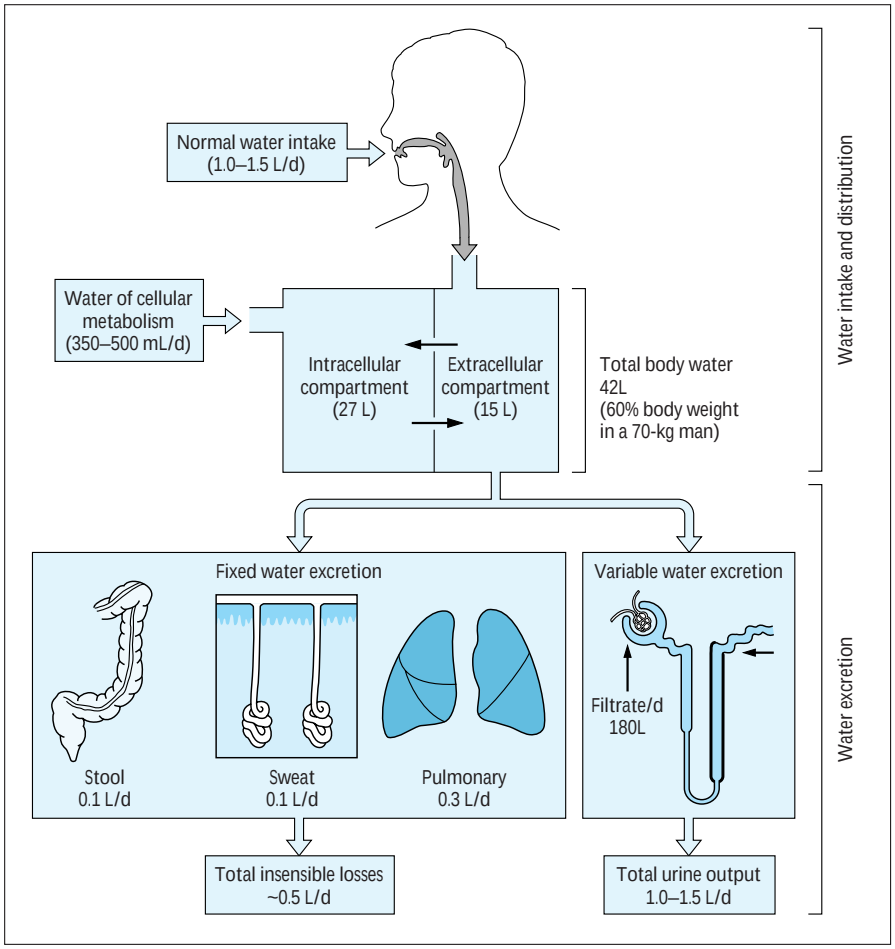


FIGURE 1-1

Principles of normal water balance. In most steady-state situations, human water intake matches water losses through all sources. Water intake is determined by thirst (*see* Fig. 1-12) and by cultural and social behaviors. Water intake is finely balanced by the need to maintain physiologic serum osmolality between 285 to 290 mOsm/kg. Both water that is drunk and that is generated through metabolism are distributed in the extracellular and intracellular compartments that are in constant equilibrium. Total body water equals approximately 60% of total body weight in young men, about 50% in young women, and less in older persons. Infants' total body water is between 65% and 75%. In a 70-kg man, in temperate conditions, total body water equals 42 L, 65% of which (22 L) is in the intracellular compartment and 35% (19 L) in the extracellular compartment.

Assuming normal glomerular filtration rate to be about 125 mL/min, the total volume of blood filtered by the kidney is about 180 L/24 hr. Only about 1 to 1.5 L is excreted as urine, however, on account of the complex interplay of the urine concentrating and diluting mechanism and the effect of antidiuretic hormone to different segments of the nephron, as depicted in the following figures.

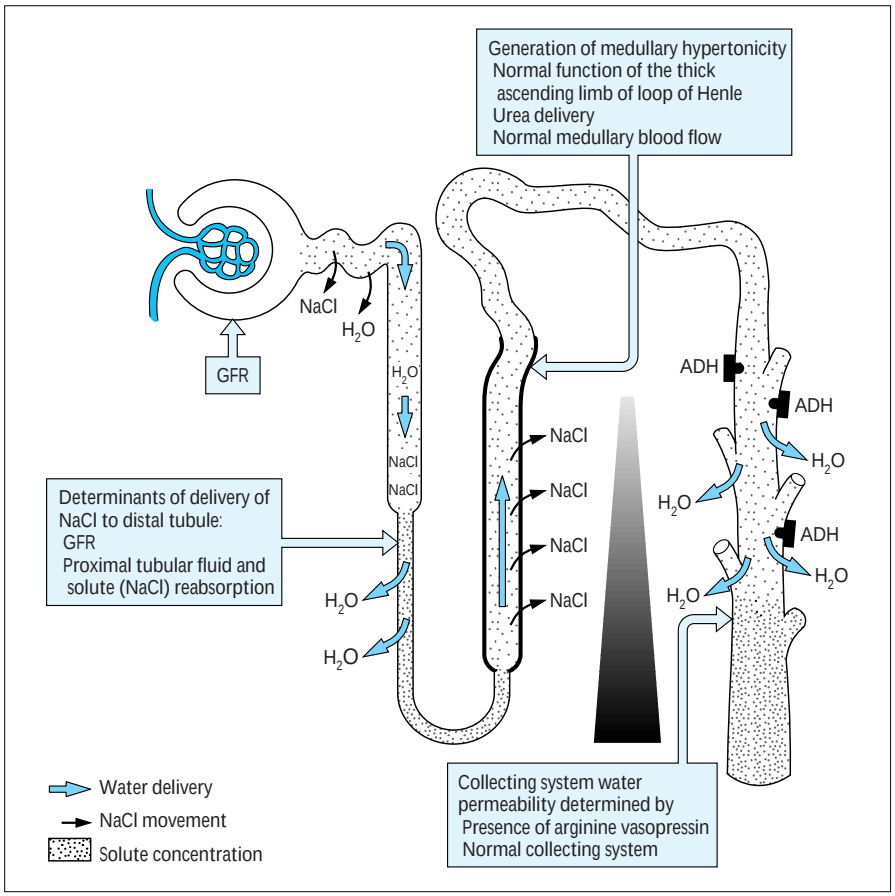


FIGURE 1-2

Determinants of the renal concentrating mechanism. Human kidneys have two populations of nephrons, superficial and juxtamedullary. This anatomic arrangement has important bearing on the formation of urine by the countercurrent mechanism. The unique anatomy of the nephron [1] lays the groundwork for a complex yet logical physiologic arrangement that facilitates the urine concentration and dilution mechanism, leading to the formation of either concentrated or dilute urine, as appropriate to the person's needs and dictated by the plasma osmolality. After two thirds of the filtered load (180 L/d) is isotonically reabsorbed in the proximal convoluted tubule, water is handled by three interrelated processes: 1) the delivery of fluid to the diluting segments; 2) the separation of solute and water (H_2O) in the diluting segment; and 3) variable reabsorption of water in the collecting duct. These processes participate in the renal concentrating mechanism [2].

1. *Delivery of sodium chloride (NaCl) to the diluting segments of the nephron* (thick ascending limb of the loop of Henle and the distal convoluted tubule) is determined by glomerular filtration rate (GFR) and proximal tubule function.
2. *Generation of medullary interstitial hypertonicity*, is determined by normal functioning of the thick ascending limb of the loop of Henle, urea delivery from the medullary collecting duct, and medullary blood flow.
3. *Collecting duct permeability* is determined by the presence of antidiuretic hormone (ADH) and normal anatomy of the collecting system, leading to the formation of a concentrated urine.

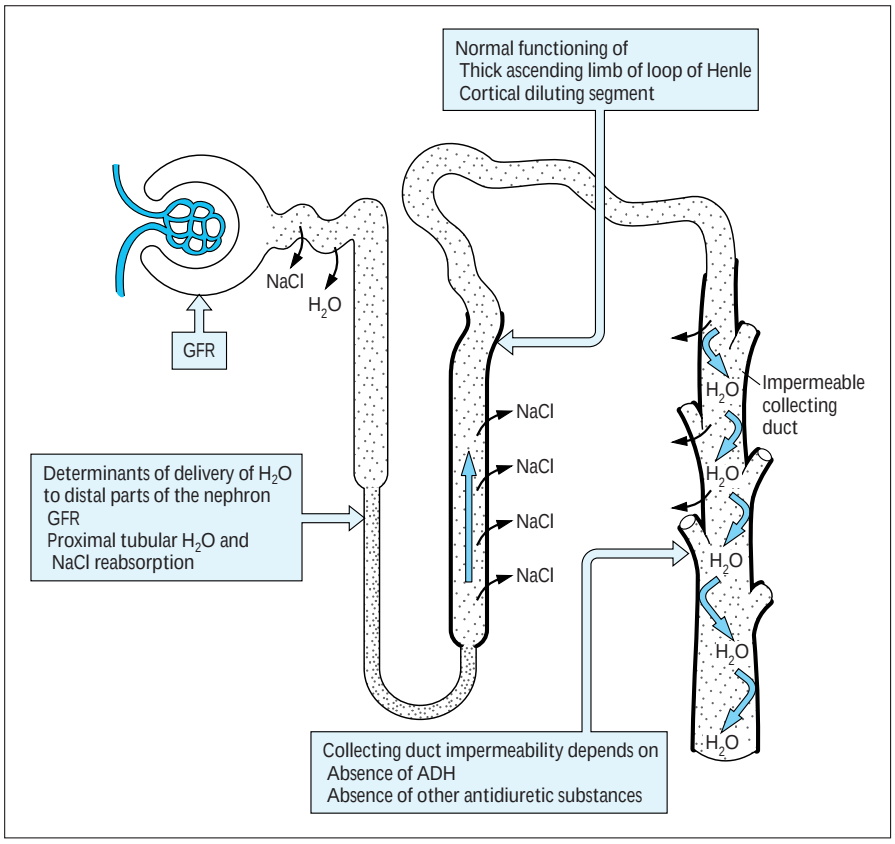


FIGURE 1-3

Determinants of the urinary dilution mechanism include 1) delivery of water to the thick ascending limb of the loop of Henle, distal convoluted tubule, and collecting system of the nephron; 2) generation of maximally hypotonic fluid in the diluting segments (*ie*, normal thick ascending limb of the loop of Henle and cortical diluting segment); 3) maintenance of water impermeability of the collecting system as determined by the absence of antidiuretic hormone (ADH) or its action and other antidiuretic substances. GFR—glomerular filtration rate; NaCl—sodium chloride; H_2O—water.

