Chapter 17: Fluids and Electrolytes

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FLUIDS AND SODIUM

PATHOPHYSIOLOGY

Total body water (TBW), which accounts for approximately 60% of total body weight, can be divided into intracellular fluid (ICF) and extracellular fluid (ECF) compartments. The ECF is comprised of intravascular fluid and extravascular, or interstitial, fluid. Body fluid compartment proportions for an adult are diagrammed in Figure 17-1. Figure 17-2 presents the individual characteristics of each compartment. Three fundamental homeostatic equilibriums govern the behavior of fluids: the osmotic equilibrium, the electric equilibrium, and the acid-base equilibrium.

FIGURE 17-1.
Relation of fluid compartments to body weight and each other. ECF = extracellular fluid; ICF = intracellular fluid; IF = interstitial (extravascular) fluid; IVF = intravascular fluid; TBW = total body water.

As a function of	TBW	ICF	ECF	IF	IVF
Total weight	60%	40%	20%	15%	5%
TBW		67%	33%	25%	8%
ECF compartment				75%	25%

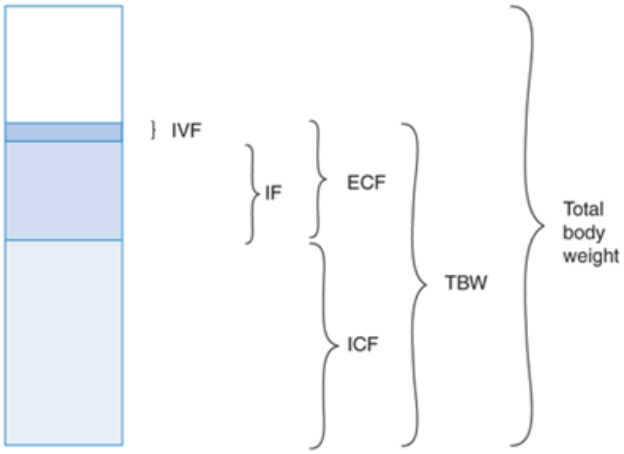
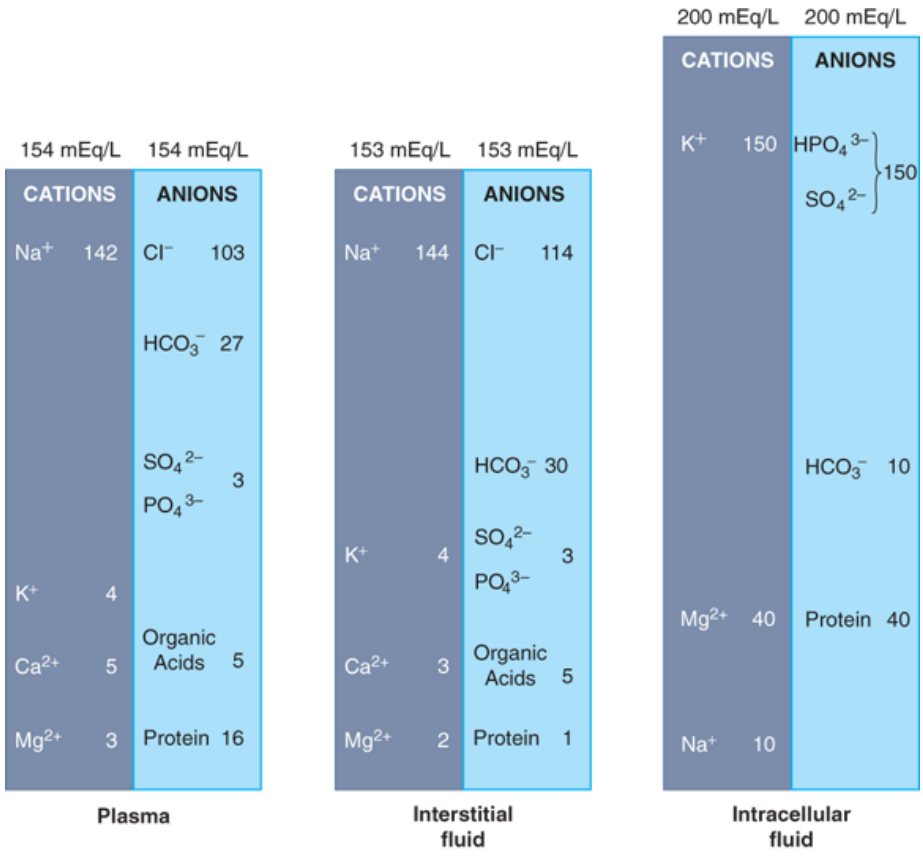


FIGURE 17-2.
Chemical composition of body fluid compartments. [Reproduced with permission from Brunicardi FC, Andersen DK, Billiar TR, et al (eds): *Schwartz's Principles of Surgery*, 10th ed. McGraw-Hill, Inc., 2015. Fig 3-2, p. 67.]



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The key point is that sodium is much more concentrated in the ECF (~140 mEq/L) than in the ICF (~10 mEq/L) but is equal in both compartments of the ECF because the capillary membrane between intravascular fluid and interstitial fluid is permeable to water and electrolytes. In contrast, the cell membrane is permeable to water but not to electrolytes, which are moved through ionic pumps against gradient to keep the intracellular sodium concentration constant around 10 mEq/L and potassium at 150 mEq/L. Table 17-1 lists the electrolyte concentration of body fluids and the most commonly used therapeutic solutions. Table 17-2 defines commonly used terms that describe measures or characteristics of electrolytes and/or disorders.

TABLE 17-1

Electrolyte Concentrations of Fluids (mEq/L)

Solution	Plasma	Interstitial	Intracellular	Normal Saline	Lactated Ringer's Solution
Cations					
Sodium	142	144	10	154	130
Potassium	4	4.5	150	—	4
Magnesium*	2	1	40	—	—
Calcium†	5	2.5	—	—	3
Total cations	153	152	200	154	137
Anions					
Chloride	104	113	—	154	109
Lactate‡	—	—	—	—	28
Phosphates	2	2	120	—	—
Sulfates	1	1	30	—	—
Bicarbonate	27	30	10	—	—
Proteins	13	1	40	—	—
Organic acids	6	5	—	—	—
Total anions	153	152	200	154	137

*Multiply by 0.411 to convert to International System of Units (SI) units in mmol/L.

†Multiply by 0.25 to convert to SI units in mmol/L.

‡Multiply by 0.323 to convert to SI units in mmol/L.

TABLE 17-2

Definition of Terms

Term	Definition	Comments
Mole	6.02×10^{23} molecules of a substance	Unit measure used in International System of Units format.
Equivalent	Mass (in grams) of a mole of a substance divided by charge of substance	Unit of measure used in conventional lab values.
Osmole	Amount of a substance (in moles) that dissociates to form 1 mole of osmotically active particles	
Osmolarity	Measure of solute concentration per unit *volume* of solvent	Osmolarity varies with changing temperature, because water changes its volume according to temperature.
Osmolality	Measure of solute concentration per unit *mass* of solvent	Osmolality is the preferred term because it remains constant with changes in temperature.
Tonicity or effective osmolality	Measure of the osmotic pressure gradient between two solutions, across a semipermeable membrane	Tonicity is affected only by solutes that cannot cross a semipermeable membrane. For example, tonicity is not affected by urea or glucose as they cross semipermeable membranes

When two solutions are separated by a membrane that is permeable only to water, water crosses into the compartment with the more concentrated solution to equalize the ion concentration in each. The force driving this movement is "osmotic pressure."[1] In human fluids, the substances that contribute the most to osmotic pressure in ECF are Na^+ and the anions HCO_3^- and Cl^-, plus glucose. In physiology, this force is called *effective osmolality* or *tonicity*. This force is not affected by molecules like urea that may enter freely into the cells. The formula to calculate **effective osmolality** or **tonicity** is

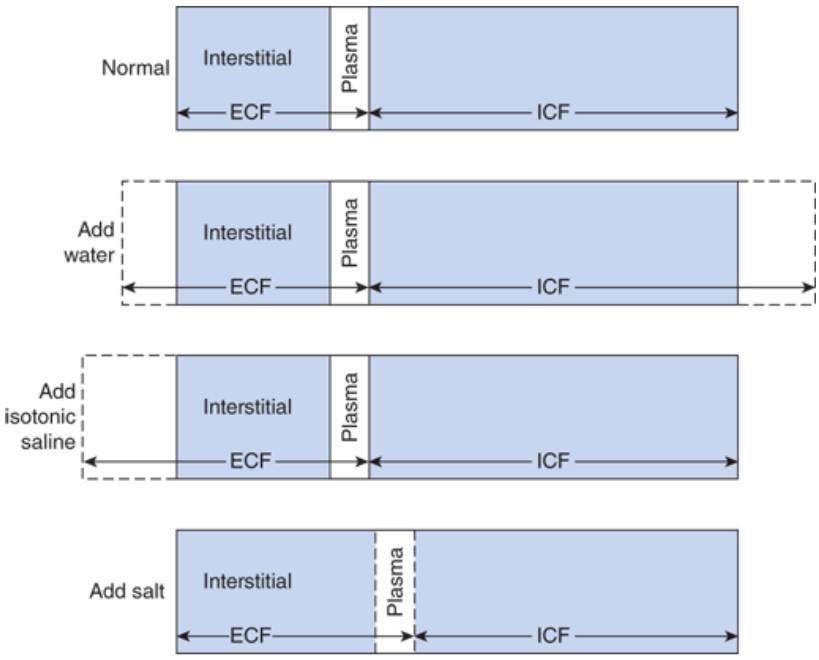
$$2 \times [Na] + glucose/18 \text{ (normal range, 275–290 mOsm/L)}$$

If values are in SI units, these are already molar (mmol/L, for example), so these do not need to be divided by their molecular weight.

When 1 L of free water is added to the ECF it crosses the cell membrane into the ICF to equalize ECF osmolality. The result is TBW expansion and slight reduction in osmolality (**Figure 17-3**). When 1 L of isotonic saline solution 0.9% is added to the ECF, there is no movement of water into the cells, and the final result is ECF expansion only[2] (Figure 17-3).

FIGURE 17-3.

Distribution of total body water into the intracellular fluid (ICF) and extracellular fluid (ECF) compartments. Addition of water expands both compartments. Addition of isotonic saline expands only the ECF, whereas addition of salt without water expands the ECF at the expense of the ICF. [Reproduced with permission from Eaton DC, Poole JP (eds): *Vander's Renal Physiology*, 8th ed. McGraw-Hill, Inc., 2013. Fig 6-1.]



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In contrast, when there is a fluid loss and a consequent increase in osmolality, the subject feels thirsty and the antidiuretic hormone (ADH) is secreted by the pituitary gland stimulated by baroreceptors and osmoreceptors, with a consequent urine water reabsorption and vasoconstriction.[1,2,3]

A useful index to roughly evaluate Na^+ balance and the ability of the kidney to concentrate or dilute the urine is the **electrolyte free water clearance (CH_2Oe)**.[2] It is expressed with the formula:

$$_CH_2Oe = V_{urine}(1 - U_{Na+} + U_{K+}/P_{Na+})$$

where V_{urine} is urine volume, U_{Na+} is the urine sodium level, U_{K+} is the urine potassium level, and P_{Na+} is the plasma sodium level. When more water is reabsorbed, $_CH_2Oe$ is negative and hyponatremia will develop. When more water is excreted, $_CH_2Oe$ is positive and hypernatremia will be present. The $_CH_2Oe$ is calculated using a 24-hour urine collection, which is not possible in the ED. The spot urine calculation of the ratio, $U_{Na+} + U_{K+}/P_{Na+}$, is a reliable compromise. In hyponatremia, the ratio is >1, and in hypernatremia it is ≤0.5. A ratio between 0.5 and 1 is considered normal.

HYPONATREMIA

The human body tightly maintains serum [Na^+] between 138 and 142 mEq/L despite what may be marked changes in daily intake depending on the person's diet. Hyponatremia is a condition of excess water relative to Na^+ and is defined as a serum [Na^+] <138 mEq/L. However, symptomatic hyponatremia rarely occurs until [Na^+] falls below 135 mEq/L or lower. In the setting of normal water intake, high circulating levels of ADH with subsequent water retention is a prerequisite for the development of hyponatremia.[3] Urine osmolality is always >100 mOsm/L H_2O with the exception of samples from patients with psychogenic polydipsia, which drives down urine osmolality below the typical minimum.

EPIDEMIOLOGY

Mild hyponatremia is common, with an incidence of 15% to 30% in hospitalized patients; only 1% to 4% of patients have sodium levels below 130 mEq/L.[4,5] Approximately 50% of cases are iatrogenic from administration of hypotonic fluids.[4,5]

CLASSIFICATION AND ETIOLOGY

The concentration of Na^+ does not give information regarding volume status. **Therefore, the first step in the evaluation should include a clinical evaluation of ECF volume status plus measured and calculated plasma osmolarities.** In *true* hyponatremia, plasma osmolality is reduced; in *factitious* hyponatremic states, it is normal or increased as shown in Table 17-3.[2]

TABLE 17-3

Classification of Hyponatremia According to Serum Osmolality

Serum Osmolality	Clinical Conditions	Mechanisms
Hyperosmolality (Hypertonic hyponatremia)	Hyperglycemia Mannitol administration Glycerol administration Maltose administration	Hyponatremia due to osmotic diuresis
Iso-osmolality (Pseudohyponatremia)	Hyperproteinemia Hyperlipidemia	Displacement of serum water by elevated concentration of lipids or protein creating laboratory misinterpretation of normal [Na^+]
Hypo-osmolality (Hypotonic hyponatremia)	See Table 17-4	Hypervolemic Normovolemic Hypovolemic

HYPEROSMOLAR HYPONATREMIA (P_{osm} >295 mOsm/kg H_2O)

Hyperosmolar hyponatremia occurs when large quantities of osmotically active solutes accumulate in the ECF space. In this setting, there is a net movement of water from the ICF to the ECF, thereby effectively diluting the ECF [Na^+]. **This happens commonly with severe hyperglycemia.** Each 100 milligram/dL increase in plasma glucose above the normal level of 100 milligrams/dL decreases the serum [Na^+] by 1.6 mEq/L.[1,2,3,4] Other causes of hypertonic hyponatremia are administration of osmotic agents like mannitol, glycerol, and maltose, causing an osmolar gap and hyponatremia. The osmolar gap is the difference between measured osmolality and calculated osmolality. Normally the difference is around 10 mOsm/L; if it is >15 mOsm/L it means that a nondetectable agent with osmotic activity is present, causing an osmolar gap. A consequent osmotic diuresis will cause [Na^+] deficit with volume depletion that must be treated with saline solution. Other substances like methanol, alcohol, ethylene glycol, and urea, although causing an osmolar gap, do not cause water movement across membranes and therefore do not cause hyponatremia (see chapter 185, "Alcohols" in Toxicology section for more details).[2]

ISO-OSMOLAR HYPONATREMIA (P_{osm} 275 TO 295 mOsm/kg H_2O)

Pseudohyponatremia is a factitiously low value of [Na^+] that may occur in the setting of severe hyperproteinemia or hyperlipidemia. This phenomena is due to displacement of serum water by an elevated concentration of lipids or protein creating laboratory misinterpretation of normal [Na+]; some laboratories use instruments that avoid this laboratory error; check with your laboratory administrator. Patients are asymptomatic; treatment is not needed.

