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# Acid-Base, Electrolyte, and Metabolic Abnormalities

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**CHAPTER OUTLINE**



Acid-base, electrolyte, and metabolic disturbances are common in the intensive care unit (ICU). Indeed, critically ill patients often suffer from compound acid-base and electrolyte disorders. Successful evaluation and management of such patients requires recognition of common patterns (e.g., hypokalemia and metabolic alkalosis), and an ability to discern one disorder from another. This chapter is intended to provide intensivists with the tools they need for diagnosis and treatment of the acid-base, electrolyte, and metabolic disorders encountered in the care of critically ill patients. By reviewing the elements of normal physiology in these areas, and presenting a general diagnostic scheme for each condition, we hope to provide readers with a foundation for approaching not only common, but novel and complex disorders.

## ACID-BASE HOMEOSTASIS

Normal acid-base balance depends on the cooperation of at least two vital organ systems: the lungs and the kidneys. The gastrointestinal (GI) tract also is involved in many acid-base disturbances. Multiorgan system involvement, therefore, provides the backdrop for the acid-base disorders commonly seen in critically ill patients.

### NORMAL ACID-BASE PHYSIOLOGY

Normal biochemical and physiologic function requires that the extracellular pH be maintained within a very narrow range. Although the "normal" range of pH in clinical laboratories is 7.35 to 7.45 pH units, the actual pH in vivo varies considerably less.[1] This tight control is maintained by a complex homeostatic mechanism involving buffers and the elimination of volatile acid by respiration.

The principal extracellular buffer system is the carbonic acid/bicarbonate pair. The equilibrium relationships of the components of this system are illustrated as follows:[1]

$$H_2O + CO_2 \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$

From these relationships, the Henderson-Hasselbalch equation is derived:

$$pH = pK + \log_{10} \frac{HCO_3^-}{\alpha_{CO2} \cdot PCO_2}$$

In this equation, $\alpha_{CO2}$ is the solubility coefficient of $CO_2$ (0.03), and pK is the equilibrium constant for this buffer pair (6.1). Rearrangement yields the Henderson equation:

$$H^+ = 24 \cdot \frac{PCO_2}{HCO_3^-}$$

It is apparent from this equation that disturbances in the proton concentration of the extracellular fluid (ECF) (and blood) may be due to perturbation in the numerator, the denominator, or both. Disturbances that affect the $P_{CO_2}$ primarily are called *respiratory* disturbances, and those that affect the $HCO_3^-$ primarily are called *metabolic*.

Acid-base homeostasis depends on compensation for a primary disturbance. Compensation for a respiratory disturbance is metabolic, and compensation for a metabolic disturbance is respiratory. Furthermore, it is clear from the previous equations that in order to mitigate the change in proton concentration or pH, the direction of the compensation must be the same as the direction of the primary disturbance. Thus, consumption of bicarbonate will be accompanied by hyperventilation and a consequent reduction in $P_{CO_2}$. A simple acid-base disturbance is considered to consist of the primary disturbance *and* its normal compensation. A complex acid-base disturbance consists of more than one primary disturbance. In order to detect complex acid-base disturbances, one must be familiar with both the direction and magnitude of normal compensation (shown in Table 57.1).[2] More than one metabolic disturbance may coexist (e.g., metabolic acidosis and metabolic alkalosis), but only one respiratory disturbance is possible at a time.

In the present section, we will discuss disorders that affect the metabolic component of acid-base homeostasis: metabolic acidosis and metabolic alkalosis. Respiratory disturbances affecting acid-base balance will be discussed elsewhere (Chapters 37 and 40).

## METABOLIC ACIDOSIS

### DEFINITION AND CLASSIFICATION

A metabolic acidosis is a process that, if unopposed, would cause *acidemia* (a high hydrogen ion concentration, or low pH, of the blood) by reducing the extracellular bicarbonate concentration. The extracellular bicarbonate concentration may be reduced by either addition of acid and consequent consumption of bicarbonate, or by primary loss of bicarbonate.

An adult eating a normal diet generates 16,000 to 20,000 mmol of acid a day.[3] Almost all of that acid is in the form of carbonic acid, resulting from $CO_2$ and water generation in the metabolism of carbohydrates and fats. Individuals with normal ventilatory capacity eliminate this prodigious acid load through the lungs, thus the term *volatile acid*. The remainder of the daily acid load, about 1 mmol/kg body weight per day, derives from metabolism of phosphate- and sulfate-rich protein (yielding phosphoric and sulfuric acid). These nonvolatile or *fixed acids* are buffered, primarily by extracellular bicarbonate under normal circumstances. The kidneys are responsible for regenerating the consumed bicarbonate by secreting hydrogen ions (protons) in the distal nephron. These secreted protons must be buffered in the tubule lumen in order to allow elimination of the daily fixed acid load within the physiologic constraint of the minimum urinary pH. The urinary buffers are composed of the filtered sodium salts of the phosphoric acid and ammonia, which is synthesized in the proximal tubule and acidified in the collecting duct to form ammonium ($NH_4^+$). Under conditions of acid loading, the normal kidney reabsorbs all the filtered bicarbonate in the proximal tubule. Urinary net acid excretion therefore comprises phosphoric acid (so-called titratable acidity, because it is quantified by titrating the urine with alkali to pH 7.40) and ammonium, less any excreted bicarbonate.[4]

Many factors modify the kidney's capacity to regulate acid-base balance. For example, renal ammoniagenesis is stimulated by acidemia, and inhibited by alkalemia, and thus participates in a homeostatic feedback loop.[1] Hyperkalemia inhibits and hypokalemia stimulates renal ammoniagenesis. Hypokalemia further stimulates acid secretion by activating the $Na^+$-$H^+$ exchanger in the proximal tubule and the $H^+/K^+$-ATPase in the collecting duct. Finally, aldosterone stimulates both proton and $K^+$ secretion in the collecting duct. For these reasons, hypokalemia tends to perpetuate a metabolic alkalosis, and hyperkalemia a metabolic acidosis.[1]

Metabolic acidosis can be caused by excessive production of fixed acid, decreased renal secretion of fixed acid, or loss of bicarbonate, either through the kidney or through the intestine.[4] The net effect of any of these processes is a reduction in the blood bicarbonate concentration. The plasma *anion gap* helps to distinguish among the various causes of metabolic acidosis. Of course, because of charge neutrality, the sum of the concentration of all cations in the plasma is equal to the sum of all the anions. By convention, however, the anion gap is defined as the difference between the plasma sodium concentration and the sum of the bicarbonate and chloride concentrations. It represents the concentration of anions that are normally unmeasured by a basic metabolic chemistry panel.[5] The anion gap normally is about 8 mmol/L, but it varies widely according to the methods employed by the clinical chemistry laboratory.[6] The anion gap is composed mainly of albumin, along with phosphates, sulfates, and organic anions.

**Table 57.1 Expected Compensation for Simple Acid-Base Disorders**

| Disorder | Primary Disturbance | Compensation | Magnitude | Time to Completion |
|---|---|---|---|---|
| Metabolic acidosis | ↓ $[HCO_3^-]$ | ↓ $P_{CO_2}$ | 1.5 • $[HCO_3^-]$ + 8 | 12-24 hours |
| Metabolic alkalosis | ↑ $[HCO_3^-]$ | ↑ $P_{CO_2}$ | 0.9 • $[HCO_3^-]$ + 9 | 12-24 hours |
| Respiratory acidosis, acute | ↑ $P_{CO_2}$ | ↑ $[HCO_3^-]$ | 1 mmol/L/10 mm Hg | <6 hours |
| Respiratory acidosis, chronic | ↑ $P_{CO_2}$ | ↑ $[HCO_3^-]$ | 3.5 mmol/L/10 mm Hg | >5 days |
| Respiratory alkalosis, acute | ↓ $P_{CO_2}$ | ↓ $[HCO_3^-]$ | 2 mmol/L/10 mm Hg | <6 hours |
| Respiratory alkalosis, chronic | ↓ $P_{CO_2}$ | ↓ $[HCO_3^-]$ | 5 mmol/L/10 mm Hg | >7 days |

There are two important pitfalls in the interpretation of the anion gap. First, because the anion gap is proportional to the plasma albumin concentration, hypoalbuminemia (common in critically ill patients) will lower the "baseline" anion gap (by approximately 2.5 mmol/L for each g/dL decline in the albumin concentration).[7] Thus, profound hypoalbuminemia may falsely lower the anion gap, and thus mask a high anion gap acidosis. Second, alkalemia increases the anion gap by causing lactate generation and by titrating plasma buffers, most notably albumin.[8] (Thus, in respiratory alkalosis, the bicarbonate concentration will be low in compensation, and the anion gap may be elevated, giving a false impression of a high anion gap metabolic acidosis by inspection of the electrolytes alone.)