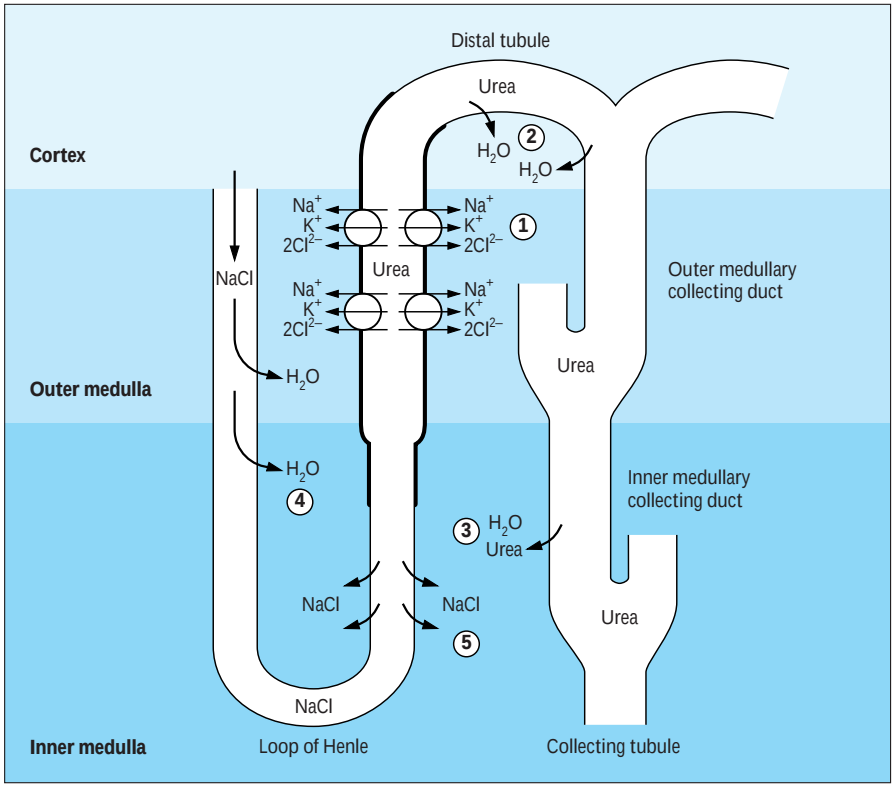


FIGURE 1-4

Mechanism of urine concentration: overview of the passive model. Several models of urine concentration have been put forth by investigators. The passive model of urine concentration described by Kokko and Rector [3] is based on permeability characteristics of different parts of the nephron to solute and water and on the fact that the active transport is limited to the thick ascending limb. 1) Through the Na^+, K^+, 2 Cl cotransporter, the thick ascending limb actively transports sodium chloride (NaCl), increasing the interstitial tonicity, resulting in tubular fluid dilution with no net movement of water and urea on account of their low permeability. 2) The hypotonic fluid under antidiuretic hormone action undergoes osmotic equilibration with the interstitium in the late distal tubule and cortical and outer medullary collecting duct, resulting in water removal. Urea concentration in the tubular fluid rises on account of low urea permeability. 3) At the inner medullary collecting duct, which is highly permeable to urea and water, especially in response to antidiuretic hormone, the urea enters the interstitium down its concentration gradient, preserving interstitial hypertonicity and generating high urea concentration in the interstitium.

(Legend continued on next page)

FIGURE 1-4 *(continued)*

4) The hypertonic interstitium causes abstraction of water from the descending thin limb of loop of Henle, which is relatively impermeable to NaCl and urea, making the tubular fluid hypertonic with high NaCl concentration as it arrives at the bend of the loop of Henle. 5) In the thin ascending limb of the loop of Henle, NaCl moves passively down its concentration gradient into the interstitium, making tubular fluid less concentrated with little or no movement of water. H_2O—water.

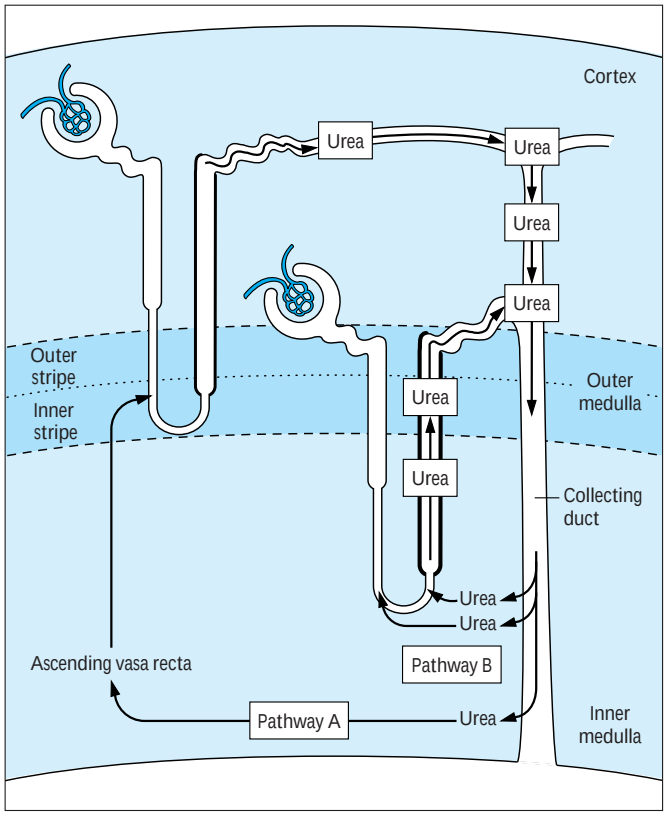


FIGURE 1-5

Pathways for urea recycling. Urea plays an important role in the generation of medullary interstitial hypertonicity. A recycling mechanism operates to minimize urea loss. The urea that is reabsorbed into the inner medullary stripe from the terminal inner medullary collecting duct (*step 3* in Fig. 1-4) is carried out of this region by the ascending vasa recta, which deposits urea into the adjacent descending thin limbs of a short loop of Henle, thus recycling the urea to the inner medullary collecting tubule (*pathway A*).

Some of the urea enters the descending limb of the loop of Henle and the thin ascending limb of the loop of Henle. It is then carried through to the thick ascending limb of the loop of Henle, the distal collecting tubule, and the collecting duct, before it reaches the inner medullary collecting duct (*pathway B*). This process is facilitated by the close anatomic relationship that the hairpin loop of Henle and the vasa recta share [4].

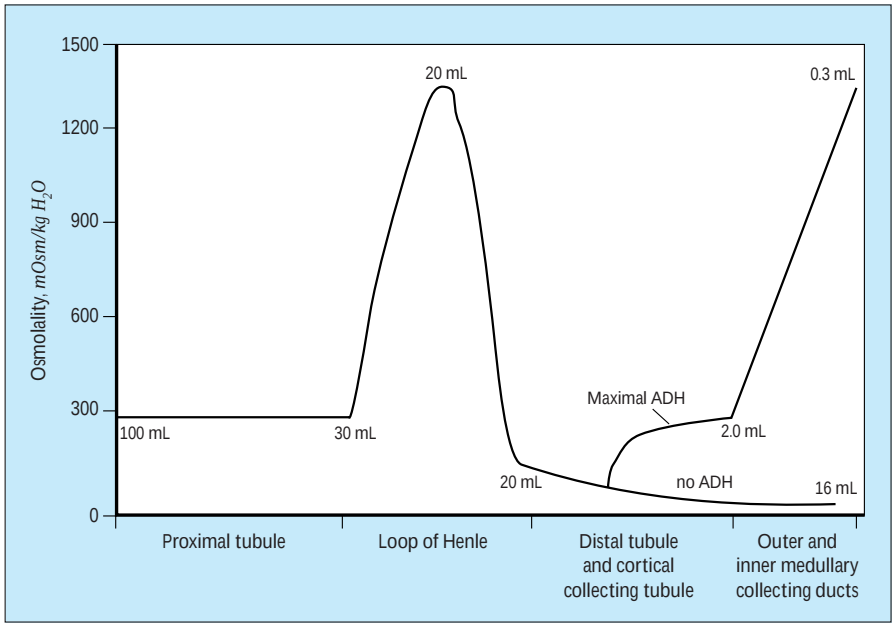


FIGURE 1-6

Changes in the volume and osmolality of tubular fluid along the nephron in diuresis and antidiuresis. The osmolality of the tubular fluid undergoes several changes as it passes through different segments of the tubules. Tubular fluid undergoes marked reduction in its volume in the proximal tubule; however, this occurs iso-osmotically with the glomerular filtrate. In the loop of Henle, because of the aforementioned countercurrent mechanism, the osmolality of the tubular fluid rises sharply but falls again to as low as 100 mOsm/kg as it reaches the thick ascending limb and the distal convoluted tubule. Thereafter, in the late distal tubule and the collecting duct, the osmolality depends on the presence or absence of antidiuretic hormone (ADH). In the absence of ADH, very little water is reabsorbed and dilute urine results. On the other hand, in the presence of ADH, the collecting duct, and in some species, the distal convoluted tubule, become highly permeable to water, causing reabsorption of water into the interstitium, resulting in concentrated urine [5].

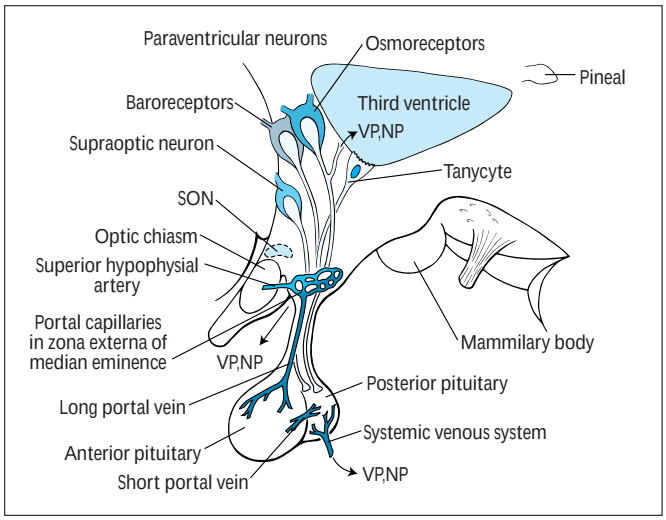


FIGURE 1-7

Pathways of antidiuretic hormone release. Antidiuretic hormone is responsible for augmenting the water permeability of the cortical and medullary collecting tubules, thus promoting water reabsorption via osmotic equilibration with the isotonic and hypertonic interstitium, respecively. The hormone is formed in the supraoptic and paraventricular nuclei, under the stimulus of osmoreceptors and baroreceptors (*see* Fig. 1-11), transported along their axons and secreted at three sites: the posterior pituitary gland, the portal capillaries of the median eminence, and the cerebrospinal fluid of the third ventricle. It is from the posterior pituitary that the antidiuretic hormone is released into the systemic circulation [6]. SON—supraoptic nucleus; VP—vasopressin; NP—neurophysin.

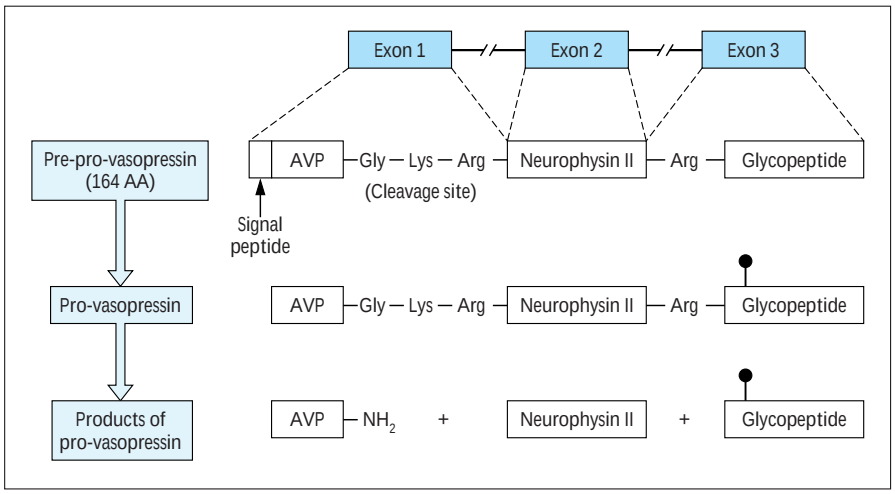


FIGURE 1-8

Structure of the human arginine vasopressin (AVP/antidiuretic hormone) gene and the prohormone. Antidiuretic hormone (ADH) is a cyclic hexapeptide (mol. wt. 1099) with a tail of three amino acids. The biologically inactive macromolecule, pre-pro-vasopressin is cleaved into the smaller, biologically active protein. The protein of vasopressin is translated through a series of signal transduction pathways and intracellular cleaving. Vasopressin, along with its binding protein, neurophysin II, and the glycoprotein, are secreted in the form of neurosecretory granules down the axons and stored in nerve terminals of the posterior lobe of the pituitary [7]. ADH has a short half-life of about 15 to 20 minutes and is rapidly metabolized in the liver and kidneys. Gly—glycine; Lys—lysine; Arg—arginine.