HYPO-OSMOLAR HYPONATREMIA (P_{osm} <275 mOsm/kg H_2O)

In Table 17-4,[6] the different causes of hypo-osmolar (hypotonic) hyponatremia according to volume status are listed.[2,3] Hyponatremia develops due to an increase in ADH secretion and activity, which causes impaired water excretion and increased water reabsorption. In situations like heart failure,[7,8] cirrhosis,[9] and nephrotic syndrome, the effective arterial blood volume is decreased because water is mainly distributed to the interstitial space. Thus Na^+ and water reabsorption are increased, and water excretion is reduced.

TABLE 17-4

Classification, Differential Diagnosis, and Features of Hyponatremia According to Volume Status

	Clinical Conditions	Orthostatic Hypotension	Edema	$U_{[Na+]}$, mEq/L*	U_{osm}, mOsm/L*
Hypervolemic hypernatremia	CHF Cirrhosis Nephrotic syndrome Acute and chronic kidney disease	Absent	Yes	Compensated: >20 Decompensated: <10	Compensated: <100 Decompensated: >100
Normovolemic hyponatremia	Psychogenic polydipsia Glucocorticoid deficit Hypokalemia Drugs SIADH	Absent	No	>20	>100
Renal hypovolemic hyponatremia	Diuretics Mineralocorticoid deficit Salt-losing nephropathy	Normally present	No	>20	>100
Extrarenal hypovolemic hyponatremia	Vomiting Diarrhea	Normally present	No	<10	>100

Abbreviations: CHF = congestive heart failure; SIADH = syndrome of inappropriate ADH excretion.

Two important hyponatremic disorders are the **syndrome of inappropriate ADH secretion** and the less common **cerebral salt-wasting syndrome.**[1,2] Both conditions are diagnoses of exclusion after dismissing other causes of hyponatremia. The onset of both syndromes is linked to chronic cerebral disease, but syndrome of inappropriate ADH secretion may also be caused by many other diseases and conditions as described in **Table 17-5**. In syndrome of inappropriate ADH secretion, volume status is normal, whereas in cerebral salt-wasting syndrome, there is hypovolemia; therefore, these two disorders are treated differently (see treatment section below).

TABLE 17-5

Causes of Syndrome of Inappropriate Antidiuretic Hormone Secretion

1. Neurologic and psychiatric disorders
   a. Infections: meningitis, encephalitis, brain abscess
   b. Vascular: thrombosis, subarachnoid or subdural hemorrhage, temporal arteritis, cavernous sinus thrombosis, stroke
   c. Malignancy: primary or metastatic
   d. Traumatic brain injury
   e. Psychosis, delirium tremens
   f. Other: Guillain-Barré syndrome, neurosurgery
2. Drugs
   a. Cyclophosphamide
   b. Carbamazepine
   c. Vinca alkaloids
   d. Thioridazine, other phenothiazines, haloperidol
   e. Selective serotonin reuptake inhibitors and selective serotonin and norepinephrine reuptake inhibitors
   f. Bromocriptine
   g. Narcotics, opiate derivatives
   h. Amiodarone
   i. Desmopressin overtreatment of DI or enuresis
3. Lung diseases
   a. Tuberculosis
   b. Lung abscess, empyema
   c. Acute respiratory failure
4. Non-CNS tumors with ectopic production of vasopressin
   a. Carcinoma of lung (small cell, bronchogenic), duodenum, pancreas, thymus, olfactory neuroblastoma, bladder, prostate, uterus
   b. Lymphoma, leukemia
   c. Sarcoma

Abbreviations: DI = diabetes insipidus.

Methylenedioxymethamphetamine (MDMA or Ecstasy) intoxication is an uncommon but important cause of hyponatremia that may be profound. This "club drug" induces inappropriate secretion of ADH and causes increased gut water absorption[10] (see also chapter 188, "Hallucinogens").

CLINICAL FEATURES

The most important symptoms of hyponatremia are due to its effects on the brain; symptoms can be divided into moderately severe and severe, according to a European clinical practice guideline.[3,4] Moderately severe symptoms often start when a plasma [Na] is <130 mEq/L and consist of headache, nausea, disorientation, confusion, agitation, ataxia, and areflexia. When [Na^+] reach levels <120 mEq/L, severe symptoms may develop including intractable vomiting, seizures, coma, and ultimately respiratory arrest due to brainstem herniation. Brain injury may become irreversible. The symptoms of hyponatremia can be due to many other conditions, and clinicians are cautioned to consider other etiologies before making treatment decisions.[4] The presence of hyponatremia-related symptoms is directly related to the rapidity of onset. After a certain period, brain cells begin to adapt to hyponatremia. Initially the hypo-osmolality drives water into the brain cells yielding swelling.[2,3] Due to the rigid skull, intracranial hypertension occurs and the described symptoms begin. After 48 hours, the brain cells start to adapt by extruding Na^+, K^+, Cl^-, and organic osmolytes like glycine and taurine from the cells, reducing cell osmolality and preventing further water uptake. In several clinical or physiologic conditions, this adaptation mechanism is impaired, as in the syndrome of inappropriate ADH secretion, in children, in menstruating women, and in hypoxia. In such cases, symptoms are more severe and persistent.

DIAGNOSIS

The diagnosis of hyponatremia and its subtypes is based on the clinical findings of volume status in association with specific laboratory values including serum [Na^+], serum osmolality, volume status, urinary sodium (U_{Na+}), and urine osmolality (U_{osm}). Acute and chronic hyponatremia are defined by an onset time of less than (acute) or greater than (chronic) 24 to 48 hours. Experts recommend that when duration is unknown, the hyponatremia should be assumed to be chronic and treated as chronic with a longer correction time. If urine osmolality is not readily available from the laboratory, it can be estimated using urinary specific gravity (π). Consider the numerals in the hundredths and thousandths decimal places of the π as whole numbers and multiply them by 35 to obtain U_{osm}. As an example, for a π of 1.0<u>05</u>, U_{osm} = 05 × 35 = 175 mOsm/L.[1] Table 17-4 lists the values of U_{Na+} and U_{osm} in different classifications of hyponatremia according to volume status and the differential diagnosis for each classification. As a rule, only in patients with edematous syndromes and in patients with vomiting and diarrhea will U_{Na+} be found to be <10 mEq/L.[6] The diagnostic criteria for syndrome of inappropriate ADH secretion are listed in **Table 17-6**.

TABLE 17-6

Syndrome of Inappropriate Secretion of Antidiuretic Hormone Diagnostic Criteria

Diagnostic Criteria
Hypotonic hyponatremia with (P_{osm} <275 mOsm/kg H_2O)
Inappropriately elevated urinary osmolality (usually >200 mOsm/kg)
Elevated urinary [Na^+] (typically >20 mEq/L)
Clinical euvolemia
Normal adrenal, renal, cardiac, hepatic, and thyroid functions

Use care when assessing patients with potential exercise-associated hyponatremia. Since the worldwide effort to encourage consuming fluids during endurance exercise beginning in the early 1980s, overhydration with hypotonic fluids is now being seen. If a postexercise athlete presents with bloating, nausea, vomiting, and edema (check wrists and fingers), consider hyponatremia; dehydration presents with excessive thirst, sunken eyes, poor skin turgor, and postural hypotension.

TREATMENT

Treatment of hyponatremia is guided by four variables: severity of symptoms, rate of onset, volume status, and the current serum [Na^+]. **When [Na^+] is <120 mEg/L, the patient presents with severe neurologic symptoms, and hyponatremia is acute, the initial treatment includes infusion of 3% hypertonic saline** as recommended by European guidelines,[4] and U.S. experts[5,11] (**Table 17-7**).

TABLE 17-7

Treatment for Hyponatremia Symptomatic with Seizures or Coma

Step 1	Assess for indication for 3% hypertonic saline: severe symptoms of hyponatremia such as seizures or coma with suspected impending brainstem herniation in setting of acute* or chronic† hyponatremia
Step 2	Infuse 100 mL of 3% hypertonic saline IV over 10–15 min‡
Step 3	Measure serum sodium level after each 3% hypertonic saline infusion
Step 4	Stop infusion when symptoms improve, or a target of 5 mEq/L (range 4–6 mEq/L) increase in serum sodium concentration is achieved.
Step 5	May repeat 100 mL of 3% hypertonic saline up to three total doses, or a total of 300 mL IV of 3% hypertonic saline.
Step 6	Keep the IV line open with minimal volume of 0.9% normal saline until cause-specific treatment is started. Limit increase in sodium level to no more than 8 mEq/L during the first 24 h.

*Both European guidelines and U.S. expert panel recommend 3% hypertonic saline infusion for acute life-threatening hyponatremia, which is most commonly due to self-induced water intoxication during endurance exercise, psychiatric illness, in association with methylenedioxymethamphetamine intoxication, or intracranial pathology or increased intracranial pressure.

†European guidelines state that regardless of onset of acute or chronic hyponatremia, presence of seizures or coma is an indication for brief infusion of hypertonic saline to improve symptoms.

‡European guidelines recommend a prompt 150-mL 3% hypertonic saline infusion over 20 minutes, then checking the serum sodium concentration after 20 minutes while repeating an infusion of 150 mL 3% hypertonic saline for the next 20 minutes, repeating this sequence up to twice more, and stopping with clinical improvement or when target sodium level is reached.

Raising serum sodium by 4 to 6 mEq/L is typically all that is required to see an improvement in severe neurologic symptoms.[4,11,12] The volume of a saline solution required to raise the serum sodium the desired amount can be calculated. First calculate the expected change in serum sodium from the infusion of a liter of saline solution. Second, determine the portion of the liter required to raise the sodium the desired amount. To calculate the expected change in serum sodium after an infusion of 1 L IV saline, use the following formula:

$$\text{Expected change in serum } Na^+ \text{ (mEq/L)} = \text{Infusate } Na^+ \text{ (mEq/L)} - \text{serum } Na^+ \text{ (mEq/L)}/(\text{TBW} + 1)$$

Estimate TBW based on age, sex, and weight of the patient. For children and adult males <65 years old, TBW is 60% of the weight; for adult females <65 years old and elderly males, TBW is 50% of the weight; for elderly females, TBW is 45% of weight. Three percent hypertonic saline contains 513 mEq/L of sodium. As an example, a clinician desires to raise the sodium level of a 68-year-old male having seizures secondary to a [Na^+] of 108 mEq/L, using 3% hypertonic saline. The man weighs 70 kg; therefore, the calculated TBW would be [$0.5_{\text{correction factor}}$ × 70 kg] = 35 L. Change in [Na^+] expected = (513 – 108)/(35 + 1) = 11.25 mEq rise in serum sodium if the man was given 1000 mL of 3% hypertonic saline. The fraction of the liter of 3% hypertonic saline required to raise serum sodium 5 mEq/L would be 444 mL of 3% hypertonic saline.

After clinical improvement in severe symptoms, the 3% hypertonic saline must be stopped and either continued at a slower rate or with a different [Na^+] in the solution. For patients with acute hyponatremia with mild or moderate symptoms, 3% hypertonic saline infusion at 0.5 to 2 mL/kg/h can be given with frequent [Na^+] checks every 2 hours. Na^+ and K^+ lost in urine should be replaced with the appropriate solution.[1,2]

In chronic hyponatremia, the [Na^+] correction should be slower than for acute hyponatremia. Rapid correction increases risk for the most dangerous complication of treatment, the osmotic demyelination syndrome. For **chronic hyponatremia [Na^+], the correction rate should**

not exceed 6 mEq/24 h in high-risk patients and 12 mEq/24 h in low-risk patients (see "Osmotic Demyelination Syndrome" section below for risks).[3,4] Hypertonic (3%) saline can be given at a low infusion rate, 0.5 to 1 mL/kg/h, with frequent [Na^+] checks. Isotonic (0.9%) saline is frequently used (sometimes before the [Na^+] is known), especially for the treatment of mild hyponatremia; however, the additional fluid load must be accounted for in treatment calculations. Loop diuretics (primarily furosemide, starting with a small dose of 20 milligrams IV) may be used in addition to treatment with saline infusions. Urine volume and [Na^+] should be strictly measured. Specific recommendations for hyponatremia treatment are summarized in **Table 17-8**.[2]

TABLE 17-8

Cause-Specific Treatment for Hyponatremia

Clinical Condition	Therapy	Cautions/Comments
Chronic heart failure and cirrhosis	Loop diuretics, water restriction. Consider vasopressin antagonists* if the above therapies fail for patients with chronic heart failure.	When vasopressin antagonists* are used serum [Na^+] should be frequently measured to avoid hypernatremia. FDA recommends against vasopressin antagonists in patients with liver disease.
Nephrotic syndrome	Water restriction	
Acute or chronic kidney disease	Water restriction	Frequent assessment of creatinine
Psychogenic polydipsia	Water restriction	Treat the underlying psychiatric disease
Hypothyroidism	Levothyroxine	Several days of therapy are typically required to correct hyponatremia.
Glucocorticoid deficiency	Hydrocortisone. If neurologic symptoms, consider vasopressin antagonists* if resistant to hydrocortisone.	When vasopressin antagonists* are used, [Na^+] should be frequently measured.
SIADH	Water restriction. Enhanced Na^+ and protein intake + furosemide. Vasopressin antagonists* can be used for [Na^+] <125 mEq/L. Demeclocycline. Lithium.	Isotonic (0.9%) NaCl may worsen hyponatremia; when vasopressin antagonists* are used, [Na^+] should be frequently measured.
Diarrhea and vomiting	Isotonic (0.9%) NaCl. Add KCl if hypokalemia is present.	Treat the cause, monitor hemodynamic status
Diuretics (most commonly thiazides)	Stop diuretic. KCl may be sufficient in patients with coexistent potassium depletion and normal dietary sodium intake. NaCl can be given orally.	Slow correction is recommended. Do not overcorrect K^+ deficit.
Mineralocorticoid deficiency	Replace volume deficit. Fludrocortisone therapy is indicated once diagnosis is confirmed.	Mechanism: volume depletion → ↑ ADH → decreases water excretion, ↑ Na loss
Salt losing nephropathies	Isotonic (0.9%) NaCl.	
Cerebral salt wasting	Isotonic (0.9%) NaCl. Fludrocortisone may be considered after the diagnosis is confirmed.	NaCl orally at home

Abbreviations: ADH = antidiuretic hormone; FDA = Food and Drug Administration; SIADH = syndrome of inappropriate antidiuretic hormone secretion.