If bicarbonate is lost (e.g., through diarrhea), or hydrochloric acid is gained (e.g., renal tubular acidosis or administration of unbuffered amino acid solutions[9]), the bicarbonate concentration falls with a commensurate increase in the plasma chloride concentration; thus the anion gap is unchanged. If, on the other hand, bicarbonate is lost in buffering an organic acid such as lactic acid or a ketoacid, the decrement in the bicarbonate concentration is more or less matched by an increase in the anion gap. These processes are illustrated in Figure 57.1.

Box 57.1 lists the causes of hyperchloremic metabolic acidosis. Two diagnoses are of particular interest in the critical care arena. First is the posthypocapnic metabolic acidosis, in which bicarbonate falls in compensation for a chronic respiratory alkalosis. When "normal" ventilation is restored, the pH falls until bicarbonate can be retained, giving the appearance of a hyperchloremic metabolic acidosis. This emphasizes the importance of observation over time in the analysis of acid-base status. The second entity of interest is a so-called dilutional hyperchloremic acidosis. This is seen in patients who are rapidly resuscitated with large volumes of isotonic saline solution. The acidosis traditionally has been attributed to dilution of blood bicarbonate. Analysis based on physical-chemistry principles may better explain the phenomenon (see later).[10]

The differential diagnosis of high anion gap metabolic acidosis is limited (Box 57.2). The most common cause in critically ill patients is a lactic acidosis. The causes of lactic acidosis are numerous. As shown in Box 57.3, they are divided into type A (imbalance between tissue oxygen demand and supply) and type B (impaired oxygen utilization).[5] Diabetic ketoacidosis (DKA) (Chapter 58) and intoxications (Chapter 68) are discussed elsewhere. Two causes of high anion gap acidosis recently added to the differential diagnosis, and of particular relevance to intensivists, are *pyroglutamic acidosis* and intoxication with *propylene glycol*.

Pyroglutamic acid is a metabolic intermediate in the γ-glutamyl cycle, one product of which is glutathione. Pyroglutamic acidosis may be congenital (caused by one of several enzyme deficiencies) or acquired.[8] The acquired syndrome may be caused by acetaminophen (which depletes glutathione, leading to uninhibited pyroglutamic acid synthesis), β-lactam antibiotics, or glycine deficiency. The

**Box 57.1 Causes of Hyperchloremic Metabolic Acidosis**

**Extrarenal Loss of Base**

Diarrhea
Pancreatic fistula
Ureteral diversion

**Extrarenal Gain of Acid**

Ammonium chloride
Hydrochloric acid
Sodium chloride

**Renal Loss of Base**

Type II renal tubular acidosis
Posthypocapnic state
Excretion of organic anions (bicarbonate precursors)
Toluene inhalation (glue sniffing)
Diabetic ketoacidosis

**Renal Acid Excretory Defect**

Type IV renal tubular acidosis
  Chronic kidney disease
  Hypoaldosteronism
  Urinary tract obstruction
Type I renal tubular acidosis
  Sickle cell nephropathy
  Lupus nephritis
  Renal transplant

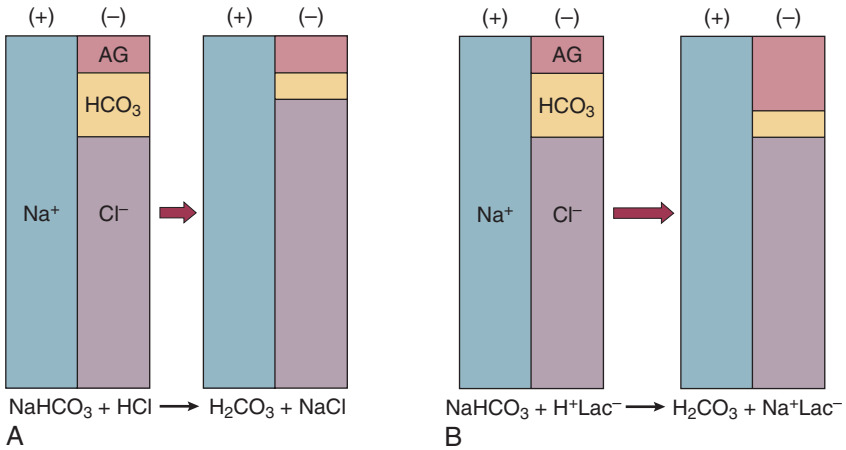


**Figure 57.1** The generation of hyperchloremic and anion gap (AG) acidoses. Blocks represent the ionic composition of the plasma, cations (+) to the left and anions (–) to the right. In each of the panels (A and B), the bar to the left represents the basal or normal state. The AG is shown in red. **A,** The change in the ionic composition of the plasma when hydrochloric acid is added. The chloride concentration increases as bicarbonate is consumed. **B,** The effect of addition of an organic acid such as lactic acid, in which case the bicarbonate is consumed and the AG increases proportionately. Cl, chloride; $H_2CO_3$, carbonic acid; Na, sodium; $NaHCO_3$, sodium bicarbonate.

**Box 57.2 Causes of High Anion Gap Metabolic Acidosis**

- Ketoacidoses
  - Diabetic
  - Alcoholic
  - Starvation
- Intoxications
  - Methanol
  - Ethylene glycol
  - Propylene glycol
  - Salicylate
- Pyroglutamic acidosis
  - Congenital
  - Acquired
- Lactic acidosis (see Box 57-3)
- Uremic acidosis

acidosis may be profound and the anion gap greater than 30 mmol/L.[11] Definitive diagnosis is made by urinary screen for organic acids. In practice, however, circumstantial evidence suggests the acquired syndrome and the diagnosis is supported by a favorable response to appropriate intervention.

Propylene glycol is a solvent for medications, many of which are commonly infused intravenously in critically ill patients, such as lorazepam, nitroglycerin, etomidate, and phenytoin. Propylene glycol is metabolized by alcohol dehydrogenase to lactic acid. High anion gap acidosis has been associated with high- and even low-dose infusions, particularly of lorazepam.[7,12] Thus, development of a high anion gap acidosis in a critically ill patient should prompt a search for a source of propylene glycol, because withdrawal of the agent will promptly alleviate the acidosis.

## CONSEQUENCES OF ACIDEMIA

It has been generally accepted that severe acidemia (pH < 7.20) is associated with a variety of deleterious effects. Of particular concern are the cardiovascular effects, including pressure-resistant arterial vasodilation, venoconstriction, diminished myocardial contractility, and impaired hepatic and renal perfusion.[13] (Some controversy exists as to which of these effects are directly caused by acidemia.[4]) A predisposition to malignant arrhythmias has been reported in vitro and in animal models. Finally, numerous metabolic derangements have been attributed to the effect of acidemia on key enzymes in metabolic pathways, resulting in sympathetic hyperactivity with diminished catecholamine responsiveness; insulin resistance and suppressed glycolysis; and reduced hepatic lactic acid uptake and metabolism.[14]

## DIAGNOSIS OF ACID-BASE DISORDERS

Acid-base disorders are revealed most commonly through the basic metabolic chemistry panel, when the plasma bicarbonate concentration is noted to be outside the normal range. If the bicarbonate is low, and if the anion gap is clearly elevated on that sample, a diagnosis of high anion gap metabolic acidosis can be made with some confidence, keeping in mind the pitfalls in the interpretation of the anion gap mentioned earlier.[7]

**Box 57.3 Causes of Lactic Acidosis**

**Type A (Tissue Oxygen Supply:Demand Mismatch)**

- Decreased tissue oxygen delivery
  - Shock
  - Hypoxemia
  - Severe anemia
  - Carbon monoxide poisoning
- Increased tissue oxygen demand
  - Grand mal seizure
  - Extreme exercise

**Type B (Impaired Tissue Oxygen Utilization)**

- Sepsis/systemic inflammatory response syndrome
- Diabetes mellitus
- Malignancy
- Thiamine deficiency
- Inborn errors of metabolism
- Human immunodeficiency virus infection
- Malaria
- Drugs/toxins
  - Ethanol
  - Metformin
  - Zidovudine
  - Didanosine
  - Stavudine
  - Lamivudine
  - Zalcitabine
  - Salicylate
  - Propofol
  - Niacin
  - Isoniazid
  - Nitroprusside
  - Cyanide
  - Catecholamines
  - Cocaine
  - Acetaminophen
  - Streptozotocin
  - Sorbitol/fructose
  - Carboplatin
  - Entecavir
  - Linezolid
- Liver failure
- Alkalemia
- D-Lactic Acidosis

If the bicarbonate is low and the anion gap normal, two possibilities exist: either a hyperchloremic metabolic acidosis or a respiratory alkalosis with metabolic compensation. These two entities can be distinguished by examination of the blood pH and blood gases, a low pH being diagnostic of the former.