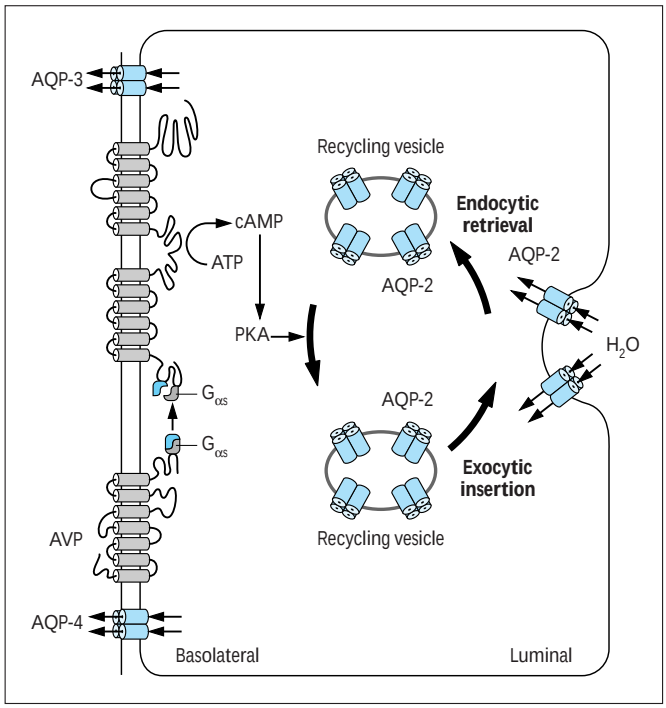


FIGURE 1-9

Intracellular action of antidiuretic hormone. The multiple actions of vasopressin can be accounted for by its interaction with the V2 receptor found in the kidney. After stimulation, vasopressin binds to the V2 receptor on the basolateral membrane of the collecting duct cell. This interaction of vasopressin with the V2 receptor leads to increased adenylate cyclase activity via the stimulatory G protein (Gs), which catalyzes the formation of cyclic adenosine 3', 5'-monophosphate (cAMP) from adenosine triphosphate (ATP). In turn, cAMP activates a serine threonine kinase, protein kinase A (PKA). Cytoplasmic vesicles carrying the water channel proteins migrate through the cell in response to this phosphorylation process and fuse with the apical membrane in response to increasing vasopressin binding, thus increasing water permeability of the collecting duct cells. These water channels are recyled by endocytosis once the vasopressin is removed. The water channel responsible for the high water permeability of the luminal membrane in response to vasopressin has recently been cloned and designated as aquaporin-2 (AQP-2) [8]. The other members of the aquaporin family, AQP-3 and AQP-4 are located on the basolateral membranes and are probably involved in water exit from the cell. The molecular biology of these channels and of receptors responsible for vasopressin action have contributed to the understanding of the syndromes of genetically transmitted and acquired forms of vasopressin resistance. AVP—arginine vasopressin.

AQUAPORINS AND THEIR CHARACTERISTICS

	AQP-1	AQP-2	AQP-3	AQP-4
Size (amino acids)	269	271	285	301
Permeability to small solutes	No	No	Urea glycerol	No
Regulation by antidiurectic hormone	No	Yes	No	No
Site	Proximal tubules; descending thin limb	Collecting duct; principal cells	Medullary collecting duct; colon	Hypothalamic—supraoptic, paraventricular nuclei; ependymal, granular, and Purkinje cells
Cellular localization	Apical and basolateral membrane	Apical membrane and intracellular vesicles	Basolateral membrane	Basolateral membrane of the prinicpal cells
Mutant phenotype	Normal	Nephrogenic diabetes insipidus	Unknown	Unknown

FIGURE 1-10

Aquaporins and their characteristics. An ever growing family of aquaporin (AQP) channels are being described. So far, about seven different channels have been cloned and characterized; however, only four have been found to have any definite physiologic role.

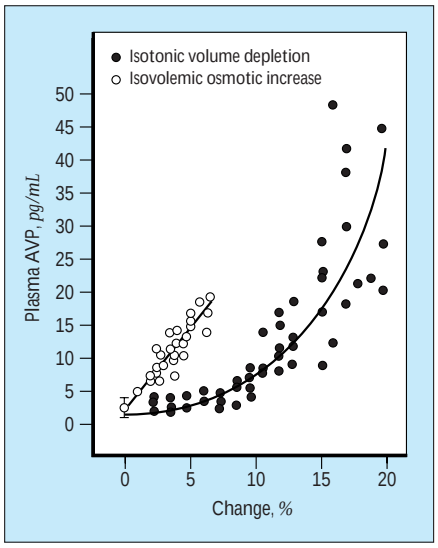


FIGURE 1-11

Osmotic and nonosmotic regulation of antidiuretic hormone (ADH) secretion. ADH is secreted in response to changes in osmolality and in circulating arterial volume. The "osmoreceptor" cells are located in the anterior hypothalamus close to the supraoptic nuclei. Aquaporin-4 (AQP-4), a candidate osmoreceptor, is a member of the water channel family that was recently cloned and characterized and is found in abundance in these neurons. The osmoreceptors are sensitive to changes in plasma osmolality of as little as 1%. In humans, the osmotic threshold for ADH release is 280 to 290 mOsm/kg. This system is so efficient that the plasma osmolality usually does not vary by more than 1% to 2% despite wide fluctuations in water intake [9]. There are several other nonosmotic stimuli for ADH secretion. In conditions of decreased arterial circulating volume (*eg*, heart failure, cirrhosis, vomiting), decrease in inhibitory parasympathetic afferents in the carotid sinus baroreceptors affects ADH secretion. Other nonosmotic stimuli include nausea, which can lead to a 500-fold rise in circulating ADH levels, postoperative pain, and pregnancy. Much higher ADH levels can be achieved with hypovolemia than with hyperosmolarity, although a large fall in blood volume is required before this response is initiated. In the maintenance of tonicity the interplay of these homeostatic mechanisms also involves the thirst mechanism, that under normal conditions, causes either intake or exclusion of water in an effort to restore serum osmolality to normal.

Control of Water Balance and Serum Sodium Concentration

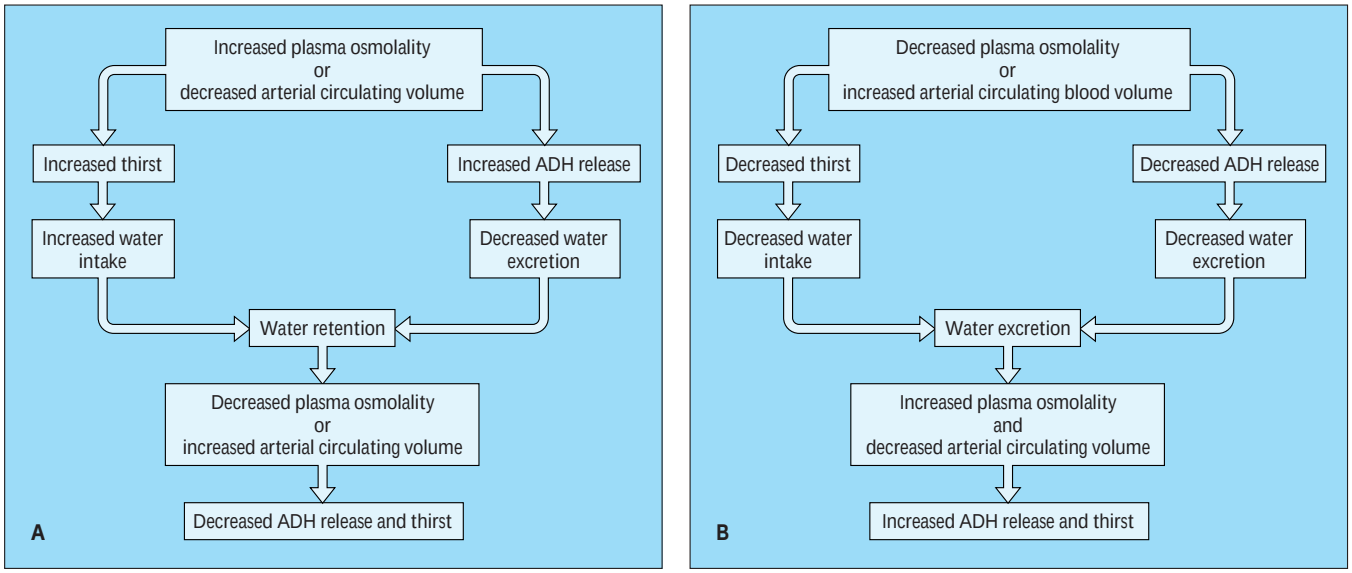


FIGURE 1-12

Pathways of water balance (conservation, **A**, and excretion, **B**). In humans and other terrestrial animals, the thirst mechanism plays an important role in water (H_2O) balance. Hypertonicity is the most potent stimulus for thirst: only 2% to 3 % changes in plasma osmolality produce a strong desire to drink water. This absolute level of osmolality at which the sensation of thirst arises in healthy persons, called the *osmotic threshold for thirst*, usually averages about 290 to 295 mOsm/kg H_2O (approximately 10 mOsm/kg H_2O above that of antidiuretic hormone [ADH] release). The so-called thirst center is located close to the osmoreceptors but is anatomically distinct. Between the limits imposed by the osmotic thresholds for thirst and ADH release, plasma osmolality may be regulated still more precisely by small osmoregulated adjustments in urine flow and water intake. The exact level at which balance occurs depends on various factors such as insensible losses through skin and lungs, and the gains incurred from eating, normal drinking, and fat metabolism. In general, overall intake and output come into balance at a plasma osmolality of 288 mOsm/kg, roughly halfway between the thresholds for ADH release and thirst [10].

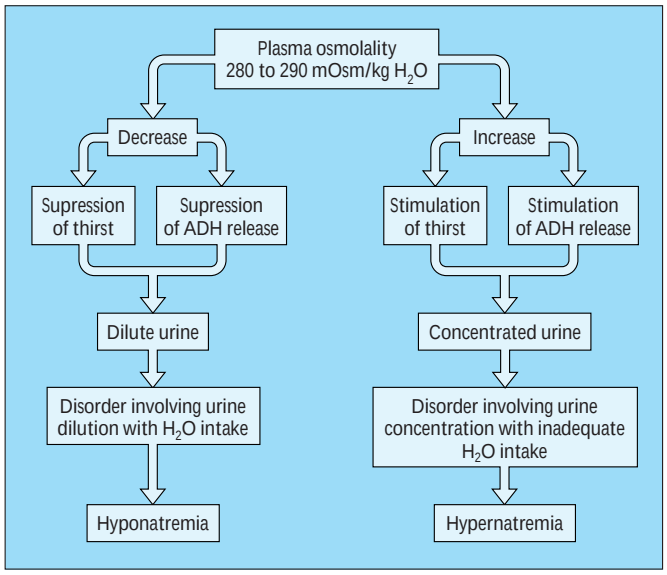


FIGURE 1-13

Pathogenesis of dysnatremias. The countercurrent mechanism of the kidneys in concert with the hypothalamic osmoreceptors via antidiuretic hormone (ADH) secretion maintain a very finely tuned balance of water (H_2O). A defect in the urine-diluting capacity with continued H_2O intake results in hyponatremia. Conversely, a defect in urine concentration with inadequate H_2O intake culminates in hypernatremia. Hyponatremia reflects a disturbance in homeostatic mechanisms characterized by excess total body H_2O relative to total body sodium, and hypernatremia reflects a deficiency of total body H_2O relative to total body sodium [11]. (*From* Halterman and Berl [12]; with permission.)