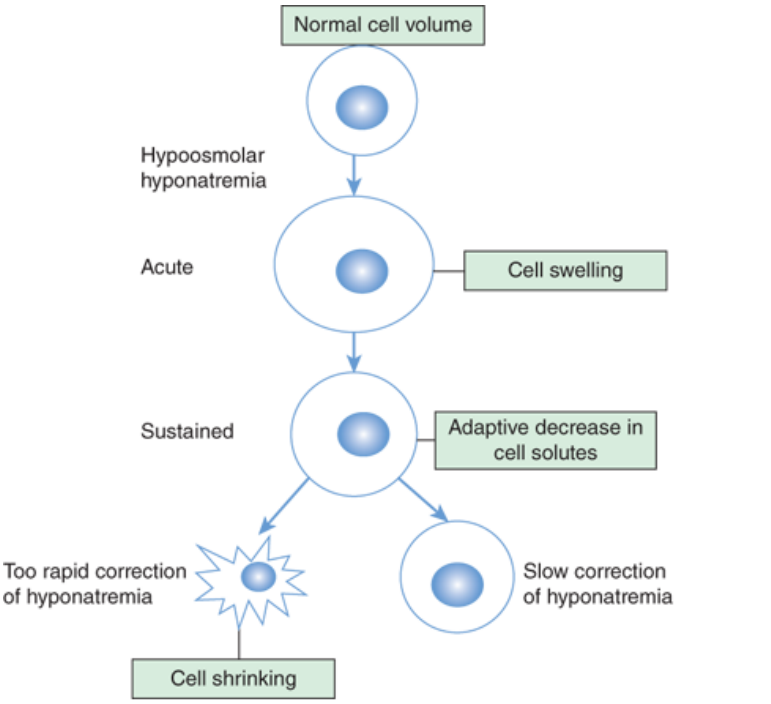
*Vasopressin antagonists or vaptans are rarely started in the ED; they are not indicated unless [Na^+] <125 mEq/L; starting doses are tolvaptan, 15 milligrams PO daily; and conivaptan, 20 milligrams loading dose IV over 30 minutes, then continuous infusion of 20 milligrams over 24 hours for 2 to 4 days.

COMPLICATIONS OF TREATMENT

Osmotic Demyelination Syndrome

Osmotic demyelination syndrome is caused by rapid correction of hyponatremia (>12 mEq/L/24 h) as water moves from cells to ECF yielding intracellular dehydration (Figure 17-4). Risk factors for osmotic demyelination syndrome include [Na^+] <120 mEq/L, chronic heart failure, alcoholism, cirrhosis, hypokalemia, malnutrition, and treatment with vasopressin antagonists such as tolvaptan. Main symptoms are dysarthria, dysphagia, lethargy, paraparesis or quadriparesis, seizures, coma, and death. The treatment of [Na^+] overcorrection is rarely done in the ED but consists of giving 5% dextrose in water at 3 mL/kg/h, loop diuretics, and desmopressin.[3,4]

FIGURE 17-4.
Adaptation of brain volume to hyponatremia and effect of correction.



HYPERNATREMIA

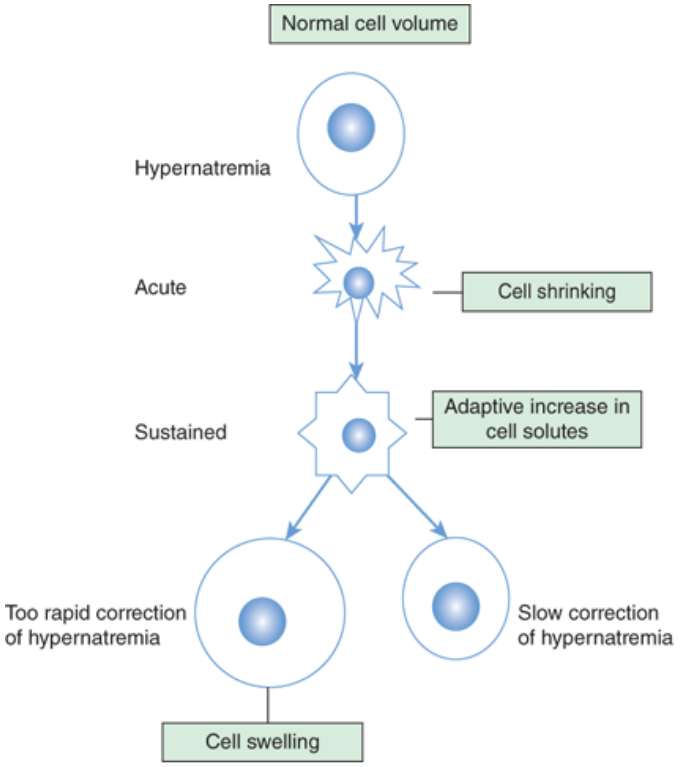
Hypernatremia is defined as serum or plasma **[Na^+] >145 mEq/L and hyperosmolality** (serum osmolality >295 mOsm/L).

PATHOPHYSIOLOGY

Hypernatremia results from a deficit in TBW and/or a net gain of Na^+ (less common). When [Na^+] and osmolality increase, normal subjects become thirsty, drink free water, and the Na^+ level returns toward normal. Any clinical situation that impairs the patient's sense of thirst, limits the availability of water, limits the kidney's ability to concentrate urine, or results in increased salt intake predisposes the patient to hypernatremia. Elderly patients, decompensated diabetics, infants, and hospitalized patients are at particular risk of developing hypernatremia. In addition, hypernatremia may be the result of loss of free water in diarrheal stools or in the urine.[13]

As in hyponatremia, symptoms will be more severe and evident when the onset is rapid; after the first 48 hours, there is an adaptation of brain cells with an increase in electrolytes and organic osmolytes and thus increased intracellular water partly correcting the initial cell shrinking (Figure 17-5).

FIGURE 17-5.
Adaptation of brain volume to hypernatremia and effect of correction.



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If severe hypernatremia develops in the course of minutes to hours, such as from a massive salt overdose in a suicide attempt, a suddenly shrinking brain may prompt intracranial hemorrhage. While the causes of hypernatremia are many, leading to varied signs and symptoms, the most serious manifestations are related to changes in the brain. If hypernatremia is corrected too rapidly, cerebral edema and potentially central herniation may occur.

CLASSIFICATION AND ETIOLOGY

Based on volume status, hypernatremia may be classified as hypovolemic hypernatremia (decreased TBW and total body Na^+ with a relatively greater decrease in TBW), hypervolemic hypernatremia (increased total body Na^+ with normal or increased TBW), or normovolemic hypernatremia (near normal total body sodium and decreased TBW)[1,2] (Table 17-9).

TABLE 17-9

Hypernatremia Classification and Features According to Volume Status

	Clinical Conditions	Orthostatic Hypotension	Edema	$U_{[Na+]}$, mEq/L	U_{osm}, mOsm/kg H_2O
Hypervolemic hypernatremia	Cushing's syndrome Primary hyperaldosteronism Salt water intake Iatrogenic	Absent unless treated with diuretics	Yes	Compensated >20	>100
Normovolemic hypernatremia	DI Central DI Partial DI Gestational DI Nephrogenic DI Hypodipsia	Absent	No	>20	Central DI <300 Partial DI >300 but <800
Renal hypovolemic hypernatremia	Osmotic diuretics Loop diuretics Postobstructive diuresis	Normally present	No	>20	>100
Extrarenal hypovolemic hypernatremia	Vomiting Diarrhea GI fistulas Sweating Burns	Normally present	No	<10	>800

Abbreviation: DI = diabetes insipidus.

CLINICAL FEATURES

History depends on hypernatremia type and may reveal nausea and vomiting, lethargy, weakness, increased thirst, low water intake, salt intake, polyuria (>3000 mL of urine/24 h), diabetes, hypercalcemia, hypokalemia, medications such as lactulose, loop diuretics, lithium, demeclocycline (may cause nephrogenic diabetes insipidus), or nonsteroidal anti-inflammatory drugs (may cause interstitial nephritis). Physical exam may reveal hypotension, tachycardia, orthostatic blood pressures, sunken eyes, dry mucous membranes (symptoms of hypovolemia) altered mental status (may be present in any the hypernatremia classifications), poor skin turgor, or edema in hypervolemic hypernatremia (Table 17-9). Without intervention, coma, seizures, and shock may occur. Signs of Cushing's syndrome may be present, including moon facies, fatty deposits between the shoulders and upper back, and thinning of the skin.

DIAGNOSIS

The diagnosis of hypernatremia and its classification are based on the clinical evaluation including volume status and specific laboratory tests, including serum electrolytes and osmolality, urine osmolality, urea/creatinine ratio, and free water deficit. A BUN/creatinine ratio >40 is indicative of hyperosmolar dehydration. The free water deficit[1,2] may be calculated with the formula:

$$\text{Free water deficit} = \text{TBW} \times P_{osm} - 285/P_{osm}$$

where TBW is calculated using age and sex (giving a correction factor for body water) times weight in kilograms (see hyponatremia treatment section for scale), $P_{osm} = 2 \times [Na^+] + \text{glucose}/18$, and 285 is used as normal plasma osmolality. As an example, a 60-kg woman

with a [Na^+] of 165 mEq/L and glucose of 130 milligrams/dL has a free water deficit calculated as follows: TBW = 0.5 × 60 = 30; P_{osm} = (2 × 165 = 330) + (130/18 = 7.2) = 337.2 mOsm/kg H_2O; free water deficit = 30 × (337.2 – 285)/337.2 = 4.64 L. Urine osmolality can be used to suggest the type of hypernatremia (**Table 17-10**). If urine osmolality is not readily available, it can be estimated using urine specific gravity (π). Consider the numerals in the hundredths and thousandths decimal places of the π as whole numbers and multiply them by 35 to estimate U_{osm}.

TABLE 17-10

Urine Osmolality Findings in Selected Hypernatremic States

Urine Osmolality (U_{osm})	Potential Hypernatremic State
U_{osm} <300 mOsm/kg H_2O	Central or nephrogenic diabetes insipidus
U_{osm} >300, <800 mOsm/kg H_2O	Partial diabetes insipidus or osmotic diuresis
U_{osm} >800 mOsm/kg H_2O	Hypertonic dehydration

TREATMENT

First, shock, hypoperfusion, or volume deficits should be treated with isotonic (0.9%) saline. Second, treat any existing underlying cause, such as diabetes insipidus (see "Diabetes Insipidus" section below) vomiting, diarrhea, or fever. Third, correct the patient's free water deficit at a rate reflecting the acuity or duration time of the hypernatremia onset (**Table 17-11**).[11,14,15] In cases of a lethal sodium chloride ingestion/load (0.75 to 3.0 grams/kg) less than 6 hours prior to presentation, FWD may be replaced rapidly with no reported adverse events.[11,14] Management requires evaluating volume status and the free water deficit (see formula above in diagnosis section). When the adaptation of brain cells is incomplete (onset over <48 hours), the correction rate of acute hypernatremia can be performed at a rate of 1 mEq/L/h. In an alert patient capable of safely drinking water, the route of administration should be two-thirds free water orally and one-third IV. If hypernatremia is chronic (onset over >48 hours), the rate of correction should be slower, to avoid the risk of cerebral edema, at no more than 0.5 mEq/L/h or 10 to 12 mEq/24 h.[11,16]

TABLE 17-11

Treatment of Hypernatremia

Treatment	Indication and Comments
Isotonic (0.9%) saline	Use for correction of volumn deficits.
Etiology-specific therapy	Treat fever with antipyretics, vomiting with antiemetics, and diabetes insipidus with desmopressin (see "Diabetes Insipidus" section below).
D_5W to replace free water deficit over 2-3 days	In cases of chronic hypernatremia, it is suggested that correcting (lowering) the sodium level should occur at a rate of no more than 0.5 mEq/L/h or 10 to 12 mEq/24 h.
0.45% normal saline at 100 mL/hour	Correct volume deficts first. A commonly used infusion for mild to moderate hypernatremia, but this therapy adds to total body sodium.
D_5W to replace free water deficit over 1-2 hours	Reserved only for those cases where acuity is known to be <6 h and the salt load is known to be lethal (0.75–3.0 grams/kg of body weight).
Hemodialysis	An alternative or as a suppliment to D_5W to replace free water deficit in life-threatenting acute cases of salt ingestion.

Abbreviation: D_5W = 5% dextrose in water.

DIABETES INSIPIDUS

Diabetes insipidus is a disease where the ability of the kidney to reabsorb free water is compromised.[2,17] The disorder is characterized by polyuria, polydipsia, and an increased volume of hypo-osmolar urine. Hypernatremia is present only when the thirst center is impaired or water intake is reduced. Diabetes insipidus can be central (also called neurogenic), due to inadequate ADH secretion, or renal (also called nephrogenic), when ADH secretion is normal or increased but the v2R receptors of the kidney's collecting duct cells do not respond appropriately to ADH. Diabetes insipidus may be congenital or acquired. In **Table 17-12**, the main causes of diabetes insipidus are listed. Congenital forms of diabetes insipidus present during infancy. Eventually, recurrent cellular dehydration causes cerebral calcifications that manifest as delayed intellectual advancement.

TABLE 17-12

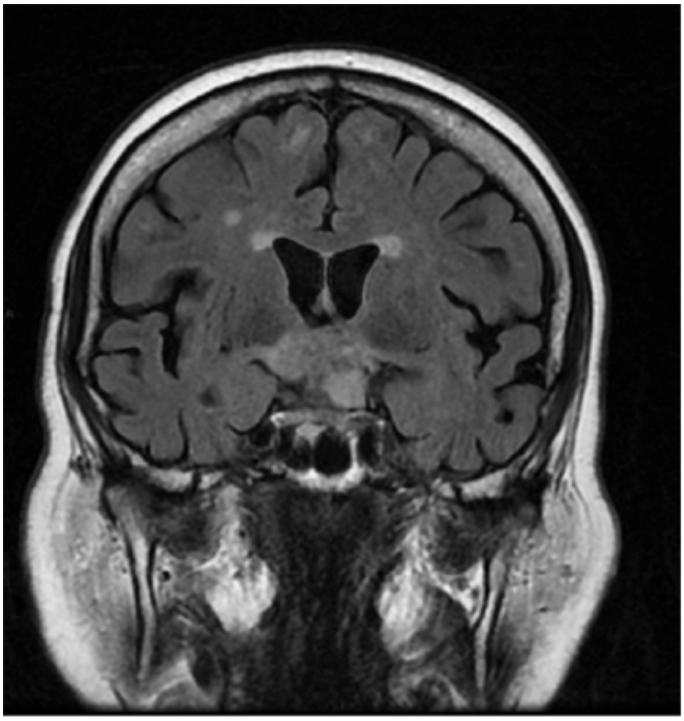
Classification of Diabetes Insipidus

Class	Acquisition	Pathophysiology
Central or neurogenic diabetes insipidus	Congenital	Structural malformations affecting the hypothalamus or pituitary Autosomal dominant (or rarely recessive) mutations in the gene encoding AVP-NPII precursor protein
	Acquired	Primary tumors (craniopharyngioma) or metastases Infection (e.g., meningitis, encephalitis) Histiocytosis and granulomatous diseases Trauma Surgery Idiopathic
Nephrogenic diabetes insipidus	Congenital	X-linked: inactivating mutations in *AVPR2* gene Autosomal: recessive or dominant mutations in *AQP-2* gene
	Acquired	Primary renal disease Obstructive uropathy Metabolic causes (e.g., hypokalemia, hypercalcemia) Sickle cell disease Drugs (e.g., lithium, demeclocycline)
Primary polydipsia or dipsogenic diabetes insipidus	Acquired	Psychogenic illness characterized by excessive fluid intake. Treatment is aimed at the psychiatric disease.