If the bicarbonate concentration is high, again there are two alternative diagnoses, requiring blood pH measurement for their differentiation: either a metabolic alkalosis or metabolic compensation for a respiratory acidosis.

Once the primary disturbance has been identified, the astute clinician, recognizing the possibility of a mixed disturbance, is obligated to ask, "Is that all there is?" This question can be answered only by an understanding of the rules of normal compensation for simple acid-base disorders (see Table 57.1).[2] Knowing at least the expected direction of compensation will allow the clinician to diagnose the most

obvious mixed disturbances. For example, if the pH is low, the bicarbonate is low, and the $P_{CO_2}$ is above 40 mm Hg, there is clearly a mixed metabolic and respiratory acidosis. Similarly, if the pH is high, the bicarbonate is high, and the $P_{CO_2}$ is below 40 mm Hg, the diagnosis is a mixed respiratory and metabolic alkalosis. More subtle mixed disorders can be diagnosed only by understanding not only the expected direction, but the expected magnitude of compensation. This will allow one to conclude, for example, whether the hyperventilation in a patient with metabolic acidosis is appropriate (expected compensation), inadequate (a separate respiratory acidosis), or excessive (a separate respiratory alkalosis).

The preceding method permits the diagnosis of simple and dual acid-base disorders. Triple acid-base disorders can be diagnosed only by comparing the change in the anion gap with the change in the plasma bicarbonate concentration. Most simply conceived, the fall in the bicarbonate should equal the rise in the anion gap (see Fig. 57.1). If the rise in the anion gap exceeds the fall in the bicarbonate, a metabolic alkalosis is said to be present in addition to the high anion gap acidosis. Conversely, if the fall in the bicarbonate exceeds the rise in the anion gap, mixed hyperchloremic and high anion gap acidoses are said to coexist. Although this analysis is useful in the case of large discrepancies, in more subtle cases it is confounded by theoretical and practical considerations.[5,15]

The classical approach to acid-base disorders described earlier has been challenged recently by proponents of a physical-chemistry approach described originally by Stewart.[16] According to this method, the pH of the blood depends on the ionization of water by the difference in the concentration of so-called strong ions (the strong ion difference, or SID). The SID offers a quantitative approach to measuring the degree of acidosis in hyperchloremic metabolic acidosis. Although there is evidence that this approach may offer prognostic capabilities in patients with severe sepsis and septic shock with hyperchloremic metabolic acidosis, the complexity of the equations for calculating the SID may make this method cumbersome in clinical settings.[17] The main utility of this construct in the critical care setting seems to be its explanation of a hyperchloremic metabolic acidosis in patients who receive large volumes of isotonic saline.

## TREATMENT OF METABOLIC ACIDOSIS

Treatment of metabolic acidosis is aimed at reversing the adverse consequences of acidemia. Treatment of hyperchloremic metabolic acidosis is straightforward. In cases of acute metabolic acidosis, treatment depends on successful therapy of the underlying cause (e.g., diarrhea) and correction of the bicarbonate deficit, usually in the form of sodium bicarbonate. One can estimate the bicarbonate deficit as follows:

$$HCO_3^- \text{ deficit} = \left([HCO_3^-]_{final} - [HCO_3^-]_{initial}\right) \times (\text{volume of distribution of } HCO_3^-)$$

The difficulty in accurately estimating this value arises from two factors: First, the apparent volume of distribution of bicarbonate varies more than twofold—from 50% of body weight to 100% of body weight—and is inversely proportional to the initial bicarbonate concentration.[18] Second, there are often many simultaneous processes in a critically ill patient that tend to ameliorate or exacerbate the metabolic acidosis, such as vomiting, shock, and liver failure. In order to avoid overshoot alkalemia, it is prudent to estimate the volume of distribution to be 50% of the body weight[14] and to target an increase in the bicarbonate concentration of no more than 8 mmol/L over 12 to 24 hours.

Sodium bicarbonate generally is considered to be the alkalinizing agent of choice for severe acidemia. Alternative alkalinizing agents such as citrate, acetate, and lactate, which under normal circumstances are oxidized in the liver to bicarbonate, should not be used to treat acidemia in patients with suspected or confirmed hepatic impairment or circulatory compromise. The sodium bicarbonate should be administered as a continuous infusion, the concentration of which should be guided by the patient's serum sodium concentration. Bolus injection of undiluted ampules of sodium bicarbonate (1000 mmol/L) should be used with great restraint and only in patients with the most severe acidemia because of the risk of hyperosmolality. Large volumes of any bicarbonate solution can lead to volume overload, a reduction in the ionized calcium concentration (see "Hypocalcemia"), and increased generation of $CO_2$. This last effect will tend to cause a respiratory acidosis in patients with ventilatory insufficiency. Plasma electrolytes and blood gases must be monitored frequently to guide adjustments in the composition of the solution and its rate of infusion.

Tris(hydroxymethyl)aminomethane, or THAM, is an amino alcohol that buffers without generating $CO_2$. It has the advantage, therefore, of avoiding a superimposed respiratory acidosis. It has been used successfully in animals and humans with various metabolic acidoses.[13,19] It is eliminated by the kidney, and thus should be used with caution in the setting of renal insufficiency. Risks include hyperkalemia, hypoglycemia, and hepatic necrosis (in neonates).[7]

The treatment of choice for lactic acidosis is reversal of the underlying cause of the acidosis (see Box 57.3). Pending resolution of the underlying disorder, however, the intensivist is often confronted with an unstable patient who is profoundly acidemic. Treatment at this stage is controversial.[5,13] The debate has focused on the potentially deleterious effects of bicarbonate administration in lactic acidosis.[20] In addition to the effects mentioned earlier, bicarbonate in animal models of lactic acidosis has been associated with increased lactate generation, reduction in intracellular pH, increased venous $P_{CO_2}$, and reduction in cardiac output. (This last effect correlates well with the reduction in ionized calcium concentration.[13]) Studies in humans likewise show no improvement in cardiac output, morbidity rate, or mortality rate with bicarbonate.[13] Continuous venovenous hemodialysis (e.g., CVVHD) may be a promising tool for treating lactic acidosis, because it provides large amounts of bicarbonate without the risks of volume overload or hypocalcemia. There are several reported cases of successful treatment of metformin-associated lactic acidosis using continuous hemodialysis.[21,22] Because of its superior short-term clearance compared with continuous renal replacement therapy, however, conventional hemodialysis remains the preferred treatment for metformin intoxication.[23] Treatment of DKA and the acidoses associated with other intoxications are discussed in Chapters 58 and 68, respectively.

## METABOLIC ALKALOSIS

### DEFINITION AND CLASSIFICATION

Metabolic alkalosis is a process leading to accumulation of extracellular bicarbonate that, if unopposed, will result in an increase in the plasma pH (alkalemia). It can be caused either by a gain of bicarbonate or a loss of fixed acid from the ECF. The causes of metabolic alkalosis have been described.[24] In its pure form, it is accompanied by hypoventilation ($CO_2$ retention).[2]

From a pathophysiologic perspective, metabolic alkalosis is divided into those factors that generate the alkalosis and those factors that maintain or perpetuate it.[24,25] Metabolic alkalosis is generated by addition of bicarbonate to the blood. This can occur either by loss of acid from the body or by addition of exogenous alkali. Loss of acid may be from the stomach (e.g., vomiting or nasogastric suction) or kidney. Renal acid loss is enhanced by a high rate of sodium delivery to the distal nephron, high circulating mineralocorticoid levels, potassium depletion, and high rates of ammoniagenesis.