Approach to the Hyponatremic Patient

EFFECTS OF OSMOTICALLY ACTIVE SUBSTANCES ON SERUM SODIUM

Substances the increase osmolality without changing serum sodium	Substances that increase osmolality and decrease serum sodium (translocational hyponatremia)
Urea	Glucose
Ethanol	Mannitol
Ethylene glycol	Glycine
Isopropyl alcohol	Maltose
Methanol	

FIGURE 1-14

Evaluation of a hyponatremic patient: effects of osmotically active substances on serum sodium. In the evaluation of a hyponatremic patient, a determination should be made about whether hyponatremia is truly hypo-osmotic and not a consequence of *translocational* or *pseudohyponatremia*, since, in most but not all situations, hyponatremia reflects hypo-osmolality.

The nature of the solute plays an important role in determining whether or not there is an increase in measured osmolality or an actual increase in effective osmolality. Solutes that are permeable across cell membranes (*eg*, urea, methanol, ethanol, and ethylene glycol) do not cause water movement and cause hypertonicity without causing cell dehydration. Typical examples are an uremic patient with a high blood urea nitrogen value and an ethanol-intoxicated person. On the other hand, in a patient with diabetic ketoacidosis who is insulinopenic the glucose is not permeant across cell membranes and, by its presence in the extracellular fluid, causes water to move from the cells to extracellular space, thus leading to cell dehydration and lowering serum sodium. This can be viewed as translocational at the cellular level, as the serum sodium level does not reflect changes in total body water but rather movement of water from intracellular to extracellular space. Glycine is used as an irrigant solution during transurethral resection of the prostate and in endometrial surgery. Pseudohyponatremia occurs when the solid phase of plasma (usually 6% to 8%) is much increased by large increments of either lipids or proteins (*eg*, in hypertriglyceridemia or paraproteinemias).

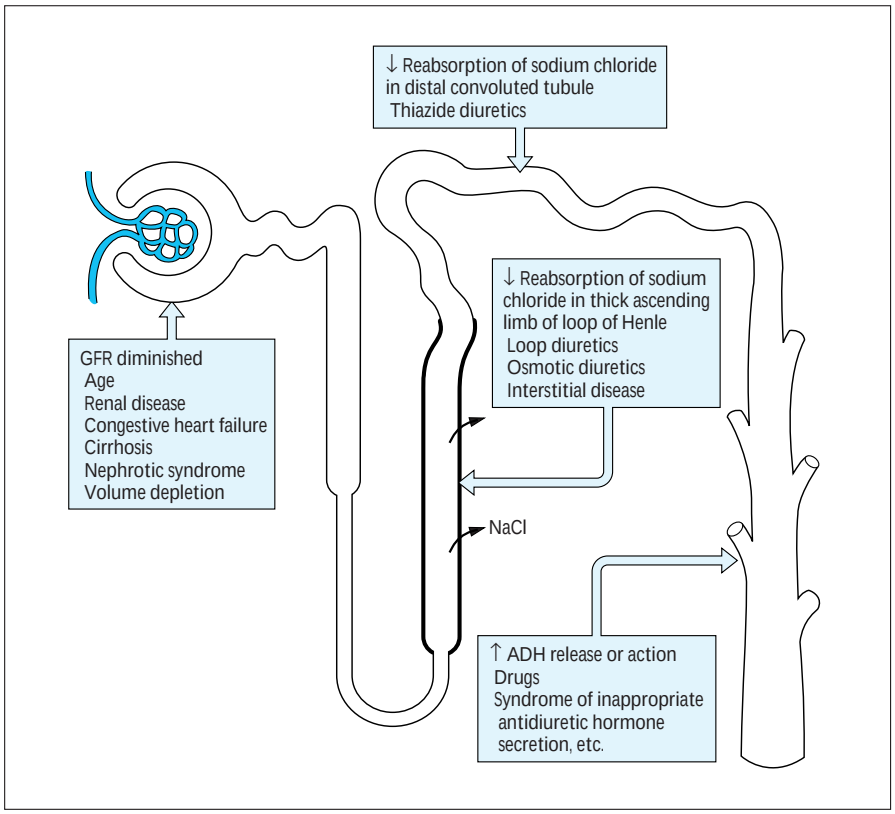


FIGURE 1-15

Pathogenesis of hyponatremia. The normal components of the renal diluting mechanism are depicted in Figure 1-3. Hyponatremia results from disorders of this diluting capacity of the kidney in the following situations:

1. *Intrarenal factors* such as a diminished glomerular filtration rate (GFR), or an increase in proximal tubule fluid and sodium reabsorption, or both, which decrease distal delivery to the diluting segments of the nephron, as in volume depletion, congestive heart failure, cirrhosis, or nephrotic syndrome.
2. *A defect in sodium chloride transport* out of the water-impermeable segments of the nephrons (*ie*, in the thick ascending limb of the loop of Henle). This may occur in patients with interstitial renal disease and administration of thiazide or loop diuretics.
3. *Continued secretion of antidiuretic hormone (ADH)* despite the presence of serum hypo-osmolality mostly stimulated by nonosmotic mechanisms [12].

NaCl—sodium chloride.

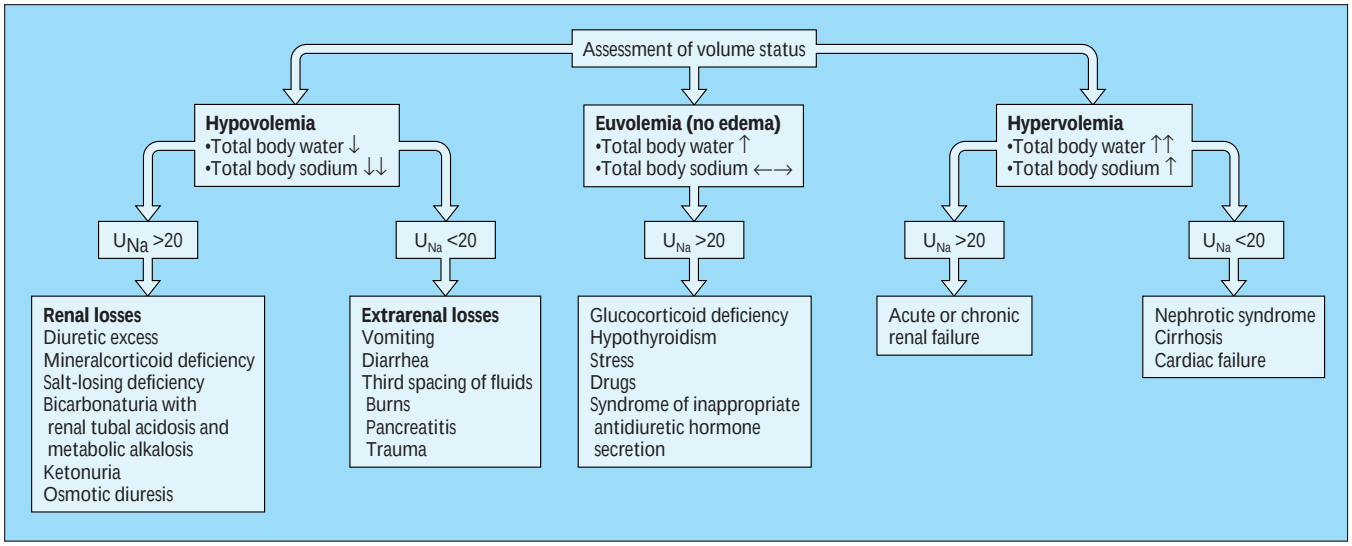


FIGURE 1-16

Diagnostic algorithm for hyponatremia. The next step in the evaluation of a hyponatremic patient is to assess volume status and identify it as hypovolemic, euvolemic or hypervolemic. The patient with hypovolemic hyponatremia has both total body sodium and water deficits, with the sodium deficit exceeding the water deficit. This occurs with large gastrointestinal and renal losses of water and solute when accompanied by free water or hypotonic fluid intake. In patients with hypervolemic hyponatremia, total body sodium is increased but total body water is increased even more than sodium, causing hyponatremia. These syndromes include congestive heart failure, nephrotic syndrome, and cirrhosis. They are all associated with impaired water excretion. Euvolemic hyponatremia is the most common dysnatremia in hospitalized patients. In these patients, by definition, no physical signs of increased total body sodium are detected. They may have a slight excess of volume but no edema [12]. (*Modified from* Halterman and Berl [12]; with permission.)

DRUGS ASSOCIATED WITH HYPONATREMIA

- Antidiuretic hormone analogues
  - Deamino-D-arginine vasopressin (DDAVP)
  - Oxytocin
- Drugs that enhance release of antidiuretic hormone
  - Chlorpropamide
  - Clofibrate
  - Carbamazepine-oxycarbazepine
  - Vincristine
  - Nicotine
  - Narcotics
  - Antipsychotics
  - Antidepressants
  - Ifosfamide
- Drugs that potentiate renal action of antidiuretic hormone
  - Chlorpropamide
  - Cyclophosphamide
  - Nonsteroidal anti-inflammatory drugs
  - Acetaminophen
- Drugs that cause hyponatremia by unknown mechanisms
  - Haloperidol
  - Fluphenazine
  - Amitriptyline
  - Thioradazine
  - Fluoxetine

FIGURE 1-17

Drugs that cause hyponatremia. Drug-induced hyponatremia is mediated by antidiuretic hormone analogues like deamino-D-arginine-vasopressin (DDAVP), or antidiuretic hormone release, or by potentiating the action of antidiuretic hormone. Some drugs cause hyponatremia by unknown mechanisms [13]. (*From* Veis and Berl [13]; with permission.)

CAUSES OF THE SYNDROME OF INAPPROPRIATE DIURETIC HORMONE SECRETION

Carcinomas	Pulmonary Disorders	Central Nervous System Disorders
Bronchogenic	Viral pneumonia	Encephalitis (viral or bacterial)
Duodenal	Bacterial pneumonia	Meningitis (viral, bacterial, tuberculous, fungal)
Pancreatic	Pulmonary abscess	Head trauma
Thymoma	Tuberculosis	Brain abscess
Gastric	Aspergillosis	Brain tumor
Lymphoma	Positive-pressure breathing	Guillain-Barré syndrome
Ewing's sarcoma	Asthma	Acute intermittent porphyria
Bladder	Pneumothorax	Subarachnoid hemorrhage or subdural hematoma
Carcinoma of the ureter	Mesothelioma	Cerebellar and cerebral atrophy
Prostatic	Cystic fibrosis	Cavernous sinus thrombosis
Oropharyngeal		Neonatal hypoxia
		Hydrocephalus
		Shy-Drager syndrome
		Rocky Mountain spotted fever
		Delirium tremens
		Cerebrovascular accident (cerebral thrombosis or hemorrhage)
		Acute psychosis
		Multiple sclerosis

FIGURE 1-18

Causes of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Though SIADH is the commonest cause of hyponatremia in hospitalized patients, it is a diagnosis of exclusion. It is characterized by a defect in osmoregulation of ADH in which plasma ADH levels are not appropriately suppressed for the degree of hypotonicity, leading to urine concentration by a variety of mechanisms. Most of these fall into one of three categories (*ie*, malignancies, pulmonary diseases, central nervous system disorders) [14].