Central diabetes insipidus is acquired in most cases, associated with various disorders that cause destruction of ADH-secreting neurons. When a diagnosis is not possible, despite imaging and other diagnostic tests, diabetes insipidus will be defined as idiopathic diabetes insipidus.

The most common clinical symptoms and signs are excessive thirst, polydipsia, and polyuria plus several nonspecific symptoms including weakness, lethargy, myalgias, and irritability. In infancy, congenital forms of diabetes insipidus present with fatigue and weakness often manifested by less activity or tiring with feeding, vomiting, polyuria, and sometimes fever. Diagnosis can be suspected in the ED by clinical presentation, but the diagnosis requires a prolonged test, requiring 4 to 18 hours. Urine osmolality is assessed after water deprivation; many cases require another assessment after a dose of desmopressin, the "water deprivation test." A spot check in the ED without water deprivation will typically reveal a U_{osm} of <300 mOsm/L. In central diabetes insipidus, a cerebral MRI is indicated (on a nonurgent outpatient basis) to evaluate the hypothalamic–pituitary area (**Figure 17-6**).

FIGURE 17-6.
MRI image of a craniopharyngioma that caused diabetes insipidus in a 46-year-old patient.



Central diabetes insipidus is treated with the synthetic hormone desmopressin, as a nasal spray, 10 micrograms (0.1 mL) every 12 hours, or PO, 0.05 milligrams every 12 hours, as starting doses. Therapy of nephrogenic diabetes insipidus includes a low-salt, low-protein diet, adequate hydration, and the careful use of one to three agents that act together to concentrate urine in these patients: a thiazide diuretic, the potassium-sparing diuretic amiloride, and indomethacin. Exogenous ADH, 5 to 10 micrograms subcutaneously, two to four times daily, is also used in noncongenital nephrogenic diabetes insipidus, as these patients have a partial response to ADH. Patients with significant electrolyte abnormalities should be admitted to the hospital, whereas stable patients suspected of having diabetes insipidus should be referred for testing.

POTASSIUM

PATHOPHYSIOLOGY

Potassium (K^+) is the major intracellular cation of the body: 98% of total body potassium in healthy subjects is intracellular, and 70% to 75% of total K^+ is in muscle tissues. The normal intracellular concentration averages 150 mEq/L, and the normal extracellular concentration is 3.5 to 5.0 mEq/L. The total body K^+ store is approximately 55 mEq/kg or 3500 mEq in a healthy 70-kg adult. Daily intake of K^+ ranges from 50 to 150 mEq. Foods rich in potassium include vegetables, fruits, dry fruits, nuts, and meat. Potassium is excreted predominantly by the kidneys (80% to 90%). Potassium is filtered freely through the renal glomerulus and then reabsorbed in the proximal and ascending tubules. It is secreted in the distal tubule in exchange for Na^+. In healthy individuals, the kidneys are able to excrete up to 6 mEq/kg/d. The several mechanisms of potassium handling along the nephron are the targets of diuretic therapy.

Extracellular [K^+] represents about 2% of total body K^+ and is influenced by two important variables: total body K^+ stores and distribution between the ICF and ECF spaces. Being mostly intracellular, an accurate calculation of total body K^+ is difficult, but an estimation of the K^+ deficit can be determined with the following equation: **estimated K^+ deficit in mEq/L = (expected serum [K^+] in mEq/L – measured serum [K^+] in mEq/L) × ICF** (calculated as 40% of total body weight).[1]

However, this equation is only reliable for healthy subjects, because critical patients sustain significant and rapid intracellular to extracellular shifting in response to severe injury (i.e., surgical stress, trauma, or burns), acid-base imbalance, catabolic states, increased extracellular osmolality, or insulin deficiency. So it is possible to have hyperkalemia in patients with a total body K^+ deficit (e.g., diabetic ketoacidosis) and hypokalemia with total body K^+ surplus.[2] These shifts are crucial considering the role of potassium in maintaining the

resting membrane potential, as the ratio of intracellular to extracellular K^+ is the most important determinate of neuromuscular and cardiovascular excitability.[18,19]

Acid-base imbalance plays an important role in critically ill patients: there is an inverse proportionality between serum pH and $[K^+]$, with $[K^+]$ rising about 0.6 mEq/L for every 0.1 decrease in pH and vice versa, through an exchange between H^+ and K^+.[1,20]

Also the duration of both hypo- and hyperkalemia influences the clinical response: chronic potassium depletion or surplus allows adaptation through shifts in intra-/extracellular K^+ concentration to maintain the resting membrane potential, thus mitigating neuromuscular and cardiac electrophysiologic effects.

HYPOKALEMIA

PATHOPHYSIOLOGY

Hypokalemia is defined as a serum $[K^+]$ of <3.5 mEq/L. The most frequent causes of hypokalemia are insufficient dietary intake (e.g., fasting, eating disorders, alcoholism), intracellular shifts (e.g., alkalosis, insulin, β_2-agonists, hypokalemic periodic paralysis), and increased losses, mainly GI (vomiting, nasogastric suction, diarrhea) or renal (diuretics,[5] hyperaldosteronism, osmotic diuresis, toxins)[21] (**Table 17-13**).

TABLE 17-13

Causes of Hypokalemia

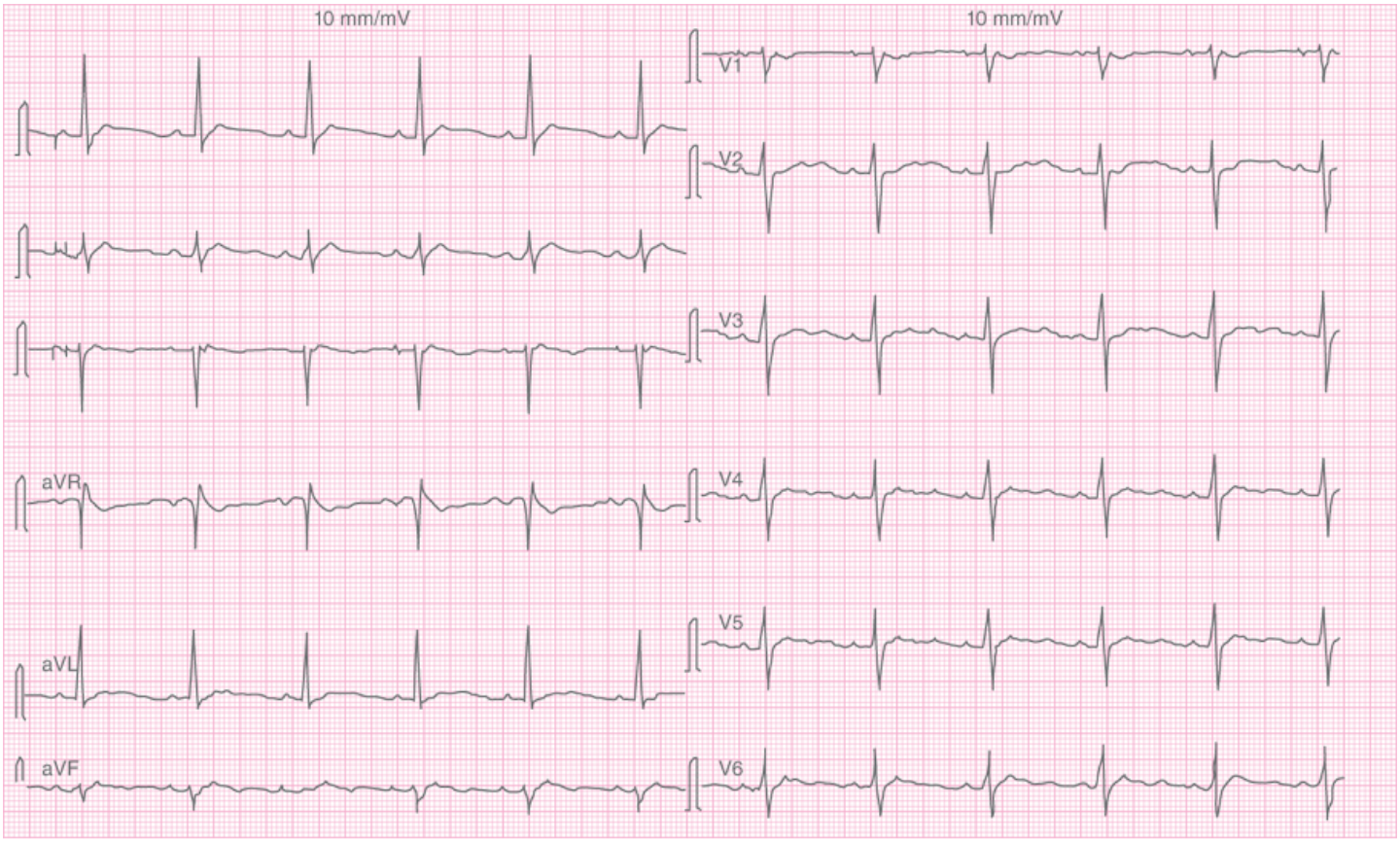
Transcellular shifts	Alkalosis* Increased plasma insulin (treatment of diabetic ketoacidosis) β-Adrenergic agonists Hypokalemic periodic paralysis (congenital) Thyrotoxic hypokalemic periodic paralysis
Decreased intake	Fasting Alcoholism (worsened by hypomagnesemia) Eating disorders
GI loss	Vomiting*, nasogastric suction Diarrhea* (including laxative, enema abuse) Malabsorption Ureterosigmoidostomy Enteric fistula Villous adenoma
Renal loss	Diuretics (carbonic anhydrase inhibitors, loop diuretics, and thiazide-like diuretics)* Primary hyperaldosteronism Secondary hyperaldosteronism Licorice ingestion Excessive use of chewing tobacco Renal tubular acidosis Postobstructive diuresis Osmotic diuresis Bartter's syndrome (mimics loop diuretic use) Gitelman's syndrome (mimics thiazide diuretic use) Apparent mineralocorticoid excess and related syndromes (Conn's, Liddle's) Drugs and toxins (aminoglycosides, echinocandins, carbenicillin, penicillins, amphotericin B, levodopa, lithium, thallium, cesium, barium, toluene, theophylline, chloroquine, steroids, etc.)
Sweat loss	Heavy exercise Heat stroke Fever
Other	Hypomagnesemia Acute leukemia and lymphomas IV hyperalimentation Recovery from megaloblastic anemia Hypothermia (accidental or induced)

*Frequently encountered etiologies in the ED.

The clinical manifestations result from abnormalities in membrane polarization and affect almost every body system, but are particularly dangerous in the excitable myocardium. Hypokalemia makes the resting potential more electronegative, thus enhancing depolarization; the reduction in $[K^+]$ conduction delays repolarization, causing prolonged QT_C, flattened T waves, and the appearance of U waves in the ECG (**Figure 17-7**).

FIGURE 17-7.

ECG of a patient with K^+ of 1.4 mEq/L, with leg paralysis and deep fatigue. The patient had been taking a thiazide-like diuretic for hypertension. Notice the prolonged QT_c and a flattened T wave with a U wave visible in V_2-V_5.



CLINICAL FEATURES

Symptoms of hypokalemia (**Table 17-14**) usually start when serum concentrations reach 2.5 mEq/L, although they may appear sooner with rapid decreases in concentration or appear later (i.e., at even lower $[K^+]$) for chronic depletion.

TABLE 17-14

Symptoms and Signs of Hypokalemia

Cardiovascular	Hypertension Orthostatic hypotension Potentiation of digitalis toxicity Dysrhythmias (usually tachyarrhythmias) T-wave flattening, QT prolongation, U waves, ST depression
Neuromuscular	Malaise, weakness, fatigue Hyporeflexia Cramps Paresthesias Paralysis Rhabdomyolysis
GI	Nausea, vomiting Abdominal distension Ileus
Renal	Increased ammonia production Urinary concentrating defects Metabolic alkalemia, paradoxical aciduria Nephrogenic diabetes insipidus
Endocrine	Glucose intolerance

Particular attention must be paid to cardiac arrhythmias, usually tachyarrhythmias (atrial fibrillation,[22] torsade de pointes, ventricular tachycardia, and ventricular fibrillation), that can be life threatening.

DIAGNOSIS

Diagnosis of hypokalemia is made with serum chemistry measurement; the etiology is investigated with additional testing. An ECG should be obtained from hypokalemic patients in the ED (Figure 17-7). Obtain blood gas analysis when alkalosis is suspected. If the cause of hypokalemia is not apparent from history, spot urinary electrolytes can be obtained before starting K^+ replacement (see **Table 17-15** for interpretation of urine K^+ values[1]); also U_{Na+}, U_{osm}, and P_{osm} should be measured, because a U_{Na+} value <30 mEq/L and a U_{osm} value less than P_{osm} suggest polyuria. Polyuria can increase K^+ excretion even if total body K^+ is depleted; thus U_{K+} may be misleading for diagnosis in the setting of polyuria.[2]

TABLE 17-15

Interpretation of Urinary Potassium

Spot Urinary Potassium	Mechanism
U_{K+} <10 mEq/L	*Decreased K^+ intake, nonrenal losses* GI losses Sweat losses Nasogastric suction ($\downarrow U_{Cl-}$)
	Transcellular shift Alkalosis ($\downarrow U_{Cl-}$) Hypomagnesemia ($\uparrow U_{Cl-}$) Hypokalemic periodic paralysis Thyrotoxic hypokalemic periodic paralysis (calculate TTKG)
U_{K+} >20 mEq/L	*Renal losses* If hypernatremia coexists consider: Hyperaldosteronism (calculate TTKG) Massive GI losses (secondary to metabolic alkalosis)

Abbreviation: TTKG = transtubular K^+ gradient.

Another useful tool for differential diagnosis is **transtubular K^+ gradient (TTKG) = $(U_{K+} \times P_{osm})/(U_{osm} \times P_{K+})$** with normal values of 8 to 9 mEq/L. Values lower than 5 mEq/L suggest hyperaldosteronism; if paralysis is present, values lower than 3 mEq/L suggest hypokalemic periodic paralysis. A calcium/phosphate ratio >1.7 on a spot urine is 100% sensitive and 96% specific for thyrotoxic hypokalemic periodic paralysis.[23,24]

TREATMENT

The treatment of hypokalemia is replacement of K^+. This should be done orally in stable patients with mild hypokalemia (>3.0 mEq/L) who are able to tolerate oral intake.[2] Foods rich in K^+ (fruits, dried fruits, vegetables) can be suggested at discharge from ED, as well as salt substitutes or K^+ supplements that should be prescribed with abundant fluids and/or food to prevent gastric irritation. Additional treatment targeted to the underlying cause should be considered. For example, it is possible to treat (and prevent) chronic hypokalemia induced by loop or thiazide diuretics by adding an adequate amount of spironolactone to the patient's chronic therapy[25]; however, the primary care physician should be aware of or guide such a change in medication. Whenever modifying diuretics or other drugs at ED discharge, recommend follow-up within 1 week for repeat assessment of renal function and $[K^+]$. In hypokalemia secondary to respiratory alkalosis (as caused by an acute anxiety disorder), the simple correction of the acid-base imbalance (through reassurance or anxiolytics) can correct $[K^+]$ without administering exogenous potassium.