Because of the kidney's prodigious ability to excrete bicarbonate, however, addition of bicarbonate to the blood is not sufficient to cause a sustained metabolic alkalosis. Some mechanism(s) to maintain the alkalosis must prevail. The most common mechanism contributing to the maintenance of metabolic alkalosis is volume depletion, either absolute or relative (e.g., congestive heart failure), which (1) reduces glomerular filtration, (2) enhances tubular bicarbonate reabsorption, and (3) causes secondary hyperaldosteronism, further enhancing urinary acidification. Another common perpetuating factor is potassium depletion, which stimulates proton secretion at several sites along the nephron.[24-26]

Patients with metabolic alkalosis and signs of volume expansion—especially hypertension—usually have excess mineralocorticoid as the explanation for the metabolic alkalosis. Aldosterone and glucocorticoids (other than dexamethasone) stimulate renal loss of acid and potassium, and thereby generate and maintain the alkalosis.

Most cases of clinically significant metabolic alkalosis are maintained by loss of chloride or potassium. Although total body sodium (and hence, volume) derangements are not directly responsible for the generation and maintenance of the metabolic alkalosis, potassium and chloride depletion are commonly seen in settings of volume depletion or excess. Therefore, from a clinical standpoint, it is useful to approach the patient with metabolic alkalosis centering on the history and physical examination, with special attention to the ECF volume status, followed by sequential analysis of blood chemistries.[26] Causes of metabolic alkalosis are shown in Box 57.4. One entity unique to critically ill patients is posthypercapnic metabolic alkalosis. This syndrome is caused by abrupt treatment (usually with tracheal intubation and mechanical ventilation) of a chronic respiratory acidosis. The renal bicarbonate retention that compensated for the chronic respiratory acidosis persists (because of volume depletion) after restoration of a normal $P_{CO_2}$, resulting in the high pH and high plasma bicarbonate characteristic of metabolic alkalosis. The key to the diagnosis is the history and sequential analysis of blood chemistries.[24]

**Box 57.4 Causes of Metabolic Alkalosis**

**Intravascular Volume Depletion, Absolute or "Effective"**

- Gastrointestinal acid loss
  - Vomiting or nasogastric suction
  - Villous adenoma
  - Chloride diarrhea
- Renal acid loss
  - Diuretics (loop, thiazide)
  - Bartter syndrome
  - Gitelman syndrome
  - Magnesium depletion
  - Posthypercapnic state
  - Congestive heart failure
  - Hepatic cirrhosis/ascites

**Intravascular Volume Expansion**

- High renin, high aldosterone
  - Renal artery stenosis
  - Accelerated hypertension
  - Renin-secreting tumor
- Low renin, high aldosterone
  - Primary aldosteronism
- Low renin, low aldosterone
  - Cushing syndrome or disease
  - Exogenous mineralocorticoid
  - Apparent mineralocorticoid excess syndrome
  - Liddle syndrome
- Renal insufficiency
  - Exogenous alkali load
  - Milk-alkali syndrome

Adapted from Palmer BF, Alpern RJ: Metabolic alkalosis. J Am Soc Nephrol 1997;8(9):1462-1469.

### CLINICAL CONSEQUENCES

Alkalemia in critically ill patients is associated with increased mortality rate.[27] Patients with combined metabolic and respiratory alkalosis have a higher mortality rate than those with respiratory alkalosis alone, and mortality rate in alkalemia is roughly proportional to the pH.[27] Although no causal relationship between alkalemia and mortality rate has been established, the pathophysiology of alkalemia is far from benign.[25]

First, metabolic alkalosis suppresses ventilation, causing $CO_2$ retention and relative hypoxemia.[28] Second, alkalemia acutely increases hemoglobin's oxygen affinity (Bohr effect). Third, respiratory alkalosis causes vasoconstriction, particularly in the cerebral circulation.[25] All these processes tend to decrease tissue oxygen delivery.[29] (Note that chronic alkalemia inhibits 2,3-diphosphoglycerate synthesis, allowing normalization of the oxyhemoglobin desaturation curve, mitigating tissue hypoxia to some extent.) These alterations in tissue oxygen delivery could be responsible at least in part for some of the clinical manifestations of metabolic alkalosis.

Because alkalemia causes a decrease in ionized calcium concentration (see discussion under "Calcium Homeostasis"), many of the neuromuscular manifestations of metabolic alkalosis overlap with those of hypocalcemia, including

paresthesias, tetany, and a predisposition to seizures.[1] The acutely diminished tissue oxygen delivery to the brain may contribute to initial confusion and obtundation seen with metabolic alkalosis.

Metabolic alkalosis often is accompanied by hypokalemia and hypomagnesemia. Thus, there is an association between alkalosis and arrythmias,[24] but an independent effect of the alkalosis on cardiac arrythmogenesis has not been established.

Increases in blood lactate concentration may occur in patients with metabolic alkalosis due to upregulation of phosphofructokinase and thus glycolysis, and because of tissue hypoxia (see earlier).[8] With severe metabolic alkalosis (arterial pH above 7.55), the tissue hypoxia may be so marked that compensatory hypoventilation will be overridden by hypoxic drive, resulting in a normal to low arterial $P_{CO_2}$ and elevated blood lactate levels (so-called "lactic alkalosis").[30]

### TREATMENT

Treatment of metabolic alkalosis entails correcting the factor(s) responsible for its maintenance and, if possible, correcting the factor that generated the alkalosis. Once the underlying diagnosis is clear (see Box 57.4), therapy is usually straightforward. If the metabolic alkalosis is maintained by chloride depletion and ECF volume contraction, the intravascular volume should be restored to normal, usually with intravenous isotonic saline.[24,25] Potassium should be given, as KCl, to replace any deficits (see "Disorders of Potassium Homeostasis"), because potassium depletion perpetuates the metabolic alkalosis. If nasogastric suction cannot be stopped, acid loss can be reduced by the use of $H_2$ blockers and proton pump inhibitors.

Treating patients with metabolic alkalosis in the setting of volume overload and diminished effective circulating volume (e.g., congestive heart failure, hepatic cirrhosis) is more challenging, because saline infusion is contraindicated. Unless hyperkalemia is present, chloride should be replenished with KCl supplementation. In rare cases of concurent hyperkalemia, acetazolamide (a carbonic anydrase inhibitor) may be of benefit as it produces a bicarbonate diuresis. Acetazolamide should be avoided in patients with hypokalemia, because the alkaline diuresis will cause renal potassium wasting.[24] Another potential complication of acetazolamide administration, particularly in patients with impending ventilatory failure, is worsening of hypercapnia owing to inhibition of red blood cell carbonic anhydrase and impaired $CO_2$ transport.[25] Hydrochloric acid infusion, as a 0.1 to 0.25 N solution, has been used with success in patients with severe metabolic alkalosis (pH > 7.55 and systemic instability such as encephalopathy or cardiac arrhythmia[24]) refractory to conventional measures.[25,31] Correction of the metabolic disturbances has been reported with infusion of 0.25 N HCl at 100 mL/hour over about 12 hours.[31] Extreme care must be taken to ensure that the infusion catheter is properly positioned within the vena cava, because the solution is highly caustic. Plasma chemistries must be monitored frequently in order to avoid overcorrection. If renal function is severely impaired or medical therapy is not possible, hemodialysis against a low-bicarbonate bath may be used.[24]

In states of primary mineralocorticoid excess, an aldosterone antagonist such as spironolactone should be used until the underlying abnormality can be corrected. Other potassium-sparing diuretics, such as amiloride and triamterene, are useful as well and are essential in managing the rare patient with Liddle syndrome.

## POTASSIUM HOMEOSTASIS

### NORMAL POTASSIUM PHYSIOLOGY

Disorders of potassium (K) homeostasis are common in hospitalized patients and may be associated with severe adverse clinical outcomes, including death.[32,33] Prevention and proper treatment of hyper- and hypokalemia depend on an understanding of the underlying physiology.