DIAGNOSTIC CRITERIA FOR THE SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION

Essential

- Decreased extracellular fluid effective osmolality (< 270 mOsm/kg H_2O)
- Inappropriate urinary concentration (> 100 mOsm/kg H_2O)
- Clinical euvolemia
- Elevated urinary sodium concentration ($U_{[Na]}$), with normal salt and H_2O intake
- Absence of adrenal, thyroid, pituitary, or renal insufficiency or diuretic use

Supplemental

- Abnormal H_2O load test (inability to excrete at least 90% of a 20–mL/kg H_2O load in 4 hrs or failure to dilute urinary osmolality to < 100 mOsm/kg)
- Plasma antidiuretic hormone level inappropriately elevated relative to plasma osmolality
- No significant correction of plasma sodium with volume expansion, but improvement after fluid restriction

FIGURE 1-19

Diagnostic criteria for the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Clinically, SIADH is characterized by a decrease in the effective extracellular fluid osmolality, with inappropriately concentrated urine. Patients with SIADH are clinically euvolemic and are consuming normal amounts of sodium and water (H_2O). They have elevated urinary sodium excretion. In the evaluation of these patients, it is important to exclude adrenal, thyroid, pituitary, and renal disease and diuretic use. Patients with clinically suspected SIADH can be tested with a water load. Upon administration of 20 mL/kg of H_2O, patients with SIADH are unable to excrete 90% of the H_2O load and are unable to dilute their urine to an osmolality less than 100 mOsm/kg [15]. (*Modified from* Verbalis [15]; with permission.)

SIGNS AND SYMPTOMS OF HYPONATREMIA

Central Nervous System

Mild
- Apathy
- Headache
- Lethargy

Moderate
- Agitation
- Ataxia
- Confusion
- Disorientation
- Psychosis

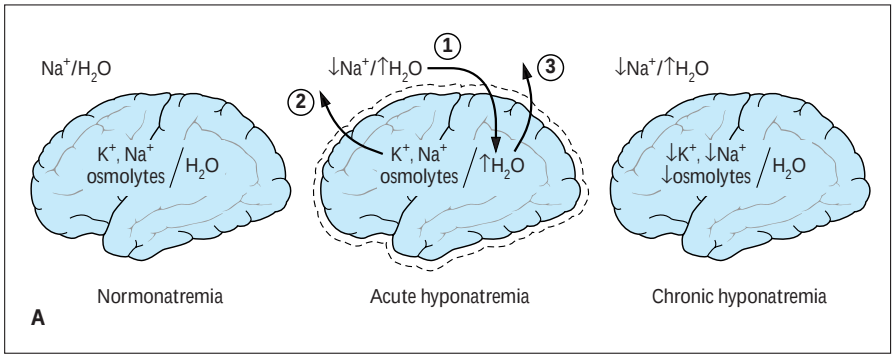
Severe
- Stupor
- Coma
- Pseudobulbar palsy
- Tentorial herniation
- Cheyne-Stokes respiration
- Death

Gastrointestinal System
- Anorexia
- Nausea
- Vomiting

Musculoskeletal System
- Cramps
- Diminished deep tendon reflexes

FIGURE 1-20

Signs and symptoms of hyponatremia. In evaluating hyponatremic patients, it is important to assess whether or not the patient is symptomatic, because symptoms are a better determinant of therapy than the absolute value itself. Most patients with serum sodium values above 125 mEq/L are asymptomatic. The rapidity with which hyponatremia develops is critical in the initial evaluation of such patients. In the range of 125 to 130 mEq/L, the predominant symptoms are gastrointestinal ones, including nausea and vomiting. Neuropsychiatric symptoms dominate the picture once the serum sodium level drops below 125 mEq/L, mostly because of cerebral edema secondary to hypotonicity. These include headache, lethargy, reversible ataxia, psychosis, seizures, and coma. Severe manifestations of cerebral edema include increased intracerebral pressure, tentorial herniation, respiratory depression and death. Hyponatremia-induced cerebral edema occurs principally with rapid development of hyponatremia, typically in patients managed with hypotonic fluids in the postoperative setting or those receiving diuretics, as discussed previously. The mortality rate can be as great as 50%. Fortunately, this rarely occurs. Nevertheless, neurologic symptoms in a hyponatremic patient call for prompt and immediate attention and treatment [16,17].



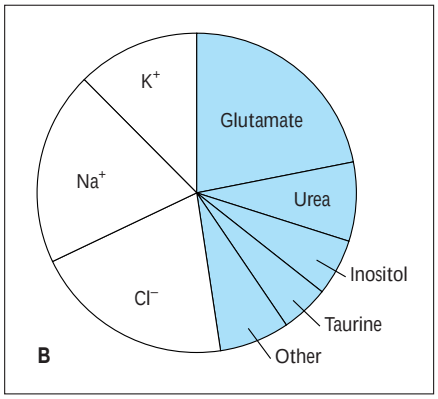


FIGURE 1-21

Cerebral adaptation to hyponatremia. **A**, Decreases in extracellular osmolality cause movement of water (H_2O) into the cells, increasing intracellular volume and thus causing tissue edema. This cellular edema within the fixed confines of the cranium causes increased intracranial pressure, leading to neurologic symptoms. To prevent this from happening, mechanisms geared toward volume regulation come into operation, to prevent cerebral edema from developing in the vast majority of patients with hyponatremia.

After induction of extracellular fluid hypo-osmolality, H_2O moves into the brain in response to osmotic gradients, producing cerebral edema (*middle panel, 1*). However, within 1 to 3 hours, a decrease in cerebral extracellular volume occurs by movement of fluid into the cerebrospinal fluid, which is then shunted back into the systemic circulation. This happens very promptly and is evident by the loss of extracellular and intracellular solutes (sodium and chloride ions) as early as 30 minutes after the onset of hyponatremia. As H_2O losses accompany the losses of brain solute (*middle panel, 2*), the expanded brain volume decreases back toward normal (*middle panel, 3*) [15]. **B**, Relative decreases in individual osmolytes during adaptation to chronic hyponatremia. Thereafter, if hyponatremia persists, other organic osmolytes such as phosphocreatine, myoinositol, and amino acids like glutamine, and taurine are lost. The loss of these solutes markedly decreases cerebral swelling. Patients who have had a slower onset of hyponatremia (over 72 to 96 hours or longer), the risk for osmotic demyelination rises if hyponatremia is corrected too rapidly [18,19]. Na^+—sodium; K^+—potassium; Cl^-—chloride.

HYPONATREMIC PATIENTS AT RISK FOR NEUROLOGIC COMPLICATIONS

Complication	Persons at Risk
Acute cerebral edema	Postoperative menstruant females
	Elderly women taking thiazides
	Children
	Psychiatric polydipsic patients
	Hypoxemic patients
Osmotic demyelination syndrome	Alcoholics
	Malnourished patients
	Hypokalemic patients
	Burn victims
	Elderly women taking thiazide diuretics

FIGURE 1-22

Hyponatremic patients at risk for neurologic complications. Those at risk for cerebral edema include postoperative menstruant women, elderly women taking thiazide diuretics, children, psychiatric patients with polydipsia, and hypoxic patients. In women, and, in particular, menstruant ones, the risk for developing neurologic complications is 25 times greater than that for nonmenstruant women or men. The increased risk was independent of the rate of development, or the magnitude of the hyponatremia [21]. The osmotic demyelination syndrome or central pontine myelinolysis seems to occur when there is rapid correction of low osmolality (hyponatremia) in a brain already chronically adapted (more than 72 to 96 hours). It is rarely seen in patients with a serum sodium value greater than 120 mEq/L or in those who have hyponatremia of less than 48 hours' duration [20,21]. (*Adapted from* Lauriat and Berl [21]; with permission.)

SYMPTOMS OF CENTRAL PONTINE MYELINOLYSIS

Initial symptoms
Mutism
Dysarthria
Lethargy and affective changes

Classic symptoms
Spastic quadriparesis
Pseudobulbar palsy

Lesions in the midbrain, medulla oblongata, and pontine tegmentum
Pupillary and oculomotor abnormalities
  Altered sensorium
  Cranial neuropathies
Extrapontine myelinolysis
  Ataxia
  Behavioral abnormalities
  Parkinsonism
  Dystonia

FIGURE 1-23

Symptoms of central pontine myelinolysis. This condition has been described all over the world, in all age groups, and can follow correction of hyponatremia of any cause. The risk for development of central pontine myelinolysis is related to the severity and chronicity of the hyponatremia. Initial symptoms include mutism and dysarthria. More than 90% of patients exhibit the classic symptoms of myelinolysis (*ie*, spastic quadriparesis and pseudobulbar palsy), reflecting damage to the corticospinal and corticobulbar tracts in the basis pontis. Other symptoms occur on account of extension of the lesion to other parts of the midbrain. This syndrome follows a biphasic course. Initially, a generalized encephalopathy, associated with a rapid rise in serum sodium, occurs. This is followed by the classic symptoms 2 to 3 days after correction of hyponatremia, however, this pattern does not always occur [22]. (*Adapted from* Laureno and Karp [22]; with permission.)

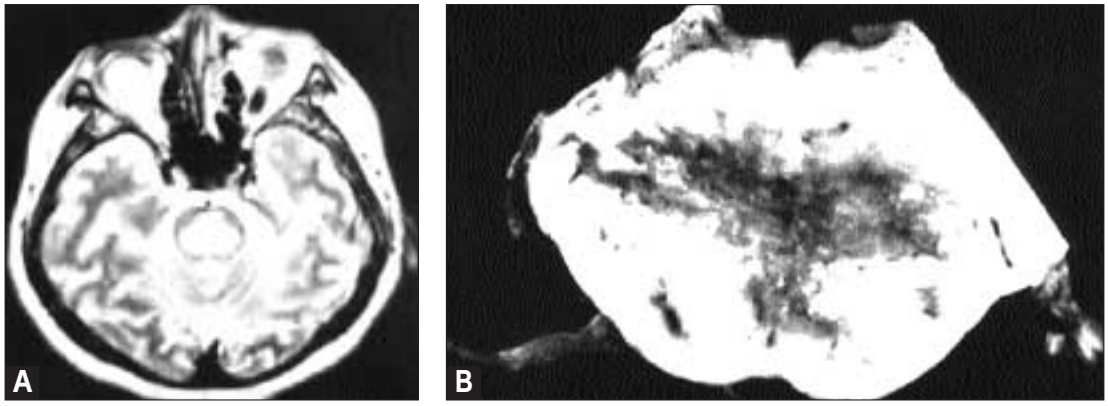


FIGURE 1-24

A, Imaging of central pontine myelinolysis. Brain imaging is the most useful diagnostic technique for central pontine myelinolysis. Magnetic resonance imaging (MRI) is more sensitive than computed tomography (CT). On CT, central pontine and extrapontine lesions appear as symmetric areas of hypodensity (not shown). On T2 images of MRI, the lesions appear as hyperintense and on T1 images, hypointense. These lesions do not enhance with gadolinium. They may not be apparent on imaging until 2 weeks into the illness. Other diagnostic tests are brainstem auditory evoked potentials, electroencephalography, and cerebrospinal fluid protein and myelin basic proteins [22]. **B**, Gross appearance of the pons in central pontine myelinolysis. (*From* Laureno and Karp [22]; with permission.)