Intravenous replacement is indicated in patients with severe (<2.5 mEq/L) hypokalemia and in symptomatic patients with moderate (2.5 to 3 mEq/L) hypokalemia. Treat patients with cardiac arrhythmias, prolonged QT_c, or when oral replacement is not tolerated or not feasible (see **Table 17-16** for common medications known to prolong QT_c). Monitor the patient's rhythm when treating with intravenous K^+.

TABLE 17-16

Common Medications Known to Prolong QTc

Antiarrhythmics	Amiodarone, sotalol, flecainide, quinidine, dronedarone, dofetilide
Vasopressors/inotropes	Epinephrine, norepinephrine, dopamine, dobutamine
Neuroleptics	Haloperidol, droperidol, chlorpromazine, olanzapine, quetiapine, risperidone, paliperidone, clozapine, aripiprazole
Antidepressants	Amitriptyline, nortriptyline citalopram, escitalopram, fluoxetine, paroxetine, sertraline, venlafaxine
Antibiotics	Macrolides, quinolones, metronidazole, cotrimoxazole
GI prokinetics	Domperidone, cisapride, metoclopramide
Antiemetics	Ondansetron, granisetron, dolasetron, promethazine
Antifungals	Fluconazole, itraconazole, voriconazole, ketoconazole, posaconazole
Antivirals	Foscarnet, amantadine, atazanavir, nelfinavir, rilpivirine, ritonavir, saquinavir, telaprevir
Antiparasitics	Chloroquine, mefloquine, quinine, hydroxychloroquine, pentamidine
Antihistaminics	Terfenadine, hydroxyzine, diphenhydramine
Others	Cocaine, lithium, methadone, tamoxifen, vardenafil, tacrolimus, pseudoephedrine

Monitor closely those patients who sustain rapid [K^+] changes due to their illness (e.g., postobstructive polyuria) or intravenous treatment. An example is diabetic ketoacidosis treatment, where rapid hypokalemia (including life-threatening arrhythmias) should be prevented by adequate IV K^+ administration prior to the detection of a rapid fall in serum potassium.

The following are **general principles in hypokalemia correction:**

1. Use KCl and avoid administering K^+ in glucose solutions, to reduce insulin-induced K^+ transfer into cells.
2. Potassium is irritating to the endothelium; adequate dilution is mandatory to prevent pain and phlebitis (maximum recommended [K^+] in 500 mL of a saline solution is 40 mEq, to be infused in 4 to 6 hours in a peripheral line. If a more aggressive correction is needed, an identical solution can be administered in a second peripheral line. Higher concentrations can be administered through a central line, but infusion rates should never exceed 20 mEq/h).
3. Reassessing serum [K^+] should be adjusted to infusion rate and coexisting factors (e.g., concomitant acid-base imbalance, volume depletion, cardiac arrhythmias).
4. ECG monitoring is recommended.
5. In most cases, hypokalemic patients are also hypomagnesemic. So Mg^{2+} (20 to 60 mEq/24 h) may be added to the infusion both to optimize tubular reuptake of potassium and to contrast proarrhythmic effect of hypokalemia.[1]

HYPERKALEMIA

PATHOPHYSIOLOGY

Hyperkalemia is defined as measured serum [K^+] of >5.5 mEq/L. The most common cause is factitious hyperkalemia due to release of intracellular potassium caused by hemolysis during phlebotomy. Other causes are listed in **Table 17-17**.

TABLE 17-17

Causes of Hyperkalemia

Pseudohyperkalemia	Tourniquet use
	Hemolysis (in vitro)*
	Leukocytosis
	Thrombocytosis
Intra- to extracellular potassium shift	Acidosis*
	Heavy exercise
	β-Blockade
	Insulin deficiency
	Digitalis intoxication
	Hyperkalemic periodic paralysis
Potassium load	Potassium supplements
	Potassium-rich foods
	IV potassium
	Potassium-containing drugs
	Transfusion of aged blood
	Hemolysis (in vivo)
	GI bleeding
	Cell destruction after chemotherapy
	Rhabdomyolysis/crush injury*
	Extensive tissue necrosis
Decreased potassium excretion	Renal failure*
	Drugs—potassium-sparing diuretics,* β-blockade, nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, cyclosporine, tacrolimus
	Aldosterone deficiency*
	Selective defect in renal potassium excretion (pseudohypoaldosteronism, systemic lupus erythematosus, sickle cell

	disease, obstructive uropathy, renal transplantation, type IV renal tubular acidosis)

*Frequent or important ED diagnostic considerations.

Clinical manifestations of hyperkalemia result from disordered membrane polarization (**Figure 17-8**). Cardiac manifestations are the most serious. In hyperkalemia the resting potential of the excitable myocardium becomes less electronegative, with a consequent partial depolarization that reduces the activation of voltage-dependent sodium channels; this results in a slower and reduced amplitude of action potential. **Table 17-18** summarizes the ECG effects that may lead to arrhythmic complications, such as sinoatrial and atrioventricular blocks and atrial paralysis (Figure 17-8). Calcium administration does not affect potassium levels; rather, calcium antagonizes the effects of hyperkalemia at the level of the cell membrane, raising the threshold potential, thus restoring the membrane potential and myocyte excitability close to normal[1] (**Figure 17-9**).

FIGURE 17-8.
Monitor strip (V_1–V_3) of a 35-year-old patient in critical condition, who was hypotensive and fatigued and rapidly deteriorated into cardiac arrest. Potassium level was 9.1 mEq/L. She was on spironolactone and steroid therapy.

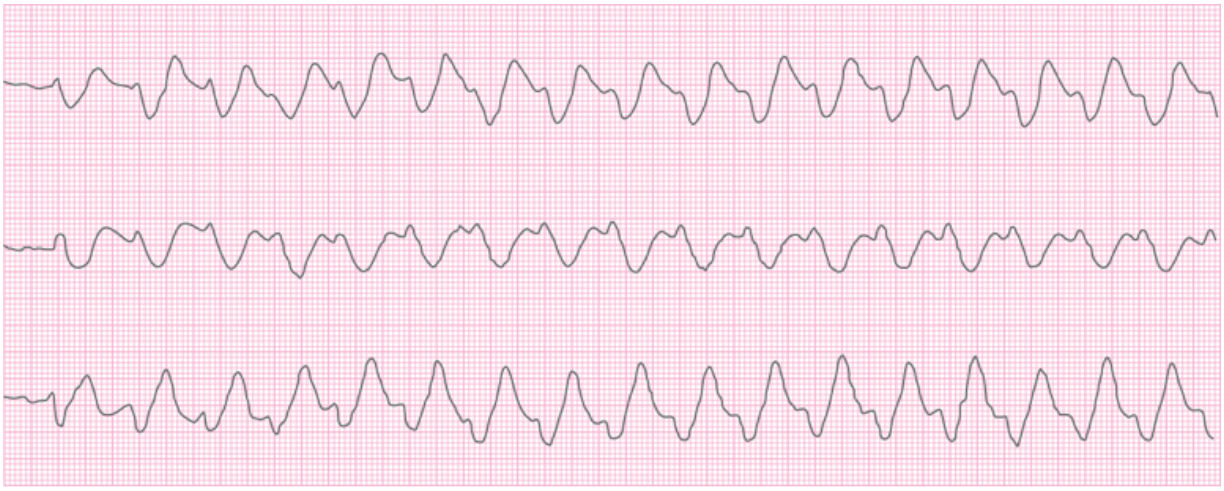


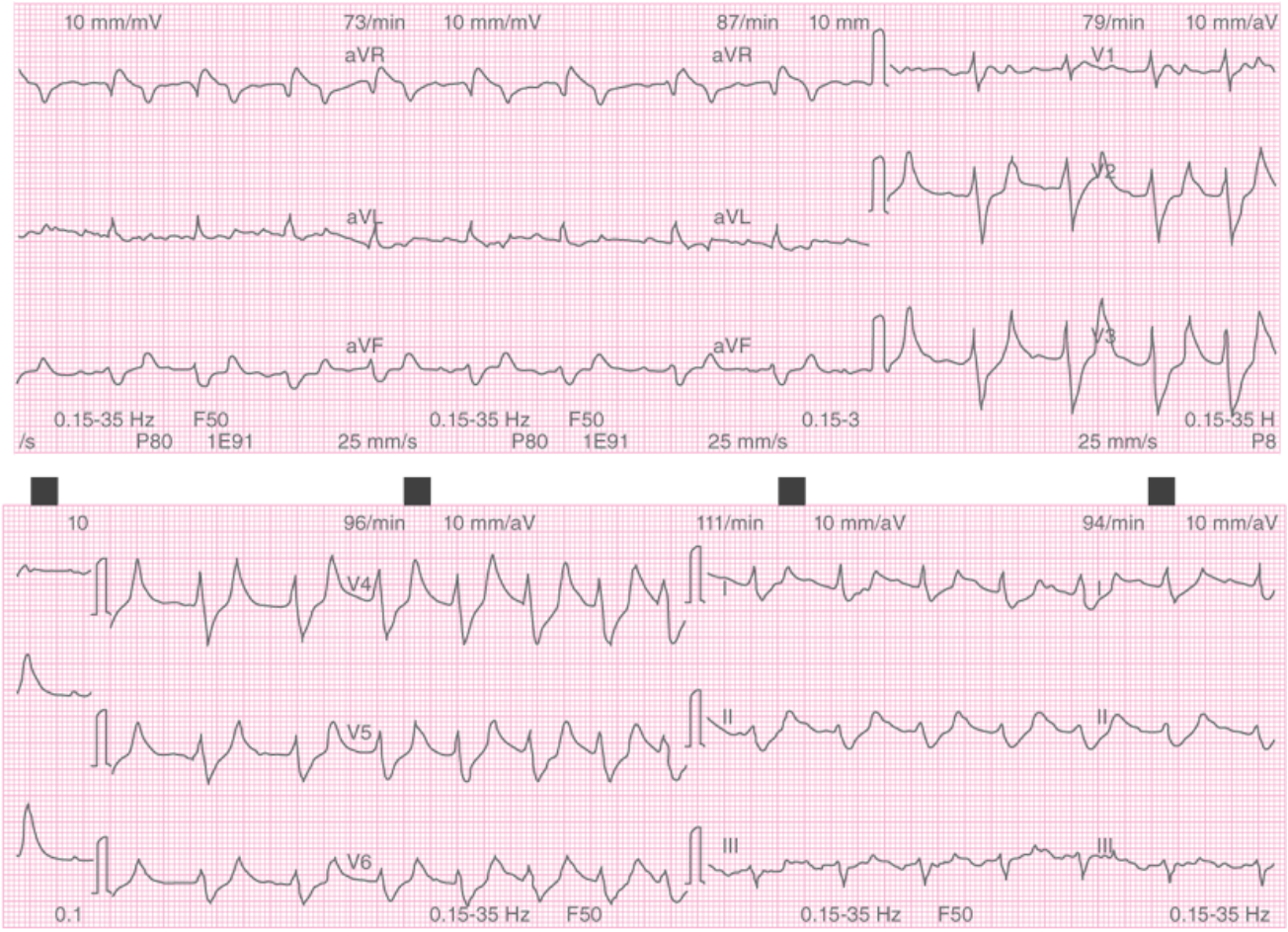
TABLE 17-18

ECG Changes Associated with Hyperkalemia

$[K^+]$ (mEq/L)	ECG Changes*
6.5–7.5	Prolonged PR interval, tall peaked T waves, short QT interval
7.5–8.0	Flattening of the P wave, QRS widening
10–12	QRS complex degradation into a sinusoidal pattern

*In chronic or slowly developing hyperkalemia, ECG changes may not occur until higher $[K^+]$ levels are reached.

FIGURE 17-9.
The same patient as in Figure 17-8 during calcium chloride infusion. She regained a pulse and became conscious. The QRS and T wave narrowed, as compared with Figure 17-8.



CLINICAL FEATURES

Cardiac dysrhythmias, such as ventricular fibrillation, sinoatrial and atrioventricular blocks until complete heart block, and asystole, may occur. Death from hyperkalemia is usually the result of diastolic arrest or ventricular fibrillation. Other common symptoms include neuromuscular dysfunctional weakness, paresthesias, areflexia, ascending paralysis, and GI effects (nausea, vomiting, and diarrhea).[26,27]

TREATMENT

A stat ECG is essential in all hyperkalemic patients (Table 17-18); **if ECG changes are present, emergency treatment of hyperkalemia should start immediately.** In addition, if ECG changes are detected in a patient whose electrolyte levels are not yet known (e.g., a dialysis patient), hyperkalemia should be suspected and treated. A symptomatic patient with a relatively small elevation of $[K^+]$ (5.0 to 6.0 mEq/L) requires identification and treatment of the underlying cause. A spot urine potassium may identify the diagnosis. An elevated spot urine potassium (>20 mEq/L) suggests an extrarenal cause (and will more likely be responsive to therapy). A low urine K^+ output (<10 mEq/L) suggests oliguric kidney failure or drug effect, such as angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers.

Emergency treatment includes continuous ECG monitoring and immediate intervention with several therapeutic medications, which based on the action mechanism, can be divided into three modalities: membrane stabilization (crucial for cardiac tissue, must be done immediately), intracellular shift of K^+, and removal/excretion of K^+ from the body. All three modalities should be administered sequentially in rapid succession. Each mode has a different onset time and duration[28] (**Table 17-19**).

TABLE 17-19

Emergency Therapy of Hyperkalemia

Therapy	Dose and Route	Onset of Action	Duration of Effect	Mechanism
Calcium chloride (10%)*	5–10 mL IV	1–3 min	30–50 min	Membrane stabilization
Calcium gluconate (10%)*	10–20 mL IV	1–3 min	30–50 min	Membrane stabilization
$NaHCO_3$	50–150 mEq IV	5–10 min	1–2 h	Shifts $[K^+]$ into cell
Albuterol (nebulized)	10–20 milligrams in 4 mL of normal saline, nebulized over 10 min	15–30 min	2–4 h	Upregulates cyclic adenosine monophosphate, shifts $[K^+]$ into cell
Insulin† and glucose‡	5–10 units regular insulin IV Glucose 25 grams (50% solution) IV	30 min	4–6 h	Shifts $[K^+]$ into cell
Furosemide	40–80 milligrams IV	Varies	Varies	Renal $[K^+]$ excretion
Sodium polystyrene sulfonate	25–50 grams PO or PR	1–2 h	4–6 h	GI $[K^+]$ excretion
Hemodialysis	—	Minutes	Varies	Removes $[K^+]$

*Calcium chloride has three times the elemental calcium when compared to calcium gluconate. 10% calcium chloride = 27.2 milligrams $[Ca^{2+}]$/mL; 10% calcium gluconate = 9 milligrams $[Ca^{2+}]$/mL. Due to its short duration, calcium administration (both chloride and gluconate) can be repeated up to four times per hour.