The total body potassium content of a 70-kg adult is about 3500 mmol, of which only 2% (about 70 mmol) is extracellular.[34] This uneven distribution reflects the large potassium concentration gradient between the intracellular (Ki ≈140 mmol/L) and the extracellular (Ke ≈ 4.5 mmol/L) space, a gradient that is maintained by the intrinsic ion permeabilities of cell membranes and by $Na^+/K^+$-ATPase, the sodium-potassium pump.[35] The Ke:Ki ratio largely determines the resting membrane potential of cells and thus is crucial for proper function of excitable tissues (muscle and nerve).[35] Small absolute changes in Ke will perturb the ratio significantly. Therefore, disturbances of Ke (measured as changes in plasma potassium concentration, or $P_K$) may have serious, even fatal, consequences mainly in the form of excitable tissue dysfunction.

It is not surprising, therefore, that the extracellular potassium concentration is tightly regulated. In fact, two separate and cooperative systems participate in potassium homeostasis. One system regulates *external potassium balance*: the total body parity of potassium elimination with potassium intake. The other system regulates *internal potassium balance*: the distribution of potassium between the intracellular and extracellular fluid compartments. This latter system provides a short-term defense against changes in the plasma potassium concentration ($P_K$) that might otherwise result from total body potassium losses or gains.

### REGULATION OF INTERNAL POTASSIUM BALANCE

Internal potassium balance serves to protect against changes in Ke; potassium tends to move out of cells during potassium depletion and into cells following potassium intake. This process tends to prevent drastic alterations of Ke:Ki.[36,37] The factors that influence internal potassium balance include hormones, acid-base status, plasma tonicity, exercise, and cell integrity (Box 57.5).

The direction and magnitude of an *acid-base*-related change in $P_K$ depend on the nature and the duration of the disturbance. The most consistent and pronounced relationship between changes in pH and $P_K$ occurs in acute mineral (hyperchloremic) acidosis, where there is a strong inverse relationship between these two variables.[38-40] Interestingly, *hypo*kalemia is seen with prolonged mineral acidosis in patients with normal renal function and reflects increased renal potassium excretion.[39] Unlike mineral acidoses, however, even severe acute organic (high anion gap)

**Box 57.5 Factors Affecting Internal Potassium Balance**

**Factors Causing Cellular Potassium Influx**

Insulin
$\beta_2$-Adrenergic receptor agonist
(Metabolic alkalosis)*

**Factors Causing Cellular Potassium Efflux**

Cell ischemia/lysis
Exercise
Plasma hypertonicity
α-Adrenergic receptor agonist
(Metabolic acidosis)*

*Factors shown in paretheses have a minor or variable effect. See text.

acidoses are not usually associated with hyperkalemia.[41-44] Indeed, organic acidoses, such as lactic acidosis, actually tend to cause cellular potassium uptake.[41] Nonetheless, factors coincident with the acidosis may alter $P_K$. For example, mesenteric ischemia may result in both lactic acidosis (from anaerobic metabolism) and hyperkalemia. Even the hyperkalemia so commonly seen in patients with DKA does not result from the acidemia; rather, it appears to be a consequence of the characteristic insulin deficiency and hyperglycemia (see discussion of hypertonicity in the next paragraph).[44] Respiratory disturbances typically alter $P_K$ less than metabolic disturbances. Alkaloses, respiratory or metabolic, have less effect on $P_K$ than their corresponding acidoses.[38] Bicarbonate administration, which was once thought to reduce the $P_K$ by stimulating cellular potassium uptake,[45] is now known to have very little if any immediate effect on internal potassium balance,[46,47] except perhaps in patients with preexisting severe metabolic acidosis.[41] It is clear, however, that longstanding alkalemia causes urinary potassium losses that may over time result in profound potassium depletion.[48]

*Hypertonicity*, as seen with hypertonic fluid administration[49] or diabetic hyperglycemic states,[50] leads to hyperkalemia, probably as a result of potassium efflux from cells by way of solvent drag. Fatal hyperkalemia has been attributed to this phenomenon in diabetic patients with end-stage renal disease (ESRD).[51]

*Exercise* causes a transient shift of potassium out of cells. Clinically significant hyperkalemia may result from exercise[52,53] (and clinically misleading local venous hyperkalemia results from fist clenching during phlebotomy[54]).

### REGULATION OF EXTERNAL POTASSIUM BALANCE

In contrast to the prodigious capacity of the kidney to excrete potassium,[55] renal potassium conservation is imperfect and explains why significant potassium depletion and hypokalemia may result from dietary potassium deficiency alone.[56]

Normally, 90% to 95% of dietary potassium is eliminated through the kidney, and only about 5% to 10% through the intestine. It is the kidney that is almost entirely responsible for matching potassium output to potassium intake in order to maintain total body potassium constant.[57] The majority of potassium excreted by the kidney derives from potassium secretion in the distal nephron (connecting tubule and collecting duct).[57] Virtually all regulation of potassium excretion takes place at this site in the nephron, under the influence of two principal factors: the rate of flow and sodium delivery through that part of the nephron, and the effect of aldosterone.[57] Potassium secretion is directly proportional to flow rate and sodium delivery through the distal nephron, explaining in part why diuretic use often is accompanied by hypokalemia.

Metabolic acidosis with acidemia results in inhibition of renal potassium secretion.[41] In contrast, metabolic alkalosis and bicarbonate delivery to the distal nephron stimulate kaliuresis by increasing the electrochemical "driving force" for potassium secretion.[57] Other anions that are poorly reabsorbed in the distal nephron (e.g., synthetic penicillins) have a similar effect to stimulate potassium secretion.[58]

It is well established that aldosterone participates in a homeostatic feedback loop with $P_K$ such that increases in $P_K$ stimulate adrenal aldosterone production, which in turn reduces $P_K$ primarily by stimulating renal potassium excretion.[57] Hypokalemia is a prominent feature of primary aldosteronism (Conn syndrome) because the high circulating aldosterone levels are accompanied by volume expansion and thus a high rate of sodium delivery to the distal nephron. When circulating aldosterone levels are high due to volume depletion (secondary aldosteronism), the increase in distal potassium secretion is offset by a decrease in distal nephron flow, thus mitigating renal potassium loss. Indeed, it is only when patients with secondary hyperaldosteronism (e.g., in congestive heart failure or hepatic cirrhosis) are treated with diuretic drugs that distal nephron flow is increased and hypokalemia may ensue.

Magnesium deficiency is associated with renal potassium wasting and may result in severe potassium depletion.[59] Because magnesium, like calcium, acts to stabilize excitable membranes, the deleterious effects of hypokalemia on the myocardium are magnified by concurrent hypomagnesemia (see "Clinical Manifestations" later).[60]

The effect of dexamethasone (a pure glucocorticoid) to enhance renal potassium excretion appears to result entirely from hemodynamic changes that cause an increase in glomerular filtration rate and distal flow rate. All other glucocorticoids tend to further stimulate potassium secretion in proportion to their mineralocorticoid activity.[57]

## DISORDERS OF POTASSIUM HOMEOSTASIS

Disorders of potassium homeostasis may be conveniently divided according to the duration of the disturbance: acute (<48 hours' duration) or chronic. Such a distinction is particularly applicable to the medical intensive care setting where blood chemistries are sampled frequently and a patient's condition and therapy may change radically over a short time. In addition, the approach to treatment varies according to the acuity of the disturbance. The treatment of acute disturbances is largely independent of their cause, whereas the rational treatment of chronic disturbances depends on understanding their pathogenesis.