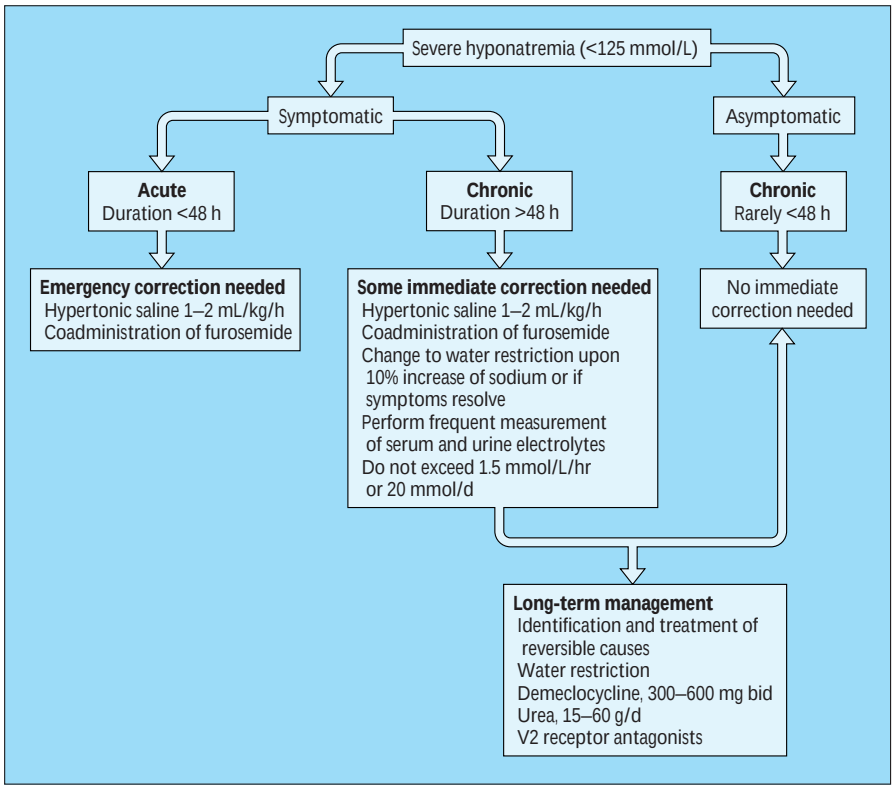


FIGURE 1-25

Treatment of severe euvolemic hyponatremia (<125 mmol/L). The evaluation of a hyponatremic patient involves an assessment of whether the patient is symptomatic, and if so, the duration of hyponatremia should be ascertained. The therapeutic approach to the hyponatremic patient is determined more by the presence or absence of symptoms than by the absolute level of serum sodium. Acutely hyponatremic patients are at great risk for permanent neurologic sequelae from cerebral edema if the hyponatremia is not promptly corrected. On the other hand, chronic hyponatremia carries the risk of osmotic demyelination syndrome if corrected too rapidly. The next step involves a determination of whether the patient has any risk factors for development of neurologic complications.

The commonest setting for acute, symptomatic hyponatremia is hospitalized, postoperative patients who are receiving hypotonic fluids. In these patients, the risk of cerebral edema outweighs the risk for osmotic demyelination. In the presence of seizures, obtundation, and coma, rapid infusion of 3% sodium chloride (4 to 6 mL/kg/h) or even 50 mL of 29.2% sodium chloride has been used safely. Ongoing careful neurologic monitoring is imperative [20].

A. GENERAL GUIDELINES FOR THE TREATMENT OF SYMPTOMATIC HYPONATREMIA*

Acute hyponatremia (duration < 48 hrs)

Increase serum sodium rapidly by approximately 2 mmol/L/h until symptoms resolve

Full correction probably safe but not necessary

Chronic hyponatremia (duration > 48 hrs)

Initial increase in serum sodium by 10% or 10 mmol/L

Perform frequent neurologic evaluations; correction rate may be reduced with improvement in symptoms

At no time should correction exceed rate of 1.5 mmol/L/h, or increments of 15 mmol/d

Measure serum and urine electrolytes every 1–2 h

*The sum of urinary cations ($U_{Na} + U_K$) should be less than the concentration of infused sodium, to ensure excretion of electrolyte-free water.

B. TREATMENT OF CHRONIC SYMPTOMATIC HYPONATREMIA

Calculate the net water loss needed to raise the serum sodium (S_{Na}) from 110 mEq/L to 120 mEq/L in a 50 kg person.

Example

Current $S_{Na} \times$ Total body water (TBW) = Desired $S_{Na} \times$ New TBW

Assume that TBW = 60% of body weight

Therefore TBW of patient = $50 \times 0.6 = 30$ L

$$\text{New TBW} = \frac{110 \text{ mEq/L} \times 30 \text{ L}}{120 \text{ mEq/L}} = 27.5 \text{ L}$$

Thus the electrolyte-free water loss needed to raise the S_{Na} to 120 mEq/L = Present TBW − New TBW = 2.5 L

Calculate the time course in which to achieve the desired correction (1 mEq/h)—in this case, 250 mL/h

Administer furosemide, monitor urine output, and replace sodium, potassium, and excess free water lost in the urine

Continue to monitor urine output and replace sodium, potassium, and excess free water lost in the urine

FIGURE 1-26

General guidelines for the treatment of symptomatic hyponatremia, **A**. Included herein are general guidelines for treatment of patients with acute and chronic symptomatic hyponatremia. In the treatment of chronic symptomatic hyponatremia, since cerebral water is increased by approximately 10%, a prompt increase in serum sodium by 10% or 10 mEq/L is permissible. Thereafter, the patient's fluids should be restricted. The total correction rate should not exceed 1.0 to 1.5 mEq/L/h, and the total increment in 24 hours should not exceed 15 mmol/d [12]. A specific example as to how to increase a patient's serum sodium is illustrated in **B**.

MANAGEMENT OPTIONS FOR CHRONIC ASYMPTOMATIC HYPONATREMIA

Treatment	Mechanism of Action	Dose	Advantages	Limitations
Fluid restriction	Decreases availability of free water	Variable	Effective and inexpensive	Noncompliance
Pharmacologic inhibition of antidiuretic hormone action				
Lithium	Inhibits the kidney's response to antidiuretic hormone	900–1200 mg/d	Unrestricted water intake	Polyuria, narrow therapeutic range, neurotoxicity
Demeclocycline	Inhibits the kidney's response to antidiurectic hormone	1200 mg/d initially; then, 300–900 mg/d	Effective; unrestricted water intake	Neurotoxicity, polyuria, photosensitivity, nephrotoxicity
V2-receptor antagonist	Antagonizes vasopressin action		Ongoing trials	
Increased solute intake				
Furosemide	Increases free water clearance	Titrate to optimal dose; coadminister 2–3 g sodium chloride	Effective	Ototoxicity, K^+ and Mg^{2+} depletion
Urea	Osmotic diuresis	30–60 g/d	Effective; unrestricted water intake	Polyuria, unpalatable gastrointestinal symptoms

FIGURE 1-27

Management options for patients with chronic asymptomatic hyponatremia. If the patient has chronic hyponatremia and is asymptomatic, treatment need not be intensive or emergent. Careful scrutiny of likely causes should be followed by treatment. If the cause is determined to be the syndrome of inappropriate antidiuretic hormone (ADH) secretion, it must be treated as a chronic disorder. As summarized here, the treatment strategies involve fluid restriction, pharmacologic inhibition of ADH action, and increased solute intake. Fluid restriction is frequently successful in normalizing serum sodium and preventing symptoms [23].

MANAGEMENT OF NONEUVOLEMIC HYPONATREMIA

Hypovolemic hyponatremia

Volume restoration with isotonic saline

Identify and correct causes of water and sodium losses

Hypervolemic hyponatremia

Water restriction

Sodium restriction

Substitiute loop diuretics for thiazide diurectics

Treatment of timulus for sodium and water retention

V2-receptor antagonist

FIGURE 1-28

Management of noneuvolemic hyponatremia. Hypovolemic hyponatremia results from the loss of both water and solute, with relatively greater loss of solute. The nonosmotic release of antidiuretic hormone stimulated by decreased arterial circulating blood volume causes antidiuresis and perpetuates the hyponatremia. Most of these patients are asymptomatic. The keystone of therapy is isotonic saline administration, which corrects the hypovolemia and removes the stimulus of antidiuretic hormone to retain fluid. Hypervolemic hyponatremia occurs when both solute and water are increased, but water more than solute. This occurs with heart failure, cirrhosis and nephrotic syndrome. The cornerstones of treatment include fluid restriction, salt restriction, and loop diuretics [20]. (*Adapted from* Lauriat and Berl [20]; with permission.)

Approach to the Hypernatremic Patient

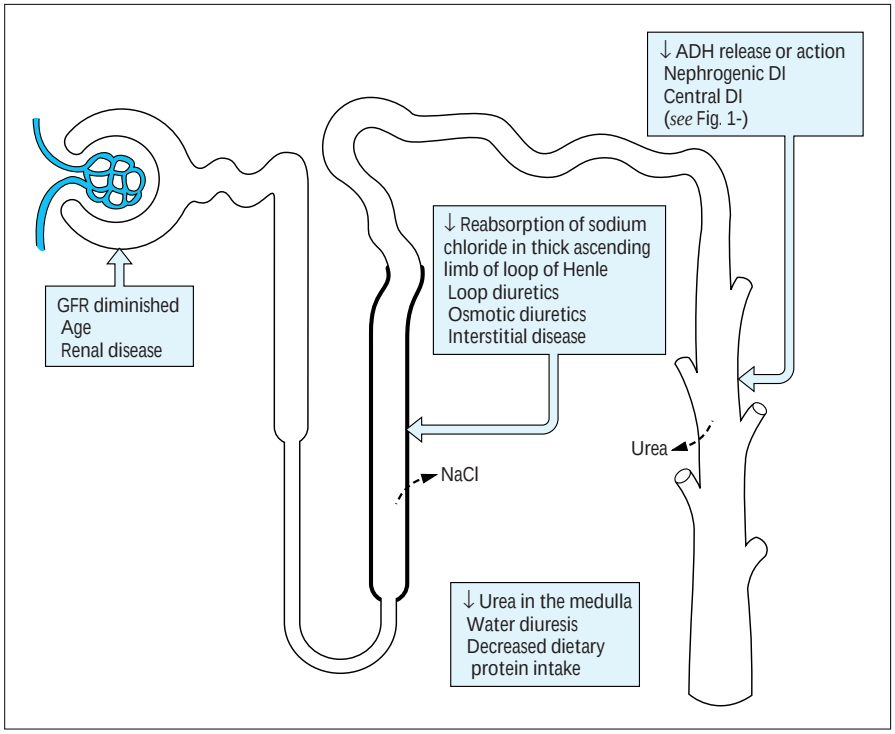


FIGURE 1-29

Pathogenesis of hypernatremia. The renal concentrating mechanism is the first line of defense against water depletion and hyperosmolality. When renal concentration is impaired, thirst becomes a very effective mechanism for preventing further increases in serum osmolality. The components of the normal urine concentrating mechanism are shown in Figure 1-2. Hypernatremia results from disturbances in the renal concentrating mechanism. This occurs in interstitial renal disease, with administration of loop and osmotic diuretics, and with protein malnutrition, in which less urea is available to generate the medullary interstitial tonicity.

Hypernatremia usually occurs only when hypotonic fluid losses occur in combination with a disturbance in water intake, typically in elders with altered consciousness, in infants with inadequate access to water, and, rarely, with primary disturbances of thirst [24]. GFR—glomerular filtration rate; ADH—antidiuretic hormone; DI—diabetes insipidus.