†Reduce dose of insulin in patients with renal failure.

‡Glucose infusion should be administered after initial bolus to prevent hypoglycemia. Glucose should not be administered in hyperglycemic patients.

A blood gas is essential if acidosis is present; treatment should correct the underlying cause of the acid-base imbalance. If pH is normal or alkaline, the therapeutic measures that act to promote an intra- to extracellular shift of $[K^+]$ will be less effective, and treatment should be aimed to improve renal excretion.

Until recently, sodium polystyrene sulfonate was the only oral agent that lowered potassium levels by enhancing excretion (rather than shifting potassium into cells). This agent has an unpleasant taste and may cause diarrhea. Two new oral agents currently in development, **patiromer** and **sodium zirconium cyclosilicate**, may prove useful to lower potassium levels for patients with mild hyperkalemia if confirmatory studies support the initial randomized controlled trials[29,30]; however, the onset of action for these new drugs is too slow to be of benefit in life-threatening hyperkalemia.

The following are **general principles in treatment of hyperkalemia:**

1. Immediate cessation of further K^+ administration, reduction of dietary intake, and suspension of drugs impairing K^+ renal excretion directly (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, K^+-sparing diuretics) or indirectly through worsening of renal function (e.g., nonsteroidal anti-inflammatory drugs, iodine contrast, antibiotics).

2. Fluid administration enhances K^+ renal excretion through increasing urine output.

3. If a patient is on digitalis,[31] hypercalcemia enhances the toxic cardiac effects of digitalis. However, in severe hyperkalemia secondary to digitalis intoxication with advanced intraventricular conduction impairment (wide, low-voltage QRS complexes), calcium administration must be considered, in association with antidigoxin antibodies.[1,32]

4. ECG continuous monitoring should be used to confirm the effects of therapy, thus reducing the frequency of rechecking $[K^+]$.

MAGNESIUM

The total body content of magnesium (Mg^{2+}) is 24 grams, or 2000 mEq, 50% to 70% of which is fixed in bone and only slowly exchangeable. Most of the remaining Mg^{2+} is found in the ICF space, with a concentration of approximately 40 mEq/L. The distribution of Mg^{2+} is similar to that of K^+, with the major portion being intracellular. It is the second most abundant intracellular cation. Normal serum $[Mg^{2+}]$ ranges between 1.5 and 2.5 mEq/L (0.7 to 1.1 mmol/L or 1.7 to 2.7 milligrams/dL). Circulating Mg^{2+} is 25% to 35% bound to proteins (mainly albumin), 10% to 15% complexed, and 50% to 60% ionized, which is the active portion. The normal dietary intake of Mg^{2+} is approximately 240 to 336 milligrams/d and is found in vegetables such as dry beans and leafy greens, meat, and cereals. Sixty percent of excreted Mg^{2+} is through stool, with the remainder via the urine. Renal reabsorption is carried out with sodium and water and is unidirectional; that means that it is impaired by volume overload, osmotic diuresis, and diuretics. About 300 enzymes have their activities regulated by Mg^{2+}; it assists the production of adenosine triphosphate, participates in nucleic acid and protein synthesis, and is involved in coagulation, platelet aggregation, and neuromuscular activity, as well as in cardiac action potential.[1,2,33]

Magnesium homeostasis is very complex and finely regulated by many factors, such as parathyroid hormone, calcitonin, ADH, glucose, insulin, glucagon, catecholamines, sodium, potassium, calcium, and phosphorus levels. Magnesium is effective therapy in severe asthma when added to standard therapy[34] (see chapter 69, "Acute Asthma").

HYPOMAGNESEMIA

PATHOPHYSIOLOGY

Table 17-20 lists the different causes of hypomagnesemia. The major causes are alcoholism, malnutrition, cirrhosis, pancreatitis, and excessive GI fluid losses.

TABLE 17-20

Causes of Hypomagnesemia

Redistribution	IV glucose
	Correction of diabetic ketoacidosis
	IV hyperalimentation
	Refeeding after starvation
	Acute pancreatitis
	Postparathyroidectomy (hungry bone syndrome)
	Osteoblastic metastasis (hungry bone syndrome)
Extrarenal loss	Nasogastric suction (infrequent)
	Lactation
	Profuse sweating, burns, sepsis
	Intestinal or biliary fistula
	Diarrhea
Decreased intake	Alcoholism (cirrhosis)
	Malnutrition, poor intake
	Small bowel resection
	Malabsorption (steatorrhea)
Renal loss	Ketoacidosis
	Saline or osmotic diuresis
	Potassium depletion
	Phosphorus depletion
	Familial hypophosphatemia
	Tubulointerstitial renal disease
Drugs	Loop diuretics
	Aminoglycosides
	Amphotericin B
	Vitamin D intoxication

	Alcohol
	Cisplatin
	Theophylline
	Proton pump inhibitors
	Calcineurin inhibitors (cyclosporine, tacrolimus)
Endocrine disorders	Syndrome of inappropriate antidiuretic hormone secretion
	Hyperthyroidism
	Hyperparathyroidism
	Hypercalcemic states
	Primary or secondary aldosteronism

IV hyperalimentation or treatment of diabetic ketoacidosis without adequate provision of Mg^{2+}, especially in a previously malnourished patient, can cause an abrupt fall in plasma magnesium levels. Acid-base imbalance affects the levels of ionized magnesium; a typical example is respiratory alkalosis that enhances neuromuscular activity (thus provoking tremors and cramps) by rapidly decreasing ionized [Mg^{2+}] and [Ca^{2+}] at the same time.

Among the iatrogenic causes, **proton pump inhibitors** may cause hypomagnesemia,[35,36] especially in association with **diuretic therapy**, probably through the inhibition of intestinal absorption. Concomitant hypomagnesemia and hypokalemia may coexist.

CLINICAL FEATURES

Magnesium is essential to a large number of enzymes, including membrane-bound adenosine triphosphatase. Consequently, hypomagnesemia may result in a wide variety of neuromuscular, GI, and cardiovascular effects (**Table 17-21**).

TABLE 17-21

Symptoms and Signs of Hypomagnesemia

Neuromuscular	Tetany
	Muscle weakness
	Chvostek and Trousseau signs
	Cerebellar (ataxia, nystagmus, vertigo)
	Confusion, obtundation, coma
	Seizures
	Apathy, depression
	Irritability
	Paresthesias
GI	Dysphagia
	Anorexia, nausea
Cardiovascular	Heart failure
	Dysrhythmias
	Hypotension
Miscellaneous	Hypokalemia
	Hypocalcemia
	Anemia

DIAGNOSIS

Hypomagnesemia is common in acute illness; it has been found in 12% of hospitalized patients and in up to 65% of medical intensive care patients.[37,38] It is likely underdiagnosed because few hospitalized patients have levels drawn.[39]

The diagnosis of hypomagnesemia in the presence of normal serum calcium levels is suggested by increased neuromuscular irritability, shown by hyperreflexia tremor, tetany, or even convulsions. Chvostek sign and Trousseau sign, findings traditionally associated with hypocalcemia, may be elicited in hypomagnesemic patients. Hypomagnesemia should be suspected in patients with alcoholism, cirrhosis, or those requiring IV fluids or hyperalimentation for prolonged periods.

The ECG changes may be similar to those caused by hypokalemia and/or hypocalcemia because they may be due to Mg^{2+} deficiency altering cardiac intracellular potassium content. As for hypokalemia, low [Mg^{2+}] levels enhance digitalis toxicity, so hypomagnesemia should be searched in ECG disturbances associated with digoxin intake, especially when both digoxin and potassium levels are normal.[40]

Low total [Mg^{2+}] can also be secondary to hypoalbuminemia; if it is not possible to measure ionized magnesium, which is unaffected by hypoalbuminemia, the following two formulas can be used to correct magnesemia for albumin level. If reference lab reports [Mg^{2+}] in mmol/L: corrected serum [Mg^{2+}] (mmol/L) = measured total [Mg^{2+}] + [0.005 × (40 – serum albumin in grams/L)]. If reference lab reports [Mg^{2+}] in milligrams/dL, use the following conversion: corrected serum [Mg^{2+}] (mEq/L) = measured total [Mg^{2+}] × 0.42 + 0.05 (4 – serum albumin in grams/dL).

TREATMENT

Hypokalemia, hypocalcemia, and hypophosphatemia are often present with severe hypomagnesemia and must be monitored carefully. Hypocalcemia does not develop until [Mg^{2+}] falls below 1.2 milligrams/dL.

The following are **general principles in treatment of hypomagnesemia:**

1. Treat or stop the cause of hypomagnesemia.
2. For asymptomatic patients (including ECG changes), magnesium supplements should be administered orally, in multiple low doses during the day, to avoid diarrhea. Magnesium lactate, chloride, gluconate, and proteinate are the formulations with minimum effect on intestinal motility.
3. For severe and symptomatic hypomagnesemia, urgent IV replacement is mandatory. The formulation most commonly used is magnesium sulfate ($MgSO_4$). In life-threatening conditions (torsade de pointes, eclampsia), 1 to 4 grams or 8 to 32 mEq diluted in at least 100 mL of 5% dextrose or normal saline (0.9%) solution can be administered in 10 to 60 minutes under continuous monitoring: ECG (risk of hypokinetic arrhythmias), noninvasive blood pressure (risk of hypotension), and ventilatory pattern (risk of respiratory depression, usually preceded by areflexia, that can be monitored as an alarm sign). As a minor side effect, flushing due to vasodilatation is common.
4. Patients with chronic Mg^{2+} deficiency may require >50 mEq of oral Mg^{2+} (6 grams of [$MgSO_4$] per day). In chronic alcoholics with delirium tremens and in patients with severe hypomagnesemia, up to 8 to 12 grams of $MgSO_4$ may be given IM (possible, but very painful) or IV the first day. The first 10 to 15 mEq (1.5 to 2.0 grams) of IV $MgSO_4$ can be given over 1 to 2 hours. This may be followed by up to 4 to 6 grams/d. Approximately half of the administered Mg^{2+} will be lost in the urine.
5. Spironolactone is effective in maintaining [Mg^{2+}] homeostasis as well as in reducing the incidence of arrhythmias in congestive heart failure patients.[41]

HYPERMAGNESEMIA

PATHOPHYSIOLOGY

Hypermagnesemia is rarely encountered in emergency medicine practice, because the kidney can increase the fractional excretion of magnesium up to nearly 100%. A small elevation in serum concentration has little clinical significance. The most common cause for hypermagnesemia can be found in patients with renal insufficiency or renal failure who ingest Mg^{2+}-containing drugs.[42] Hypermagnesemia is more commonly seen in the perinatal setting secondary to the treatment of pre-eclampsia or eclampsia. It has been described as a serious, life-threatening consequence of magnesium-containing laxative abuse in patients with normal renal function.[43,44] Other causes of hypermagnesemia include lithium ingestion, volume depletion, or familial hypocalciuric hypercalcemia (**Table 17-22**).

TABLE 17-22

Causes of Hypermagnesemia

Renal Failure	Acute or Chronic
Increased magnesium load	Magnesium-containing laxatives, antacids, or enemas*
	Treatment of pre-eclampsia/eclampsia (mothers and neonates)
	Diabetic ketoacidosis (untreated)*
	Tumor lysis
	Rhabdomyolysis*
Increased renal magnesium absorption	Hyperparathyroidism
	Familial hypocalciuric hypercalcemia
	Hypothyroidism
	Mineralocorticoid deficiency, adrenal insufficiency (Addison's disease)

*Most likely presentation relevant to the ED.

CLINICAL FEATURES

Hypermagnesemia rarely produces symptoms. Magnesium decreases the transmission of neuromuscular messages and thus acts as a CNS depressant and decreases neuromuscular activity. Signs and symptoms related to [Mg^{2+}] can be found in Table 17-23.

TABLE 17-23

Symptoms and Signs of Hypermagnesemia

Level (mEq/L)	Clinical Manifestations
2.0–3.0	Nausea
3.0–4.0	Somnolence
4.0–8.0	Loss of deep tendon reflexes
8.0–12.0	Respiratory depression
12.0–15.0	Hypotension, heart block, cardiac arrest

DIAGNOSIS

Serum [Mg^{2+}] is usually diagnostic. **The possibility of hypermagnesemia should be considered in patients with hyperkalemia or hypercalcemia.** Hypermagnesemia also should be suspected in patients with renal failure, particularly in those who are taking magnesium-

containing antacids or laxatives.

TREATMENT

Immediate cessation of Mg^{2+} administration is required. If renal failure is not evident, dilution by IV fluids followed by furosemide (40 to 80 milligrams IV) may be indicated. Calcium directly antagonizes the cardiac effects of magnesium because it reverts the calcium channel blockade provoked by elevated [Mg^{2+}]. Severe symptomatic hypermagnesemia can be treated with 10 mL of 10% $CaCl_2$ IV over 2 to 3 minutes. Further infusion of 40 to 60 mL during the next 24 hours can be administered. Patients with renal failure may benefit from dialysis using a decreased [Mg^{2+}] bath that lowers serum [Mg^{2+}].

CALCIUM

PATHOPHYSIOLOGY

Calcium is the most abundant mineral in the body. The total body [Ca^{2+}] is 15 grams/kg of body weight, or about 1 kg in an average-sized adult. Calcium is 99% bound in bone as phosphate and carbonate (mineral apatite), with the remainder in the teeth, soft tissues, plasma, and cells. The normal daily intake of Ca^{2+} is 800 to 3000 milligrams, one third of which is absorbed primarily in the small bowel by active (vitamin D–dependent) and passive (concentration-dependent) absorption. Excretion of Ca^{2+} is primarily via the stool.

The cell content of Ca^{2+} is 10,000 times lower than the plasma content, and this gradient is maintained by Ca-ATPase, Ca^{2+}-specific channels and by Na/Ca exchangers.

Plasma [Ca^{2+}] is between 8.5 and 10.5 milligrams/dL (4.3 to 5.3 mEq/L or 2.2 to 2.7 mmol/L) and is present in three different forms: ionized calcium, 50% of total (4.5 to 5.6 milligrams/dL; 1.1 to 1.4 mmol/L), which is the only active fraction; protein bound calcium, 40% of total, which is inactive and not filtered by glomerulus; and complexed calcium, 10% of total, which is bound to anions like phosphate, carbonate, and citrate.

It is necessary to be aware of **standard units** used by different laboratories to express calcium value: **1 mEq/L = 2 milligrams/dL = 0.5 mmol/L.** The ionized fraction is the only biologically active fraction; a decrease in albumin decreases the total [Ca^{2+}] but does not change the ionized fraction. On average, 0.8 milligram of Ca^{2+} binds to 1 gram of protein. Therefore, total serum [Ca^{2+}] is equal to ionized [Ca^{2+}] plus the product of 0.8 and total protein. Alkalosis produces a decrease in ionized fraction with no change in the total serum [Ca^{2+}]. Each 0.1 rise in pH lowers ionized [Ca^{2+}] by about 3% to 8%. The opposite effect is produced by acidosis.