**Box 57.6 Causes of Acute Hyperkalemia**

**Excessive Potassium Intake**

Oral
Intravenous
Blood transfusion
Cardioplegic solutions

**Transcellular Potassium Shift**

With acute renal failure
  Rhabdomyolysis
  Tumor lysis syndrome
Tissue infarction
  Mesenteric
  Limb
Hypertonicity
  Hyperglycemia
Metabolic acidosis
Drug-induced
  Digitalis intoxication
  Succinylcholine
Hyperkalemic periodic paralysis
Pseudohyperkalemia
  Thrombocytosis
  Leukocytosis
  In vitro hemolysis
  Fist clenching with phlebotomy

## ACUTE HYPERKALEMIA (BOX 57.6)

### Excessive Potassium Intake

Given an acute potassium load, a normal individual will excrete about 50% in the urine and transport about 90% of the remainder into cells over 4 to 6 hours.[61] It is possible to overwhelm this adaptive mechanism such that if too much potassium is taken in too quickly, significant hyperkalemia will result. Such events are almost always iatrogenic (i.e., overly aggressive potassium replacement therapy).[62] One's ability to tolerate a potassium load declines with disordered internal balance (see later) and impaired renal potassium excretory capacity.[63] In such circumstances, an otherwise tolerable increase in potassium intake may cause clinically significant hyperkalemia: Doses of oral potassium supplements as small as 30 to 45 mmol have resulted in severe hyperkalemia in patients with impaired external or internal potassium homeostasis.[64]

KCl, used as a supplement, is the drug most commonly implicated in acute hyperkalemia.[63,65] Banked blood represents a trivial potassium load under most circumstances, because a unit of fresh banked blood, either whole or packed cells, contains only about 7 mmol of potassium.[66] (The potassium concentration in banked blood does increase substantially as the blood ages, however.[67]) Thus, severe hyperkalemia would result only from massive transfusion of compatible blood.[67,68] Infants[69] or patients with renal insufficiency may develop hyperkalemia from an otherwise tolerable transfusion.

Patients undergoing open heart surgery are exposed to cardioplegic solutions containing KCl typically at about 16 mmol/L,[70] which may lead to clinically significant hyperkalemia in the postoperative period, especially in patients with diabetes mellitus with or without renal failure.[71]

### Abnormal Potassium Distribution

Acute hyperkalemia may result from sudden redistribution of intracellular potassium to the extracellular space. If only 2% of intracellular potassium were to leak unopposed from cells, $P_K$ would immediately double. Fortunately, such dramatic circumstances are rarely encountered. Nevertheless, smaller degrees of potassium redistribution commonly result in clinically significant hyperkalemia.

Among the most impressive syndromes associated with acute hyperkalemia are those involving *rapid cell lysis*. The *tumor lysis syndrome* results from treatment of chemosensitive bulky tumors with release of intracellular contents, including potassium, into the ECF.[72] Extreme hyperkalemia even causing sudden death[73] has featured prominently in some series of patients. Most of such patients were in renal failure from acute uric acid nephropathy, thus impairing their ability to excrete the potassium load.[73] *Rhabdomyolysis*, either traumatic or nontraumatic, may result in sudden massive influx of potassium to the extracellular space.[74] Hyperkalemia is present in about 40% of patients upon presentation with rhabdomyolysis[75] and is more common among patients whose course is complicated by oliguric acute renal failure.[76] Rhabdomyolysis is commonly associated with the use of alcohol[75] and cocaine.[77] Extreme hyperkalemia in this latter context has been reported.[78] Statin drugs are frequently associated with rhabdomyolysis,[79] rarely causing extreme hyperkalemia.[80] Other circumstances that may result in redistributive hyperkalemia include severe extensive burns, hemolytic transfusion reactions, and mesenteric ischemia or infarction.

### Pharmacologic Agents

Two drugs may rarely cause acute hyperkalemia by redistribution: digitalis glycosides and succinylcholine. Massive digitalis overdose has been associated with extreme hyperkalemia.[81,82] Succinylcholine depolarizes the motor end plate and in normal individuals causes a trivial amount of potassium leak from muscle, resulting in an increase in $P_K$ by about 0.5 mmol/L.[83] In patients with neuromuscular disorders, muscle damage, or prolonged immobilization, however, muscle depolarization may be more widespread, causing severe hyperkalemia.[84] Prolonged use of nondepolarizing neuromuscular blockers in critically ill patients may predispose to succinylcholine-induced hyperkalemia.[85]

### Hyperkalemic Periodic Paralysis

This rare syndrome of episodic hyperkalemia and paralysis is caused by a mutation of the skeletal muscle sodium channel, inherited in an autosomal dominant pattern.[86] Attacks may be precipitated by exercise, fasting, exposure to cold, and potassium administration, and prevented by frequent carbohydrate snacks. Attacks are usually brief and treatment consists of carbohydrate ingestion. Severe attacks may require intravenous glucose infusions.[87]

### Acute Renal Failure

Hyperkalemia accompanies acute renal failure in 30% to 50% of cases. It is seen most commonly in oliguric renal failure. Contributing factors include tissue destruction (e.g., tumor lysis syndrome, rhabdomyolysis) and increased catabolism.[88]

### Pseudohyperkalemia

Pseudohyperkalemia refers to a measured potassium level that is higher than that circulating in the patient's blood. It has a number of possible causes. First, it may be caused by efflux of potassium out of blood cells in the test tube after phlebotomy. This may be seen in a *serum* specimen in cases of thrombocytosis[89] or leukocytosis,[90] when the clot causes cell lysis in vitro. These days, many clinical laboratories measure electrolytes in plasma (unclotted) specimens. Even under these conditions, extreme leukocytosis may cause pseudohyperkalemia if the specimen is chilled for a long time before the plasma is separated, leading to passive potassium leak from cells.[91] Hemolysis during specimen collection will falsely raise $P_K$ *or* plasma potassium concentration by liberating intraerythrocyte potassium. Second, if the patient's arm is exercised by fist clenching with a tourniquet in place before the specimen is drawn, the sampled blood potassium concentration will rise significantly as a result of local muscle release of intracellular potassium.[54]

## ACUTE HYPOKALEMIA

Hypokalemia that develops over hours is virtually always the result of redistribution of potassium from the extracellular to the intracellular space. The causes of acute hypokalemia are summarized in Box 57.7. Selected causes are discussed as follows.

### Treatment of Diabetic Ketoacidosis

It is well recognized that patients presenting in DKA are always severely depleted in total body potassium as a result of glucose-driven osmotic diuresis, poor nutrition, and vomiting during the development of DKA.[44] Paradoxically, most patients in DKA have a normal $P_K$ upon admission.[92] Insulin deficiency and hyperglycemia appear to account for the preservation of a normal $P_K$ despite severe total body potassium depletion.[44] Once therapy for DKA is instituted, however, $P_K$ typically plummets as potassium is rapidly taken up by cells. Potassium replacement at rates up to 120 mmol per hour have been reported, with total potassium supplementation of 600 to 800 mmol within the first 24 hours of treatment.[93] Hypokalemia in this setting may lead to respiratory arrest.[94]

### Refeeding

A situation analogous to DKA arises during aggressive refeeding after prolonged starvation or with aggressive "hyperalimentation" of chronically ill patients. The glucose-stimulated hyperinsulinemia and tissue anabolism shift potassium into cells, rapidly depleting extracellular potassium.[95] Death in the setting of refeeding has been reported and may be partly due to rapid cellular uptake of other ions (e.g., phosphorus, magnesium).[96]

### Pharmacologic Agents

Specific *$\beta_2$-adrenergic receptor agonists* (e.g., albuterol) may cause electrophysiologically significant hypokalemia, especially when given to patients who are potassium depleted from the use of diuretic drugs.[97] *Epinephrine*, given intravenously in a dose about 5% of that recommended for cardiac resuscitation, causes a fall in $P_K$ by about 1 mmol/L.[98] Such a dose achieves plasma levels of epinephrine comparable to those seen after acute myocardial infarction and may explain the transient hypokalemia following resuscitation from cardiac arrest even without the use of exogenous epinephrine (postresuscitation hypokalemia).[99,100] A rare cause of severe hypokalemia is poisoning with *soluble barium salts* such as chloride, carbonate, hydroxide, and sulfide. Soluble barium salts are used in pesticides and some depilatories, which may be ingested accidentally or intentionally.[101] Thiopentone, a barbiturate used to induce coma for refractory intracranial hypertension, is associated with redistributive hypokalemia in the majority of treated patients within 12 hours of initiating therapy.[102]

### Hypokalemic Periodic Paralysis

Three forms of this rare syndrome have been described: familial, sporadic, and thyrotoxic.[103,104] All have in common attacks of muscle weakness accompanied by acute hypokalemia caused by cellular potassium uptake. Death may occur due to ventilatory failure or cardiac dysrhythmias. The *familial* variety—resulting from a skeletal muscle calcium channelopathy[86]—is inherited in an autosomal dominant pattern, with onset of clinical manifestations typically in the second decade of life. Attacks may occur after carbohydrate or salt ingestion or exercise. Administration of potassium orally or intavenously will abort an acute attack but is ineffective in preventing attacks.[103] The *sporadic* variety of hypokalemic periodic paralysis is identical to the familial form except for the absence of a hereditary pattern. *Thyrotoxic* periodic paralysis was first described in Asians but is now recognized to be nearly ubiquitous.[104] The usual onset of symptoms is in the third decade. Severe hypophosphatemia may accompany the hypokalemia.[105] Treatment of the disorder is the same as treatment of hyperthyroidism.