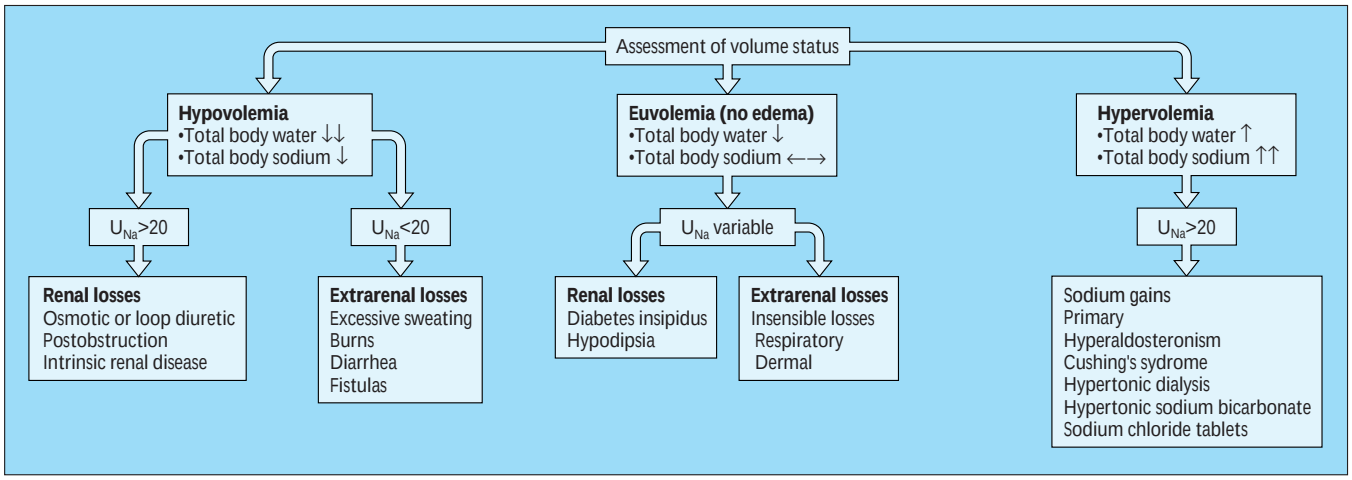


FIGURE 1-30

Diagnostic algorithm for hypernatremia. As for hyponatremia, the initial evaluation of the patient with hypernatremia involves assessment of volume status. Patients with hypovolemic hypernatremia lose both sodium and water, but relatively more water. On physical examination, they exhibit signs of hypovolemia. The causes listed reflect principally hypotonic water losses from the kidneys or the gastrointestinal tract.

Euvolemic hyponatremia reflects water losses accompanied by inadequate water intake. Since such hypodipsia is uncommon, hypernatremia usually supervenes in persons who have no access to water or who have a neurologic deficit that impairs thirst perception—the very young and the very old. Extrarenal water loss occurs from the skin and respiratory tract, in febrile or other hypermetabolic states. Very high urine osmolality reflects an intact osmoreceptor–antidiuretic hormone–renal response. Thus, the defense against the development of hyperosmolality requires appropriate stimulation of thirst and the ability to respond by drinking water. The urine sodium (U_{Na}) value varies with the sodium intake. The renal water losses that lead to euvolemic hypernatremia are a consequence of either a defect in vasopressin production or release (central diabetes insipidus) or failure of the collecting duct to respond to the hormone (nephrogenic diabetes insipidus) [23]. (*Modified from* Halterman and Berl [12]; with permission.)

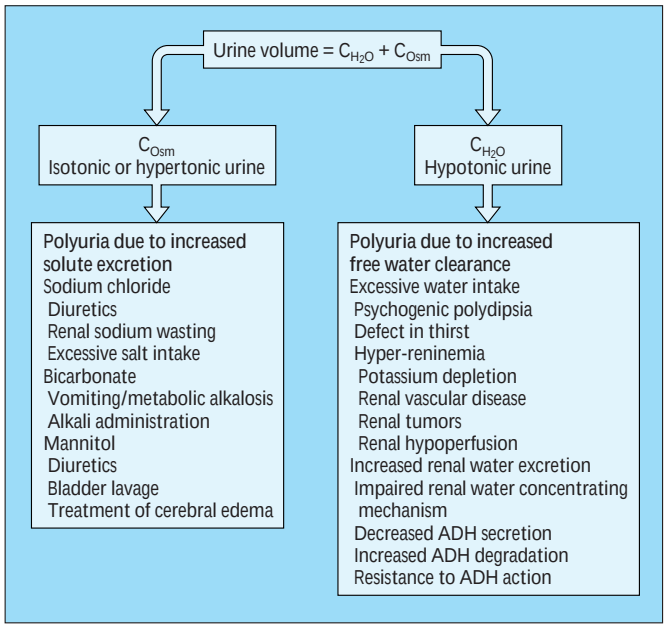


FIGURE 1-31

Physiologic approach to polyuric disorders. Among euvolemic hypernatremic patients, those affected by polyuric disorders are an important subcategory. Polyuria is arbitrarily defined as urine output of more than 3 L/d. Urine volume can be conceived of as having two components: the volume needed to excrete solutes at the concentration of solutes in plasma (called the *osmolar clearance*) and the other being the *free water clearance*, which is the volume of solute-free water that has been added to (positive free water clearance [CH_2O]) or subtracted (negative CH_2O) from the isotonic portion of the urine osmolar clearance (Cosm) to create either a hypotonic or hypertonic urine.

Consumption of an average American diet requires the kidneys to excrete 600 to 800 mOsm of solute each day. The urine volume in which this solute is excreted is determined by fluid intake. If the urine is maximally diluted to 60 mOsm/kg of water, the 600 mOsm will need 10 L of urine for effective osmotic clearance. If the concentrating mechanism is maximally stimulated to 1200 mOsm/kg of water, osmotic clearance will occur in a minimum of 500 mL of urine. This flexibility is affected when drugs or diseases alter the renal concentrating mechanism.

Polyuric disorders can be secondary to an increase in solute clearance, free water clearance, or a combination of both. ADH—antidiuretic hormone.

WATER DEPRIVATION TEST

Diagnosis	Urine Osmolality with Water Deprivation (mOsm/kg H_2O)	Plasma Arginine Vasopressin (AVP) after Dehydration	Increase in Urine Osmolality with Exogenous AVP
Normal	> 800	> 2 pg/mL	Little or none
Complete central diabetes insipidus	< 300	Indetectable	Substantial
Partial central diabetes insipidus	300–800	< 1.5 pg/mL	> 10% of urine osmolality after water deprivation
Nephrogenic diabetes insipidus	< 300–500	> 5 pg/mL	Little or none
Primary polydipsia	> 500	< 5 pg/mL	Little or none

* Water intake is restricted until the patient loses 3%–5% of weight or until three consecutive hourly determinations of urinary osmolality are within 10% of each other. (Caution must be exercised to ensure that the patient does not become excessively dehydrated.) Aqueous AVP (5 U subcutaneous) is given, and urine osmolality is measured after 60 minutes. The expected responses are given above.

FIGURE 1-32

Water deprivation test. Along with nephrogenic diabetes insipidus and primary polydipsia, patients with central diabetes insipius present with polyuria and polydipsia. Differentiating between these entities can be accomplished by measuring vasopressin levels and determining the response to water deprivation followed by vasopressin administration [25]. (*From* Lanese and Teitelbaum [26]; with permission.)

CLINICAL FEATURES OF DIABETES INSIPIDUS

- Abrupt onset
- Equal frequency in both sexes
- Rare in infancy, usual in second decade of life
- Predilection for cold water
- Polydipsia
- Urine output of 3 to 15 L/d
- Marked nocturia but no diurnal variation
- Sleep deprivation leads to fatigue and irritability
- Severe life-threatening hypernatremia can be associated with illness or water deprivation

FIGURE 1-33

Clinical features of diabetes insipidus. Other clinical features can distinguish compulsive water drinkers from patients with central diabetes insipidus. The latter usually has abrupt onset, whereas compulsive water drinkers may give a vague history of the onset. Unlike compulsive water drinkers, patients with central diabetes insipidus have a constant need for water. Compulsive water drinkers exhibit large variations in water intake and urine output. Nocturia is common with central diabetes insipidus and unusual in compulsive water drinkers. Finally, patients with central diabetes insipidus have a predilection for drinking cold water. Plasma osmolality above 295 mOsm/kg suggests central diabetes insipidus and below 270 mOsm/kg suggests compulsive water drinking [23].

CAUSES OF DIABETES INSIPIDUS

Central diabetes insipidus	Nephrogenic diabetes insipidus
Congenital	Congenital
Autosomal-dominant	X-linked
Autosomal-recessive	Autosomal-recessive
Acquired	Acquired
Post-traumatic	Renal diseases (medullary cystic disease, polycystic disease, analgesic nephropathy, sickle cell nephropathy, obstructive uropathy, chronic pyelonephritis, multiple myeloma, amyloidosis, sarcoidosis)
Iatrogenic	Hypercalcemia
Tumors (metastatic from breast, craniopharyngioma, pinealoma)	Hypokalemia
Cysts	Drugs (lithium compounds, demeclocycline, methoxyflurane, amphotericin, foscarnet)
Histiocytosis	
Granuloma (tuberculosis, sarcoid)	
Aneurysms	
Meningitis	
Encephalitis	
Guillain-Barré syndrome	
Idiopathic	

FIGURE 1-34
Causes of diabetes insipidus. The causes of diabetes insipidus can be divided into central and nephrogenic. Most (about 50%) of the central causes are idiopathic; the rest are caused by central nervous system involvement with infection, tumors, granuloma, or trauma. The nephrogenic causes can be congenital or acquired [23].

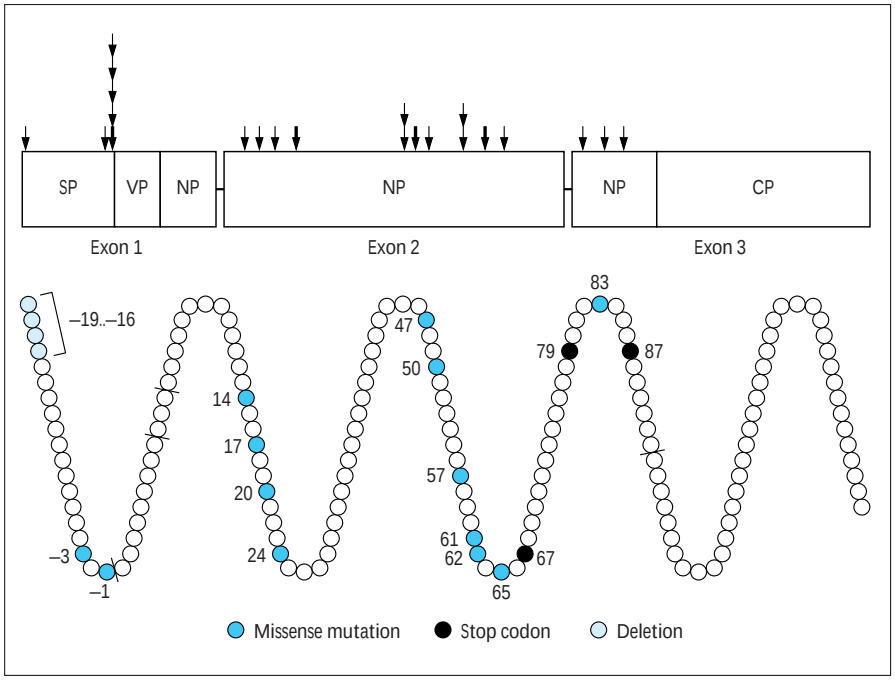


FIGURE 1-35
Congenital central diabetes insipidus (DI), autosomal-dominant form. This condition has been described in many families in Europe and North America. It is an autosomal dominant inherited disease associated with marked loss of cells in the supraoptic nuclei. Molecular biology techniques have revealed multiple point mutations in the vasopressin-neurophysin II gene. This condition usually presents early in life [25].
A rare autosomal-recessive form of central DI has been described that is characterized by DI, diabetes mellitus (DM), optic atrophy (OA), and deafness (DIDMOAD or Wolfram's syndrome). This has been linked to a defect in chromosome-4 and involves abnormalities in mitochondrial DNA [27].
SP—signal peptide; VP—vasopressin; NP—neurophysin; GP—glycoprotein.