The role of Ca^{2+} is crucial for muscle and cardiac contraction, nerve conduction, cell growth, enzyme activation, and coagulation, and consequently, any hypo- or hypercalcemia leads to severe dysfunctions.

HOMEOSTASIS OF CALCIUM

The organs involved in the homeostasis of calcium are bones, kidneys, and the intestines, whereas the major determinates are three hormones and one receptor.[1,2,44,45]

1. **1,25-Dihydroxycholecalciferol (active vitamin D_3)**[45] is formed in the distal tubule. It promotes Ca^{2+} absorption from intestine, but this activity is modulated by physiologic conditions that may enhance it (pregnancy and growth) or reduce it (oxalates and phytates in food and aging).

2. Parathyroid hormone **(PTH)** is secreted by parathyroid glands when [Ca^{2+}] is low and is regulated by Ca^{2+}-sensing receptor, vitamin D_3, and Mg^{2+} (hypomagnesemia inhibits PTH secretion). PTH stimulates bone demineralization by activating osteoclasts and by increasing the synthesis of vitamin D_3 and increasing Ca^{2+} reabsorption from kidney.

3. **Calcitonin** is a peptide secreted by C-cells of the thyroid gland when [Ca^{2+}] is high. It inhibits the activity of osteoclasts and thus bone resorption.

4. **Ca^{2+}-sensing receptor**[46,47] is mainly present on plasma membranes of parathyroids, kidney, bones, and thyroid. It becomes active in case of hypercalcemia and inhibits the production of PTH. In the kidney, activated Ca^{2+}-sensing receptor provokes hypercalciuria and polyuria preventing nephrocalcinosis. The activation of the receptor also stimulates the secretion of calcitonin and inhibits osteoclast formation.

Urinary secretion of calcium is variable and influenced by many different factors. Hypercalcemia, metabolic acidosis, hypervolemia, and loop diuretics increase urinary secretion of [Ca^{2+}]. PTH, vitamin D_3, metabolic alkalosis, hypovolemia, and the chronic use of thiazides reduce secretion.

HYPOCALCEMIA

PATHOPHYSIOLOGY

Hypocalcemia is defined by an ionized [Ca^{2+}] level <2.0 mEq/L (<4 milligrams/dL; or <1.1 mmol/L). Homeostasis is regulated by the maintenance of the gradient between cells and ECF, is controlled by the above described mechanism, and is mediated intracellularly by phosphates, cyclic adenosine monophosphate, and ion pumps.[44] Any process that interferes with cell metabolism, such as shock or sepsis, will tend to reduce ionized [Ca^{2+}] by allowing increased net movement of Ca^{2+} across the cell membrane into the cytoplasm of the poorly functioning cells. As an example, serum [Ca^{2+}] may be low after trauma, especially with the fat embolism syndrome, not only due to cell dysfunction and binding of calcium to free fatty acids but also because of fatty inhibition of cell membrane calcium pumps.

ETIOLOGY

Table 17-24[1,2,47,48] lists the most common causes of hypocalcemia and the primary mechanism of each. Table 17-25 lists the principal drugs that cause hypocalcemia.[2]

TABLE 17-24

Some Causes of Hypocalcemia

Cause	Mechanism
Decreased calcium absorption	
Vitamin D deficiency Decreased oral intake Decreased intestinal absorption Decreased production of $25(OH)D_3$ Decreased synthesis of $1,25(OH2)D_3$ Malabsorption syndromes	Malnutrition Intestinal bypass, gastrectomy Liver failure Renal failure, hyperphosphatemia
Increased calcium excretion/reduced bone resorption	
Alcoholism	Hypomagnesemia causing inhibition of PTH secretion, PTH resistance to bone resorption
Hypoparathyroidism	Genetic, autoimmune, surgical, tumoral
Pseudohypoparathyroidism	Resistance to PTH action
Hypomagnesemia	Inhibition of PTH secretion, PTH resistance to bone resorption
Drugs (Table 17-25)	
Miscellaneous	
Sepsis	
Acute pancreatitis	Fatty acids combine with $[Ca^{2+}]$ to form insoluble Ca^{2+} soaps and lead to a reduction of serum $[Ca^{2+}]$
Massive transfusions	
Rhabdomyolysis	

Abbreviations: $25(OH)D_3$ = 25-hydroxyvitamin D_3; $1,25(OH2)D_3$ = 1,25-dihydroxyvitamin D_3; PTH = parathyroid hormone.

TABLE 17-25

Drugs That Can Cause Hypocalcemia

Phosphates (e.g., enemas, laxatives)
Phenytoin, phenobarbital
Gentamicin, tobramycin, dactinomycin, foscarnet
Cisplatin
Citrate
Loop diuretics
Glucocorticoids
Magnesium sulfate
Bisphosphonates, calcitonin, denosumab
Cinacalcet

CLINICAL FEATURES

The severity of signs and symptoms depends greatly on the rapidity of the decrease in [Ca^{2+}]. **Table 17-26** lists the different signs and symptoms that can be seen in the course of hypocalcemia.[1,2]

TABLE 17-26

Symptoms and Signs of Hypocalcemia

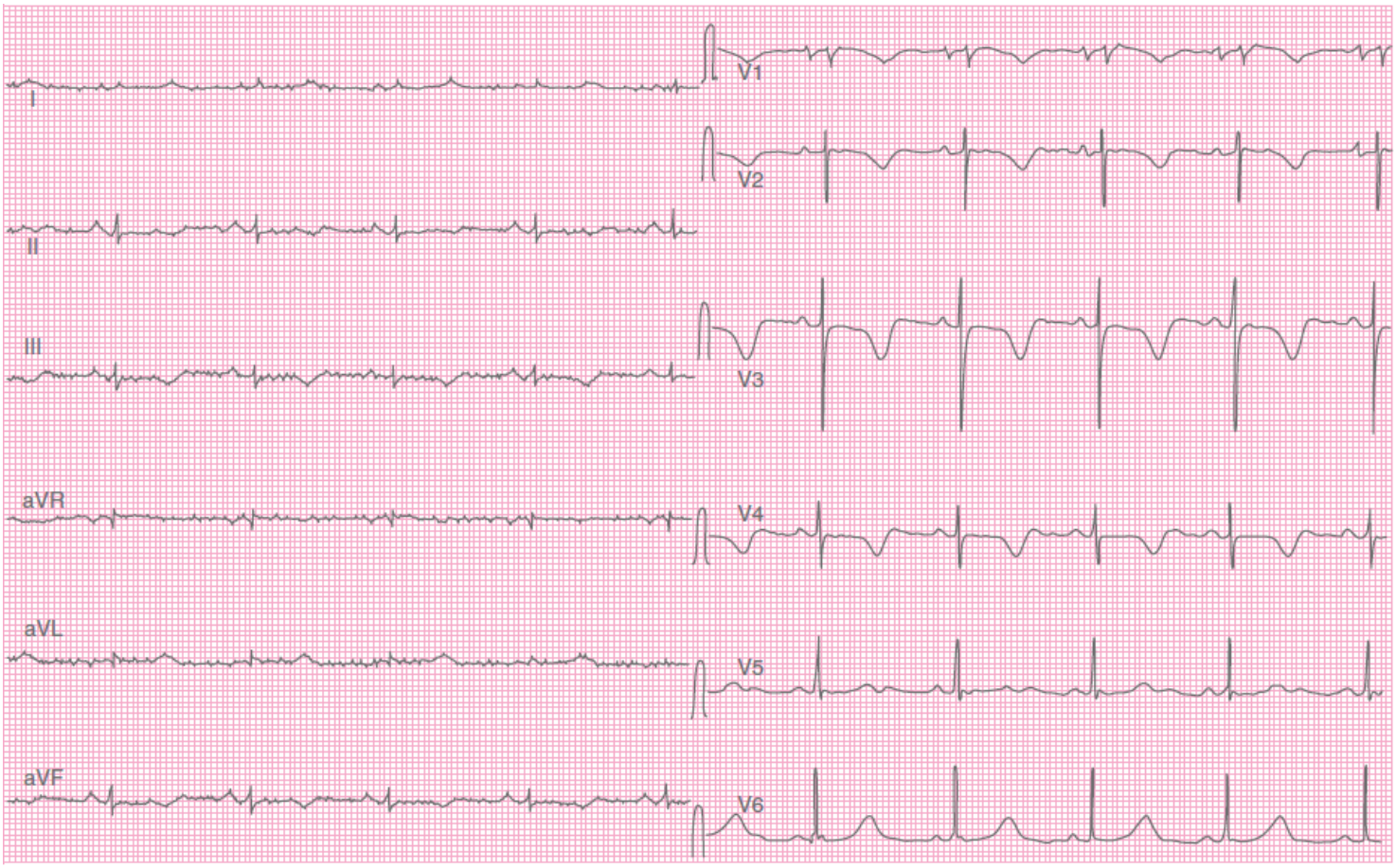
Muscular	Weakness, fatigue Spasms, cramps
Neurologic	Tetany Chvostek sign, Trousseau sign Circumoral and digital paresthesias Impaired memory, confusion Hallucinations, dementia, seizures Extrapyramidal disorders
Dermatologic	Hyperpigmentation Coarse, brittle hair Dry, scaly skin
Cardiovascular	Heart failure Ventricular arrhythmias, torsade de pointes Vasoconstriction
Skeletal	Osteodystrophy Rickets Osteomalacia
Miscellaneous	Dental hypoplasia Cataracts Decreased insulin secretion

Neuromuscular and cardiovascular signs and symptoms predominate. As serum [Ca^{2+}] falls, neuronal membranes become increasingly more permeable to sodium, thereby enhancing excitation, causing smooth and skeletal muscle contractions. Irritability, confusion, dementia, extrapyramidal symptoms, seizures, and hallucination may occur.

Decreased ionized [Ca^{2+}] reduces the strength of myocardial contraction primarily by inhibiting relaxation. The most characteristic ECG finding in hypocalcemia is a prolonged QT_C interval.[18,19] The T wave may be of normal width, and it is the ST segment that is actually prolonged. In very severe hypocalcemia, T waves may present abnormalities that may mimic ischemia (Figure 17-10). This finding is usually seen with total serum calcium levels <6.0 milligrams/dL.

FIGURE 17-10.

ECG of a patient with severe hypocalcemia (Ca^{2+} 4.5 milligrams/dL) who was complaining of chest and abdominal pain, pain in the legs, and Trousseau sign. A very long QT_C and T wave abnormalities mimicking ischemia are evident.



A positive Chvostek sign (twitch at the corner of the mouth when the examiner taps over the facial nerve just in front of the ear) and Trousseau sign (carpal spasm produced when the examiner applies a blood pressure cuff to the upper arm and maintains a pressure above systolic for 2 to 3 minutes; the fingers are spastically extended at the interphalangeal joints and flexed at the metacarpophalangeal joints with wrist flexion and forearm pronation) are classically associated with hypocalcemia (but also may occur in respiratory alkalosis, which shifts ionized calcium to the protein-bound form). These diagnostic signs have not been subjected to rigorous assessment, and there is no agreement on sensitivity or specificity.[49,50]

DIAGNOSIS

In addition to total serum [Ca^{2+}], a full electrolyte panel, renal function tests, ionized [Ca^{2+}], and magnesium levels aid in the diagnosis. An albumin level should be obtained because hypoalbuminemia may falsify the diagnosis.

In cases where acid-base abnormalities are suspected, a blood gas analysis to evaluate pH should be obtained. Also consider a phosphate level. Blood samples for PTH and vitamin D_3 levels should be drawn (but results are not required) before starting therapy.

TREATMENT

Treatment of hypocalcemia is tailored to the individual patient and directed toward the underlying cause. If a patient is asymptomatic or if the hypocalcemia is not severe or prolonged for >10 to 14 days, oral Ca^{2+} therapy with or without vitamin D may be sufficient. Ca^{2+} lactate, ascorbate, carbonate, and gluconate are available in oral preparations and contain variable percentages of elemental calcium; 1 mEq of elemental calcium is equal to 20 milligrams of elemental calcium. **Regimens can be 500 to 3000 milligrams of elemental calcium by mouth daily, in one dose or up to three divided doses. The dose must be individualized for each patient, according to the cause and severity of hypocalcemia.**

IV calcium is recommended only in cases of symptomatic or severe hypocalcemia[2] (ionized [Ca^{2+}] <1.9 mEq/L or <0.95 mmol/L), because IV Ca^{2+} administration causes vasoconstriction and possible ischemia, especially in patients with low cardiac output who already have significant peripheral vasoconstriction. **IV calcium gluconate is preferred over IV calcium chloride** in nonemergency settings due to the dangers of extravasation with calcium chloride (calcinosis cutis). **With severe acute hypocalcemia, 10 mL of 10% $CaCl_2$ (or 10 to 30 mL of 10% Ca^{2+} gluconate) may be given IV over 10 to 20 minutes and repeated every 60 minutes until symptoms resolve or followed by a continuous IV infusion of 10% $CaCl_2$ at 0.02 to 0.08 mL/kg/h (1.4 to 5.6 mL/h in a 70-kg patient).**[51] The serum [Ca^{2+}] should then be rechecked before continuing parenteral Ca^{2+}. **IV Ca^{2+} should be used with caution in patients taking digitalis, because hypercalcemia can potentiate digitalis toxicity.**[52] Symptomatic patients after thyroid or parathyroid surgery are often treated with parenteral Ca^{2+}.

During massive transfusions, if the blood is being given faster than 1 unit every 5 minutes, 10 mL of 10% $CaCl_2$ can be given after every 4 to 6 units of blood if a patient is in shock or has heart failure despite adequate volume replacement therapy.

Hypocalcemia is difficult to correct if hypomagnesemia is also present because of reduction of PTH and Ca^{2+} releases from bone. Therefore, magnesium should be replaced before, or in conjunction with, Ca^{2+} replacement.[44,45]

HYPERCALCEMIA

Hypercalcemia is relatively common. It is defined as a total [Ca^{2+}] >10.5 milligrams/dL or an ionized [Ca^{2+}] level >2.7 mEq/L.

PATHOPHYSIOLOGY

Because calcium is necessary for cellular functions, every organ and system is affected by hypercalcemia, and clinical manifestations are dependent on the level of [$Ca2^{+}$]: mild hypercalcemia, 10.5 to 11.9 milligrams/dL; moderate, 12 to 13.9 milligrams/dL; severe, >14 milligrams/dL.[2,4,53]

Neuromuscular changes include decreased sensitivity, responsiveness, and strength of muscular contraction and nerve conduction. The conduction of the heart is slowed and automaticity is decreased with a shortening of the refractory period. Increased sensitivity to cardiac glycosides may be seen.

Loss of concentrating ability is the most frequent renal effect of hypercalcemia. This is a reversible tubular defect, which results in polyuria and volume depletion even in the presence of thirst. Potassium wasting resulting in hypokalemia may occur in up to one third of patients. Nephrocalcinosis and nephrolithiasis may result from hypercalcemia and can be exacerbated by volume depletion. As the hypercalcemia persists, increasing microscopic Ca^{2+} deposits in the kidney can lead to progressive renal insufficiency.