### Pseudohypokalemia

Severe leukocytosis may cause spuriously low plasma potassium concentrations if blood cells are left in contact with the plasma for a long time at room temperature or higher. This phenomenon results from ongoing cell metabolism in vitro with glucose and potassium uptake.[59] Unexpected hypokalemia and hypoglycemia in

**Box 57.7 Causes of Acute Hypokalemia**

- Treatment of diabetic ketoacidosis
- Refeeding syndrome
- Rapid cell production
  - Vitamin $B_{12}$ treatment of pernicious anemia
  - GM-CSF treatment of leukopenia
- Pharmacologic agents
  - $\beta_2$-Adrenergic receptor agonists
  - Epinephrine
  - Soluble barium salts
- Hypokalemic periodic paralysis
  - Familial
  - Sporadic
  - Thyrotoxic
- Pseudohypokalemia

GM-CSF, granulocyte-macrophage colony-stimulating factor.

the setting of leukocytosis should alert the clinician to this phenomenon.

## CHRONIC HYPERKALEMIA

### Renal Failure

Patients with chronic kidney disease tend to maintain a normal $P_K$ until renal function declines to about 10% of normal.[106] Aldosterone and insulin both appear to play a role in the extrarenal potassium adaptation in chronic kidney disease.[107] This explains why patients with chronic kidney disease who are mineralocorticoid or insulin deficient have a particular predisposition to hyperkalemia.[108]

### Mineralocorticoid Deficiency

Mineralocorticoid deficiency may result from global adrenal insufficiency (*Addison's disease*) or from selective defects in the renin-angiotensin-aldosterone axis (see Chapter 59). Hyperkalemia in the setting of unexplained hypotension should immediately raise one's suspicion for adrenal insufficiency. A common setting for isolated mineralocorticoid deficiency is the syndrome of *hyporeninemic hypoaldosteronism*.[108] This syndrome is most often seen in elderly patients with diabetes mellitus and moderate renal insufficiency. Hyperkalemia is a universal finding. An associated hyperchloremic metabolic acidosis (type IV renal tubular acidosis) is characteristic.[108] In addition to diabetes mellitus, two other systemic diseases are associated with this syndrome: the acquired immunodeficiency syndrome[109,110] and systemic lupus erythematosus.[111]

Aldosterone deficiency may be induced by a variety of pharmacologic agents acting at different sites in the renin-angiotensin-aldosterone axis. *β-Adrenergic receptor blockers* and, to a greater extent, *cyclooxygenase inhibitors* (COX-1 and COX-2) predispose patients to hyperkalemia by suppressing renin release.[112] As a general rule, COX inhibitors should be avoided in patients with renal insufficiency or who are otherwise prone to hyperkalemia either because of diabetes or the use of other implicated drugs. *Converting enzyme inhibitors* and *angiotensin receptor blockers* decrease aldosterone biosynthesis. These drugs are reported to be implicated in 10% to 38% of hyperkalemia in hospitalized patients.[113] Volume depletion and hypotension increase the risk of hyperkalemia with all these agents.

High- and low-dose *heparin* therapy decreases circulating aldosterone levels by selectively inhibiting aldosterone biosynthesis.[114] Hyperkalemia is seen with the use of low-molecular-weight heparins as well, particularly in patients with diabetes mellitus.[115]

### Renal Potassium Secretory Defect

An isolated defect in renal potassium secretion (often with a renal tubular acidosis) is associated with *sickle cell disease* or trait,[116] *systemic lupus erythematosus*,[111] and after *renal transplantation*.[117] In this last circumstance, the hyperkalemia is exacerbated by the use of *cyclosporine* and *tacrolimus* for immunosuppresion.[118,119] A syndrome of hyperkalemic (type IV) distal renal tubular acidosis is seen in patients with *urinary tract obstruction*.[120]

The so-called *potassium-sparing diuretics* (spironolactone, eplerenone, amiloride, and triamterene) impair renal potassium excretion by blocking sodium reabsorption in the distal nephron. Two antibiotics, *pentamidine*[121] and *trimethoprim*,[122,123] cause hyperkalemia, occasionally severe, by blocking sodium reabsorption in the distal nephron.

## CHRONIC HYPOKALEMIA

Chronic hypokalemia is virtually always the result of altered external balance: insufficient potassium intake, excessive potassium losses, or a combination of the two. Losses most often are either GI or renal.

### Inadequate Potassium Intake

Because renal potassium conservation is not perfect, severe dietary potassium restriction will cause hypokalemia in 3 to 7 days in normal humans.[56] In one series of hypokalemic hospitalized patients, inadequate potassium supplementation during intravenous therapy contributed to the development of severe hypokalemia in 45% of cases and was the sole cause in 6%.[124] Other disorders associated with nutritional hypokalemia include anorexia nervosa, alcoholism, and malignancy.

### Excessive Potassium Losses

Hypokalemia may develop as a result of both upper and lower GI fluid losses, but the pathogenesis is quite different in the two situations. With *diarrhea*, the potassium is lost from the gut.[125] *Gastric fluid losses* (e.g., vomiting or gastric suction) are associated with hypokalemia. Paradoxically, however, most of the potassium losses are renal, not gastric. Gastric fluid potassium concentration is only 5 to 10 mmol/L. Thus, only massive gastric fluid losses would, alone, significantly deplete total body potassium stores. The gastric fluid losses, however, stimulate renal potassium secretion in several ways. First, by generating a metabolic alkalosis and increasing bicarbonate delivery to the distal nephron, potassium secretion is stimulated. The metabolic alkalosis also leads to cellular proton loss and potassium uptake that, in renal epithelial cells, enhances potassium secretion. Finally, the volume contraction that usually accompanies GI fluid losses causes secondary aldosteronism, which further augments urinary potassium losses. Thus, in this situation, urinary potassium concentration is typically high while urinary chloride concentration is low due to volume contraction. (Urinary sodium losses may be high because of natriuresis obligated by the bicarbonaturia.)

All *diuretics* work by inhibiting sodium and chloride reabsorption by the nephron. Those drugs that act proximal to the potassium secretory site in the nephron promote a kaliuresis by increasing delivery of fluid distally and causing secondary aldosteronism. Thus, hypokalemia frequently accompanies the use of the two most common classes of diuretics: thiazides and loop diuretics.[126] Carbonic anhydrase inhibitors exert an additional kaliuretic effect by shunting bicarbonate-rich, chloride-poor fluid to the distal nephron.[127] Combining two potassium-wasting diuretics for added diuretic effect (e.g., furosemide plus metolazone) can result in severe hypokalemia. In such cases, $P_K$ has been found to fall below 3.5 mmol/L in over 80% of patients and below 3.0 mmol/L in more than half.[126]

Various antibiotic agents may cause renal potassium wasting and thereby hypokalemia; 90% of patients receiving *amphotericin B* require potassium supplementation.[128] *Penicillin* antibiotics, particularly polyanionic derivatives such as

carbenicillin and ticarcillin, have been associated with hypokalemia.[129]

*Mineralocorticoids* predispose to hypokalemia by stimulating renal potassium excretion. Mineralocorticoid excess may be *primary*[130] (Conn syndrome) or *secondary* to diminished real or "effective" circulating volume. All glucocorticoid drugs except dexamethasone possess some mineralocorticoid activity. Therefore, prolonged administration of these agents can cause severe hypokalemia. In edematous patients with secondary aldosteronism (e.g., congestive heart failure, hepatic cirrhosis) hypokalemia commonly ensues only when diuretic therapy enhances distal nephron flow rate.