TREATMENT OF CENTRAL DIABETES INSIPIDUS

Condition	Drug	Dose
Complete central DI	dDAVP	10–20 (g intranasally q 12–24 h
Partial central DI	Vasopressin tannate	2–5 U IM q 24–48 h
	Aqueous vasopressin	5–10 U SC q 4–6 h
	Chlorpropamide	250–500 mg/d
	Clofibrate	500 mg tid–qid
	Carbamazepine	400–600 mg/d

FIGURE 1-36

Treatment of central diabetes insipidus (DI). Central DI may be treated with hormone replacement or drugs. In acute settings when renal water losses are extensive, aqueous vasopressin (pitressin) is useful. It has a short duration of action that allows for careful monitoring and avoiding complications like water intoxication. This drug should be used with caution in patients with underlying coronary artery disease and peripheral vascular disease, as it can cause vascular spasm and prolonged vasoconstriction. For the patient with established central DI, desmopressin acetate (dDAVP) is the agent of choice. It has a long half-life and does not have significant vasoconstrictive effects like those of aqueous vasopressin. It can be conveniently administered intranasally every 12 to 24 hours. It is usually tolerated well. It is safe to use in pregnancy and resists degradation by circulating vasopressinase. In patients with partial DI, agents that potentiate release of antidiuretic hormone can be used. These include chlorpropamide, clofibrate, and carbamazepine. They work effectively only if combined with hormone therapy, decreased solute intake, or diuretic administration [23].

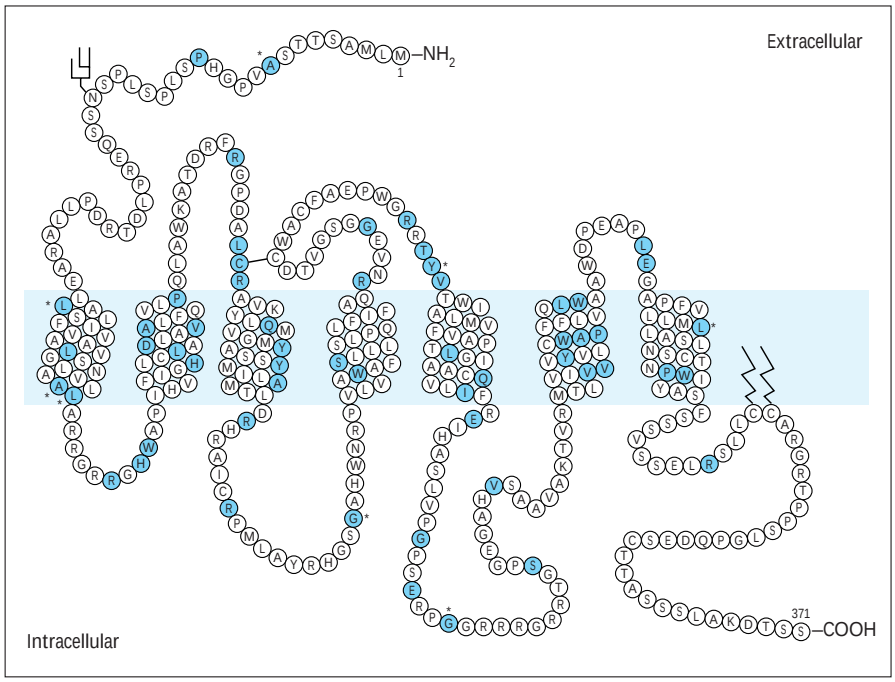


FIGURE 1-37

Congenital nephrogenic diabetes insipidus, X-linked–recessive form. This is a rare disease of male patients who do not concentrate their urine after administration of antidiuretic hormone. The pedigrees of affected families have been linked to a group of Ulster Scots who emigrated to Halifax, Nova Scotia in 1761 aboard the ship called "Hopewell." According to the Hopewell hypothesis, most North American patients with this disease are descendants of a common ancestor with a single gene defect. Recent studies, however, disproved this hypothesis [28]. The gene defect has now been traced to 87 different mutations in the gene for the vasopressin receptor (AVP-R2) in 106 presumably unrelated families [29]. (*From* Bichet, *et al.* [29]; with permission.)

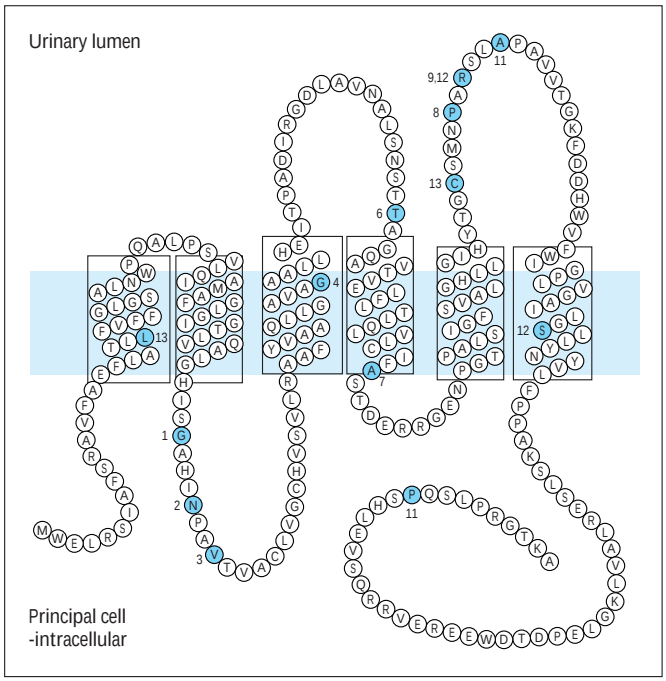


FIGURE 1-38

Congenital nephrogenic diabetes insipidus (NDI), autosomal-recessive form. In the autosomal recessive form of NDI, mutations have been found in the gene for the antiiuretic hormone (ADH)–sensitive water channel, AQP-2. This form of NDI is exceedingly rare as compared with the X-linked form of NDI [30]. Thus far, a total of 15 AQP-2 mutations have been described in total of 13 families [31]. The acquired form of NDI occurs in various kidney diseases and in association with various drugs, such as lithium and amphotericin B. (*From* Canfield *et al.* [31]; with permission.)

ACQUIRED NEPHROGENIC DIABETES INSIPIDUS: CAUSES AND MECHANISMS

Disease State	Defect in Generation of Medullary Interstitial Tonicity	Defect in cAMP Generation	Downregulation of AQP-2	Other
Chronic renal failure	✔	✔	✔	Downregulation of V_2 receptor message
Hypokalemia	✔	✔	✔	
Hypercalcemia	✔	✔		
Sickle cell disease	✔			
Protein malnutrition	✔		✔	
Demeclocycline		✔		
Lithium		✔	✔	
Pregnancy				Placental secretion of vasopressinase

FIGURE 1-39

Causes and mechanisms of acquired nephrogenic diabetes insidpidus. Acquired nephrogenic diabetes insipidus occurs in chronic renal failure, electrolyte imbalances, with certain drugs, in sickle cell disease and pregnancy. The exact mechanism involved has been the subject of extensive investigation over the past decade and has now been carefully elucidated for most of the etiologies.

PATIENT GROUPS AT INCREASED RISK FOR SEVERE HYPERNATREMIA

- Elders and infants
- Hospitalized patients receiving
  - Hypertonic infusions
  - Tube feedings
  - Osmotic diuretics
  - Lactulose
  - Mechanical ventilation
- Altered mental status
- Uncontrolled diabetes mellitus
- Underlying polyuria

FIGURE 1-40

Patient groups at increased risk for severe hypernatremia. Hypernatremia always reflects a hyperosmolar state. It usually occurs in a hospital setting (reported incidence 0.65% to 2.23% of all hospitalized patients) with very high morbidity and mortality (estimates of 42% to over 70%) [12].

SIGNS AND SYMPTOMS OF HYPERNATREMIA

Central Nervous System
Mild
- Restlessness
- Lethargy
- Altered mental status
- Irritability

Moderate
- Disorientation
- Confusion

Severe
- Stupor
- Coma
- Seizures
- Death

Respiratory System
Labored respiration

Gastrointestinal System
Intense thirst
Nausea
Vomiting

Musculoskeletal System
Muscle twitching
Spasticity
Hyperreflexia

FIGURE 1-41
Signs and symptoms of hypernatremia. Hypernatremia always reflects a hyperosmolar state; thus, central nervous system symptoms are prominent in affected patients [12].

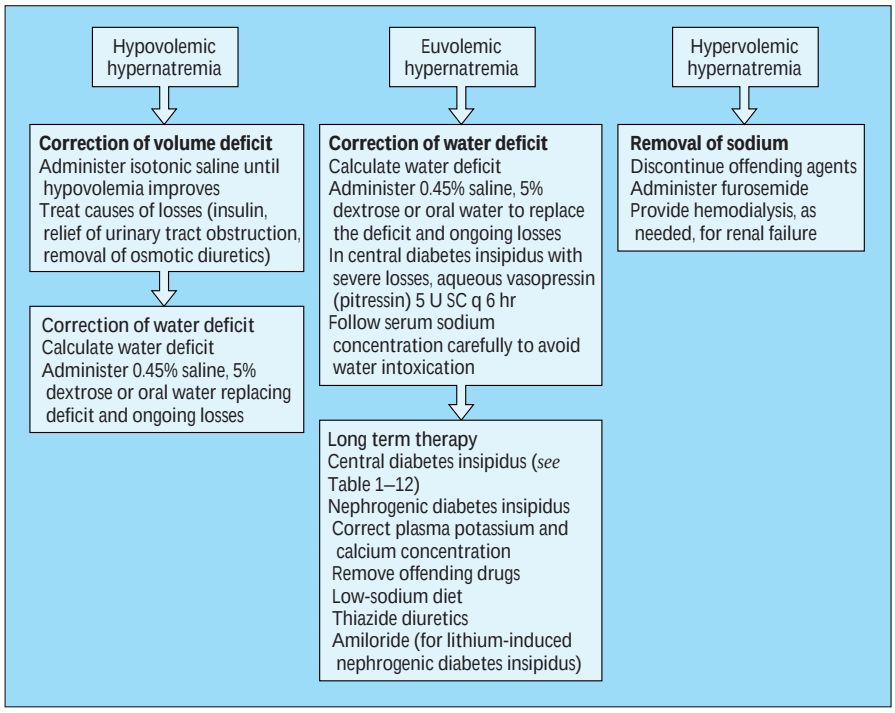


FIGURE 1-42
Management options for patients with hypernatremia. The primary goal in the treatment of hypernatremia is restoration of serum tonicity. Hypovolemic hypernatremia in the context of low total body sodium and orthostatic blood pressure changes should be managed with isotonic saline until blood pressure normalizes. Thereafter, fluid management generally involves administration of 0.45% sodium chloride or 5% dextrose solution. The goal of therapy for hypervolemic hypernatremias is to remove the excess sodium, which is achieved with diuretics plus 5% dextrose. Patients who have renal impairment may need dialysis. In euvolemic hypernatremic patients, water losses far exceed solute losses, and the mainstay of therapy is 5% dextrose. To correct the hypernatremia, the total body water deficit must be estimated. This is based on the serum sodium concentration and on the assumption that 60% of the body weight is water [24]. (*Modified from* Halterman and Berl [12]; with permission.)

GUIDELINES FOR THE TREATMENT OF SYMPTOMATIC HYPERNATREMIA*

Correct at a rate of 2 mmol/L/h
Replace half of the calculated water deficit over the first 12–24 hrs
Replace the remaining deficit over the next 24–36 hrs
Perform serial neurologic examinations (prescribed rate of correction can be decreased as symptoms improve)
Measure serum and urine electrolytes every 1–2 hrs

*If $U_{Na} + U_K$ is less than the concentration of P_{Na}, then water loss is ongoing and needs to be replaced.

FIGURE 1-43
Guidelines for the treatment of symptomatic hypernatremia. Patients with severe symptomatic hypernatremia are at high risk of dying and should be treated aggressively. An initial step is estimating the total body free water deficit, based on the weight (in kilograms) and the serum sodium. During correction of the water deficit, it is important to perform serial neurologic examinations.

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