ETIOLOGY

More than 90% of occurrences are associated with hyperparathyroidism[2,54] or malignancy, the latter being the most likely presentation in the ED. A list of potential causes of hypercalcemia and the relative mechanism of onset is provided in **Table 17-27**.[2]

TABLE 17-27

Causes of Hypercalcemia

Cause	Mechanism
Hypercalcemia due to increased bone Ca^{2+} resorption	
Primary hyperparathyroidism Malignancy Pseudohyperparathyroidism Renal failure Addison's disease Hyperthyroidism Immobilization	↑ PTH Osteolysis, PTH-related protein (PTHrP) production PTH Secondary and tertiary hyper-PTH due to chronic hypocalcemia ↑ Albumin, bone reabsorption Osteoclast activation
Hypercalcemia due to decreased urinary Ca^{2+} excretion	
Familial hypercalcemic hypocalciuria Thiazides	Mutation of CaSR Increased kidney Ca^{2+} reabsorption in proximal tubule
Hypercalcemia due to increased GI Ca^{2+} absorption	
Granulomatous diseases (sarcoidosis, tuberculosis, coccidioidomycosis, histoplasmosis) Milk (calcium)-alkali syndrome Vitamin D intoxication	1α-Hydroxylase activity Vitamin D_3 ↑Ca^{2+} intake and absorption, ↑renal reabsorption due to nephrogenic diabetes insipidus

Abbreviations: CaSR = Ca^{2+}-sensing receptor; PTH = parathyroid hormone.

CLINICAL FEATURES

Hypercalcemic patients with plasma total [Ca^{2+}] below 12.0 milligrams/dL are usually asymptomatic, but higher levels can cause a wide variety of symptoms (Table 17-28).

TABLE 17-28

Signs and Symptoms of Hypercalcemia

General Malaise, weakness Polydipsia, dehydration	*Cardiovascular* Hypertension Dysrhythmias Vascular calcifications ECG abnormalities QT shortening Coving of ST-T wave Widening of T wave Digitalis sensitivity
Neurologic Confusion Apathy, depression, stupor Decreased memory Irritability Hallucinations Headache Ataxia Hyporeflexia, hypotonia Mental retardation (infants)	*Gastrointestinal* Anorexia, weight loss Nausea, vomiting Constipation Abdominal pain Peptic ulcer disease Pancreatitis
Metastatic calcification Band keratopathy Conjunctivitis Pruritus	
Skeletal Fractures Bone pain Deformities	*Urologic* Polyuria, nocturia Renal insufficiency Nephrolithiasis

Patients with total [Ca^{2+}] >14 to 16 milligrams/dL are usually very weak, lethargic, and confused. Polyuria and polydipsia are due to impaired renal tubular reabsorption of water and result in volume depletion. Total [Ca^{2+}] >15.0 milligrams/dL may cause somnolence, stupor, and even coma. A mnemonic sometimes used for the signs and symptoms of hypercalcemia is *stones* (renal calculi), *bones* (osteolysis), *moans* (psychiatric disorders), and *groans* (peptic ulcer disease, pancreatitis, and constipation).

Hypercalcemia should be investigated in patients with extensive metastatic bone disease, particularly if the primary site involves the breast, lungs, or kidneys, and in individuals with combinations of clinical problems, such as renal calculi, pancreatitis, or ulcer disease.

On ECG, hypercalcemia may be associated with depressed ST segments, widened T waves, and shortened ST segments and QT intervals. Bradyarrhythmias may occur, with bundle-branch patterns that may progress to second-degree block or complete heart block. Levels of [Ca^{2+}] above 20 milligrams/dL may cause cardiac arrest.

DIAGNOSIS

True hypercalcemia must be confirmed by measuring ionized [Ca^{2+}][55]; then electrolytes, CBC, phosphate, magnesium, BUN, creatinine, and alkaline phosphatase will help determine the cause. The acuity of hypercalcemia can be determined or suggested using the medical history together with an ECG, chest x-ray, and laboratory investigation. The need for other studies such as serum or urine protein electrophoresis, PTH and vitamin D levels, thyroid tests, or bone scans should be individualized and will not determine what is done in the ED. Normally, acute, severe hypercalcemia is not caused by hyperparathyroidism. Malignancies, in particular lymphoma, leukemia, and metastatic bone cancer, are common causes of severe, acute hypercalcemia. A corrected calcium level should be calculated if albumin is not in the normal range: Corrected Ca^{2+} (milligrams/dL) = measured total Ca^{2+} (milligrams/dL) + 0.8 (4.0 – serum albumin [grams/dL]), where 4.0 represents the average albumin level in grams/dL. If the reference lab reports values in mmol/L, use the following formula:

Corrected Ca^{2+} (mmol/L) = measured total Ca^{2+} (mmol/L) + 0.02 (40 – serum albumin [grams/L]), where 40 represents the average albumin level in grams/L. If the values listed in the corrected calcium formulas for normal albumin do not match your institution's lab, adjust this value accordingly.

TREATMENT

Symptomatic patients or asymptomatic patients with [Ca^{2+}] levels above 14 milligrams/dL should receive treatment starting with volume repletion. Administer **0.9% normal saline at 500 to 1000 mL/h for 2 to 4 hours** as tolerated by the patient. In general, 3 to 4 L should be given over the first 24 hours, then 2 to 3 L per 24 hours until a urine output of 2 L/d is achieved.[56] Furosemide is recommended to promote a diuresis of 150 to 200 mL/h, which increases the calciuric effect,[1,56] with an initial dose of 20 to 40 milligrams. Larger doses may be required. Hypokalemia and/or hypomagnesemia should be assessed and treated, especially if furosemide is being used.

Decreased mobilization of [Ca^{2+}] from bone through reduction of osteoclastic activity can be obtained with **corticosteroids,** such as prednisone, 1 to 2 milligrams/kg PO, or hydrocortisone, 200 to 300 milligrams IV initial dose, in Addison's disease or in steroid-responsive malignancies.

In very severe cases, it will be necessary to receive **hemodialysis** to quickly remove calcium from blood.[53] In the ED, initiating bisphosphonates or calcitonin is not mandatory. However, for hypercalcemia associated with malignancy, intravenous bisphosphonates are now considered first-line therapy;[56] examples are pamidronate or zoledronate (zoledronic acid). Zoledronic acid is recommended;[56] for a corrected [Ca^{2+}] level of 12 milligrams/dL or higher, 4 milligrams as a single dose can be given IV over 15 minutes. Calcitonin works more rapidly than bisphosphonates and can be given at a dose of 4 units/kg SC or IM.

PHOSPHORUS

Phosphorus (PO_4^{3-}) is an essential mineral that exists mainly as hydroxyapatite (85%) or as an intracellular constituent (10% to 15%). Only about 1% is in the ECF, so serum measurements may not accurately reflect total body stores. It is involved in oxidative phosphorylation and mitochondrial respiration, and it is the essential component of adenosine triphosphate, a requirement for cellular energy metabolism.[2,57] Serum [PO_4^{3-}] decreases with age from a range of 4.0 to 7.0 milligrams/dL in newborns to 2.5 to 5.0 milligrams/dL in adults. The total body phosphorus store in a normal man is approximately 700 grams (10 to 15 grams/kg). Metabolism of phosphorus is strictly linked to that of calcium. The only active status of PO_4^{3-} is in biological fluids. Homeostasis of PO_4^{3-} is mainly regulated by gut absorption and urine excretion. Gut absorption is localized in two different sites. The first is the duodenum, which is inhibited by calcitonin and is stimulated by a vitamin D_3 and low phosphate intake. The second is the jejunum and ileum, where absorption is passive and dependent on PO_4^{3-} concentration in the gut.

Excretion is predominantly in the urine by the glomerulus, with the majority reabsorbed in the proximal tubules. Excretion is regulated by PTH, which lowers serum phosphate by increasing renal excretion, and by a hormone secreted by osteoclasts and osteoblasts, the fibroblast growth factor-23, that increases PO_4^{3-} excretion and inhibits intestinal absorption. Proximal tubule absorption increases when serum [PO_4^{3-}] levels drop and with hypoparathyroidism, volume depletion, hypocalcemia, or the presence of growth hormone. Excretion increases in the presence of volume expansion, hypercalcemia, acidosis, hypomagnesemia, hypokalemia, glucocorticoids, diuretics, calcitonin, or PTH.[57]

HYPOPHOSPHATEMIA

PATHOPHYSIOLOGY

Hypophosphatemia is defined as serum [PO_4^{3-}] <2.5 milligrams/dL, but severe symptoms may not occur until the [PO_4^{3-}] level drops to <1 milligram/dL. Because phosphorus is abundant in many foods and readily absorbed, hypophosphatemia is relatively unusual. Mechanisms include a shift of phosphate into cells, increased renal excretion, and decreased GI absorption (**Table 17-29**). Only when depletion is present will clinical manifestations occur and require treatment. It is important to understand pseudohypophosphatemia, which occurs when a

patient is treated with mannitol, which binds to molybdate in the serum, causing an artificially low value when [PO_4^{3-}] is measured by the laboratory.

TABLE 17-29

Causes of Hypophosphatemia

Shift from ECF to ICF without depletion of PO_4^{3-}	Glucose Insulin Catecholamines Respiratory alkalosis
Shift from ECF to ICF with depletion of PO_4^{3-}	Hyperalimentation Refeeding syndrome
Decreased intestinal absorption	Low intake Malabsorption Chronic use of calcium acetate or bicarbonate, aluminum hydroxide Vitamin D deficiency
Increased renal loss	Hyperparathyroidism Increased fibroblast growth factor (FGF-23) Genetic hypophosphatemia mutations Tubular acidosis Fanconi's syndrome Hypokalemia Hypomagnesemia Polyuria Acidosis
Miscellaneous causes	Alcoholism (poor intake, vitamin D deficiency) Diabetic ketoacidosis (osmotic diuresis) Toxic shock syndrome
Drugs	See Table 17-30

Severe hypophosphatemia can occur in patients with prolonged use of antacids, such as aluminum hydroxide, magnesium hydroxide, or calcium carbonate. Several other drugs may cause hypophosphatemia with different mechanism (Table 17-30).

TABLE 17-30

Drugs That Cause Hypophosphatemia and Underlying Mechanism

Osmotic diuretics, loop diuretics, carbonic anhydrase inhibitor	↓ Renal reabsorption and phosphaturia
Acyclovir	Inhibition of Na/Pi-IIa cotransporter
Acetaminophen	↓ Renal reabsorption and phosphaturia
Tyrosine kinase inhibitors	Ca^{2+} and phosphate reabsorption and secondary hyperparathyroidism
Bisphosphonates	Inhibits bone resorption
Aminoglycosides, tetracyclines, valproic acid	Induction of Fanconi's syndrome
Cyclophosphamide, cisplatin	↑ Phosphaturia
Corticosteroids	↓ Intestinal phosphate absorption and phosphaturia

Critically ill patients are particularly at risk for hypophosphatemia, which occurs in up to 30% of those admitted to the intensive care unit with sepsis, trauma, and pulmonary diseases. The mechanism is glucose infusions, starvation, refeeding, shock, acidosis, alkalosis, diuretics, and catecholamine treatment.

CLINICAL FEATURES

Symptoms are due to the depletion of adenosine triphosphate and the reduction of erythrocyte 2,3-diphosphoglycerate. The final outcome will be cellular dysfunction and hypoxia. The main symptoms of hypophosphatemia are listed in **Table 17-31**.[58]

TABLE 17-31

Symptoms and Signs of Hypophosphatemia

Hematologic
Reduced survival and function of platelets and red and white blood cells
Impaired macrophage function
Neuromuscular
Weakness, tremors, circumoral and fingertip paresthesias, decreased deep tendon reflexes, decreased mental status, anorexia
Cardiac
Impaired myocardial function
Metabolic
Insulin resistance

TREATMENT

When symptomatic, hypophosphatemia can be corrected both orally and IV. Possible adverse effects of IV therapy include hypocalcemia with consequent myocardial depression, arrhythmias, acute kidney injury, and calcifications. The suggested doses for PO_4^{3-} replacement are listed in Table 17-32, and the commonly used preparations are described in Table 17-33.[2,58]

TABLE 17-32

IV PO_4^{3-} Replacement Dose (6–72 h)

Serum [PO_4^{3-}] (milligrams/dL)	Dose (mmol/kg)	Duration (h)
<1	0.6	6–72
1–1.7	0.3–0.4	6–72
1.8–2.2	0.15–0.2	6–72

TABLE 17-33

PO_4^{3-} Preparations

Preparation	PO_4^{3-} Content	Na^+ Content	K^+ Content
Neutral Na/K PO_4 (PO)	8 mmol	7.1 mEq	7.1 mEq
Sodium PO_4^{3-} (IV)	3 mmol/mL	4 mEq/mL	0
Potassium PO_4^{3-} (IV)	3 mmol/mL	0	4.4 mEq/mL

In asymptomatic or mildly symptomatic patients, hypophosphatemia may be treated orally with skimmed milk ([PO_4^{3-}] 1 gram/L) or oral preparations like Neutra-Phos®, one to two tabs PO four times daily, or K-Phos®, one tab PO four times daily, which contain 150 to 250 milligrams per tablet (PO_4^{3-}: 1 mmol/L = 3.1 milligrams/dL). A treatment regimen of 50 mmol/d for 7 to 10 days is sufficient to replace deficits, but in severe hypophosphatemia, higher doses may be necessary.

HYPERPHOSPHATEMIA

Hyperphosphatemia is defined as serum [PO_4^{3-}] >4.5 milligrams/dL and is rarely encountered in emergency medicine practice. The causes can be divided in three groups according to mechanism: decrease in renal excretion of PO_4^{3-}, addition or movement of PO_4^{3-} from ICF to ECF, and drugs (Table 17-34).[57] In clinical practice, the most important cause of hyperphosphatemia is acute or chronic renal failure.

TABLE 17-34

Causes of Hyperphosphatemia

Decrease in renal excretion of PO_4^{3-}	Acute and chronic renal failure* Hypoparathyroidism, pseudohypoparathyroidism
Shift of PO_4^{3-} from ICF to ECF	Hemolysis* Rhabdomyolysis* Tumor lysis syndrome Respiratory acidosis Diabetic ketoacidosis
Addition of PO_4^{3-} exogenous to the ECF	Oral or IV treatment of hypophosphatemia Phosphate-containing laxatives, antacids*
Drugs	Excess of vitamin D Growth hormone Bisphosphonates

*Most likely presentation relevant to the ED.

Hyperphosphatemia worsens renal tubulointerstitial disease, renal osteodystrophies, and cardiovascular disease. The acute symptoms are due to renal failure, hypocalcemia, and hypomagnesemia.

It is important to lower phosphorus intake with a careful protein-containing diet and to avoid excessive vitamin D intake to limit intestinal absorption.[59] In very high PO_4^{3-} levels, it is necessary to remove it with hemodialysis. Phosphate binders like calcium carbonate or calcium acetate bind intestinal phosphate, decreasing its absorption.[60]

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