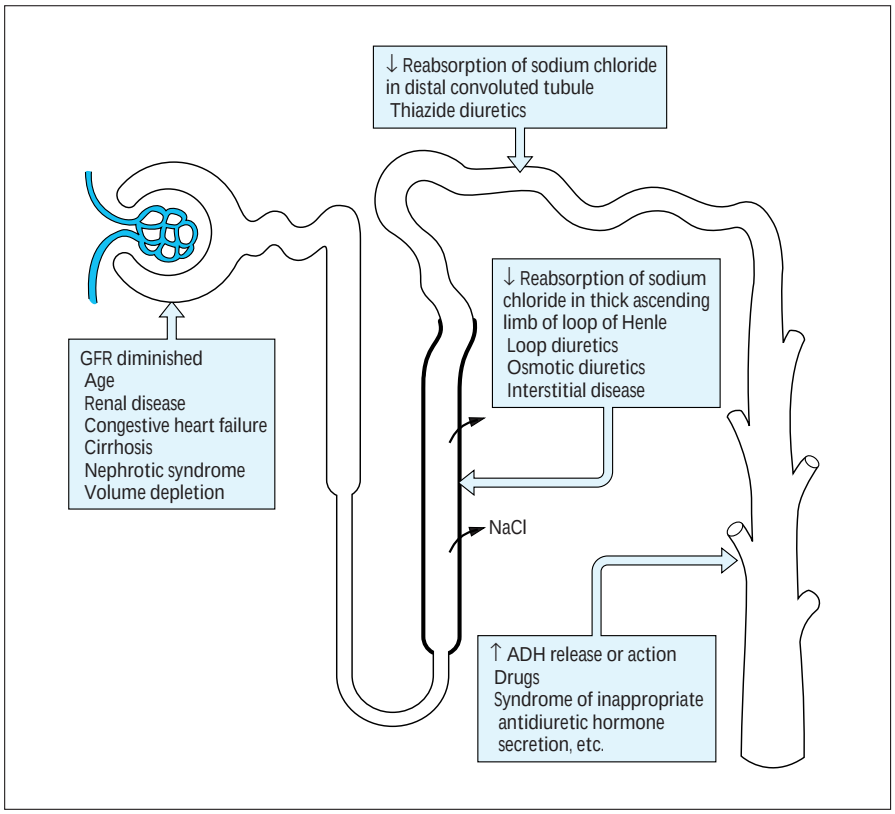


FIGURE 1-15

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.

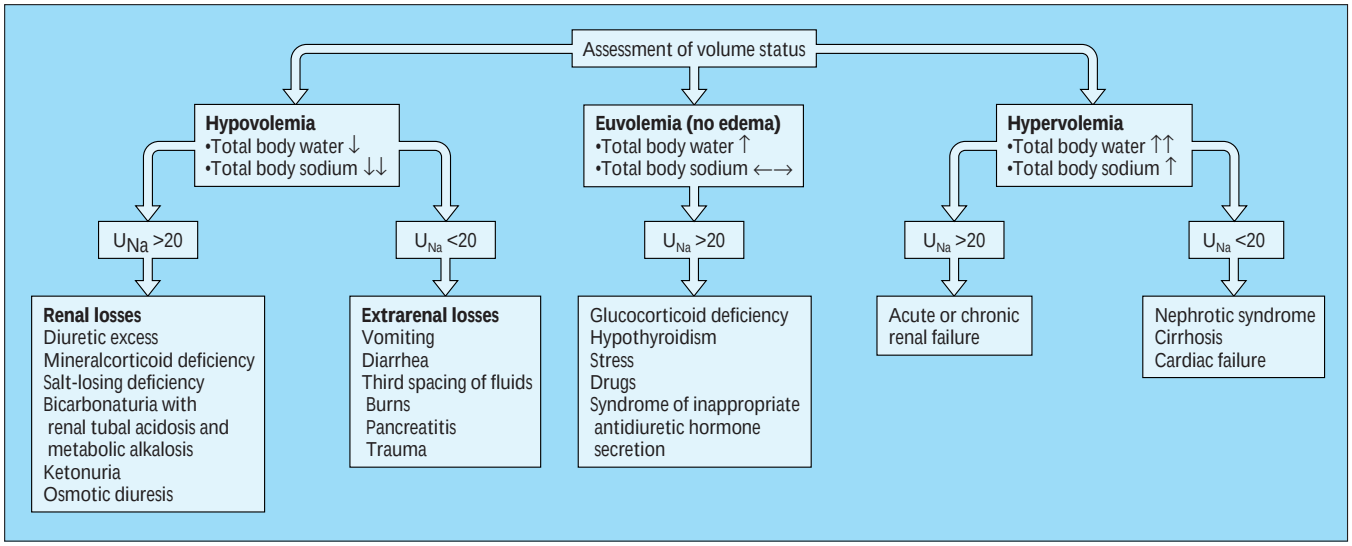


FIGURE 1-16

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

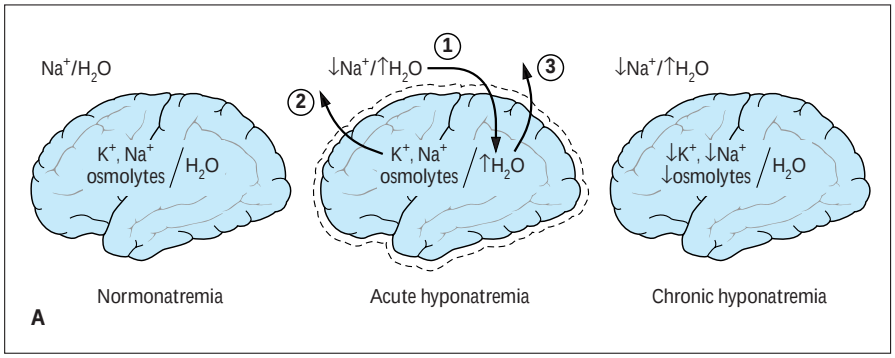
Severe
- Stupor
- Coma
- Pseudobulbar palsy
- Tentorial herniation
- Cheyne-Stokes respiration
- Death

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].



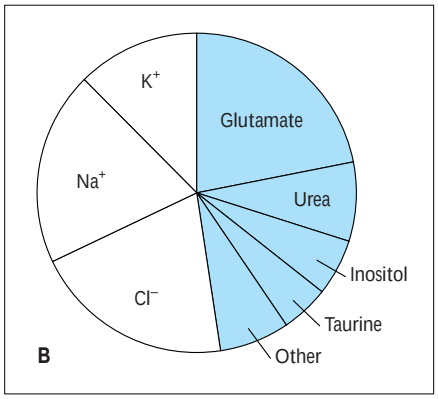


FIGURE 1-21

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.