*Magnesium deficiency* is associated with renal potassium wasting and may result in severe potassium depletion (see later). Because magnesium, like calcium, acts to stabilize excitable membranes, the deleterious effects of hypokalemia on the myocardium are magnified by concurrent hypomagnesemia.[131] The intensive care setting is fraught with potential causes of hypomagnesemia (see discussion under "Magnesium Homeostasis").

*Hypercalcemia* causes a salt and water diuresis and is therefore commonly associated with renal hypokalemia (see "Calcium Homeostasis").[132] In one series, one third of hypercalcemic patients were hypokalemic with no other predisposing factors; the prevalence was 52% in patients with hypercalcemia of malignancy. $P_K$ was inversely proportional to the plasma calcium concentration.[133]

Several inborn tubular transport abnormalities are associated with chronic hypokalemia (and metabolic alkalosis). *Bartter* and *Gitelman* syndromes are associated with volume contraction and normal blood pressure, and *Liddle* syndrome with hypertension.[134]

## CLINICAL MANIFESTATIONS OF POTASSIUM IMBALANCE

Alterations in $P_K$ have a variety of adverse clinical consequences, the expression of which may be magnified in the critically ill patient. The most serious of these manifestations are those involving excitable tissues.

### CLINICAL MANIFESTATIONS OF HYPERKALEMIA

#### Cardiac Effects

Hyperkalemia depolarizes the cell membrane, slows ventricular conduction, and decreases the duration of the action potential. These changes produce the classic electrocardiogram (ECG) manifestations of hyperkalemia including (in order of their usual appearance) peaked T waves, prolongation of the PR interval, widening of the QRS complex, loss of the P wave, "sine wave" configuration or ventricular fibrillation, and asystole.[135,136] These ECG changes may be modified by a multitude of factors such as ECF, pH, calcium concentration, sodium concentration, and the rate of rise of $P_K$.[135]

ECG changes may not accompany changes in $P_K$. If present, these ECG changes certainly suggest hyperkalemia. However, in the absence of the classic ECG changes, the clinician should not be lulled into a false sense of security when evaluating a hyperkalemic patient. Normal ECGs occur despite extreme hyperkalemia,[137] and the first cardiac manifestation of hyperkalemia may be ventricular fibrillation.[138] Consequently, $P_K$ greater than 6.5 mmol/L, even with a normal ECG, should be treated as an emergency (see "Treatment of Potassium Imbalance").

#### Neuromuscular Effects

Hyperkalemia may result in paresthesias and weakness progressing to a flaccid paralysis, which typically spares the diaphragm. Reflexes are depressed or absent. Cranial nerves are rarely involved and sensory changes are minimal.[139]

#### Metabolic Effects

Hyperkalemia decreases renal ammoniagenesis, which by itself may produce a mild hyperchloremic metabolic acidosis[140] and will limit the kidney's ability to excrete an acid load and thus prevent correction of a metabolic acidosis.[141]

### CLINICAL MANIFESTATIONS OF HYPOKALEMIA

Although less immediately life threatening than hyperkalemia, hypokalemia has many detrimental effects in critically ill patients. Along with cardiac and neuromuscular manifestations are many more subtle effects.

#### Cardiac Effects

Hypokalemia hyperpolarizes the cell membrane and prolongs the cardiac action potential.[142] These changes are associated with the following ECG manifestations: ST-segment depression, a decrease in T-wave amplitude, and an increase in U-wave amplitude.[135,136] However, because all of these changes are nonspecific, the ECG is an even less reliable index of hypokalemia than it is of hyperkalemia.

Hypokalemia may be associated with an increased incidence of arrhythmias and conduction defects. It is well established that potassium depletion increases the cardiac toxicity of digitalis glycosides.[143] However, controversy exists as to whether hypokalemia per se induces ventricular arrhythmias in patients not taking digitalis. There is an increase in benign ventricular ectopy in hypokalemic patients without acute myocardial ischemia.[144] The clinical importance of this observation is unclear. In individuals hospitalized with acute myocardial infarction, however, a correlation between hypokalemia and ventricular tachycardia and fibrillation was observed.[145] Because potassium repletion did not reduce the occurrence of these arrhythmias, it is unlikely that hypokalemia was the sole arrhythmogenic factor.[145] A recent study of patients presenting with acute myocardial infarction showed a U-shaped relationship between mean in-hospital $P_K$ and mortality rate, such that $P_K$ less than 3.5 mmol/L or greater than 4.5 mmol/L were each associated with higher in-hospital mortality rates. The lowest mortality rate was seen in patients with $P_K$ 3.5 to 4.0 mmol/L, implying that potassium supplementation to achieve higher concentrations was not justifiable.[146]

#### Neuromuscular Effects

Modest hypokalemia generally presents as weakness, myalgias, muscle fatigue, and "restless" legs. With more severe hypokalemia (less than 2 mmol/L), paralysis may supervene. This usually involves the extremities but may progress to include the trunk and muscles of ventilation. As with hyperkalemia, cranial nerves typically are spared and sensory function usually remains intact.[59] It is important to note that

these manifestations may be masked by concomitant hypocalcemia and may only appear when calcium is replenished. Conversely, in patients with hypokalemia and hypocalcemia, tetany may develop only after potassium replacement.[59] Smooth muscle dysfunction (ileus, gastroparesis) is more commonly seen with hypokalemia than with hyperkalemia.

In addition to the effects of potassium depletion on the electrical properties of the neuromuscular system, profound hypokalemia may result in muscle injury and frank rhabdomyolysis, even in bed-bound patients.[147]

#### Miscellaneous Effects

Hypokalemia and potassium depletion are associated with glucose intolerance,[148] increased protein catabolism, polydipsia and polyuria,[59] and metabolic alkalosis.[149]

## EVALUATION OF DISORDERS OF POTASSIUM HOMEOSTASIS

The diagnostic approach to disorders of potassium homeostasis may be focused by dividing them according to their duration: acute (or of unknown duration) versus chronic.

### EVALUATION OF ACUTE HYPERKALEMIA

When $P_K$ rises abruptly or if $P_K$ is high (greater than 6.5 mmol/L) on initial presentation of the patient, the first step is to obtain an ECG to look for electrophysiologic evidence of hyperkalemia. In the presence of such signs, treatment for hyperkalemia should begin urgently (see "Treatment of Potassium Imbalance"). At the same time, an unclotted blood sample should be obtained, using meticulous phlebotomy technique, for another set of electrolytes, glucose, blood urea nitrogen (BUN) and creatinine, and complete blood count (CBC). Urine should be tested for heme pigments to exclude acute rhabdomyolysis or hemolysis. The patient's list of medications and diet should be reviewed promptly, looking for exogenous sources of potassium and drugs that may impair potassium tolerance (see Box 57.6).

### EVALUATION OF CHRONIC HYPERKALEMIA

Figure 57.2 outlines an approach to the patient with hyperkalemia lasting for days. Failure to stimulate cortisol release with a cosyntropin stimulation test (see Chapter 59) supports a diagnosis of Addison's disease. Absent that diagnosis, the patient is likely to have either selective aldosterone deficiency or tubular unresponsiveness to aldosterone. Assessment of the renin-angiotensin-aldosterone axis is most simply done by measuring plasma renin activity (PRA) and aldosterone levels in the basal and diuretic/posture-stimulated state.[108] Tubular unresponsiveness to aldosterone is assessed by measuring the potassium secretory effect of 9a-fludrocortisone (9a-F, Florinef). One index of the driving force for potassium secretion that may be useful in this regard is the transtubular potassium gradient (TTKG), calculated as follows:

$$\text{TTKG} = \frac{U_K}{P_K} \times \frac{P_{osm}}{U_{osm}}$$

where $P_{osm}$ and $U_{osm}$ are plasma and urine osmolalities, respectively.[150] A spot urine potassium : creatinine ratio may be used instead of the TTKG.

### EVALUATION OF ACUTE HYPOKALEMIA

Hypokalemia accompanied by serious cardiac or neuromuscular manifestations is an emergency. Likewise, urgent therapy is indicated for profound hypokalemia ($P_K$ less than 2.0 mmol/L) even in the absence of clinical complications. In addition, moderate hypokalemia ($P_K$ less than 3.0 mmol/L) in patients taking digitalis,[143] and perhaps with acute myocardial ischemia,[145] should be treated urgently because of the risk of ventricular arrhythmias. In all these situations, it is imperative that the blood specimen be

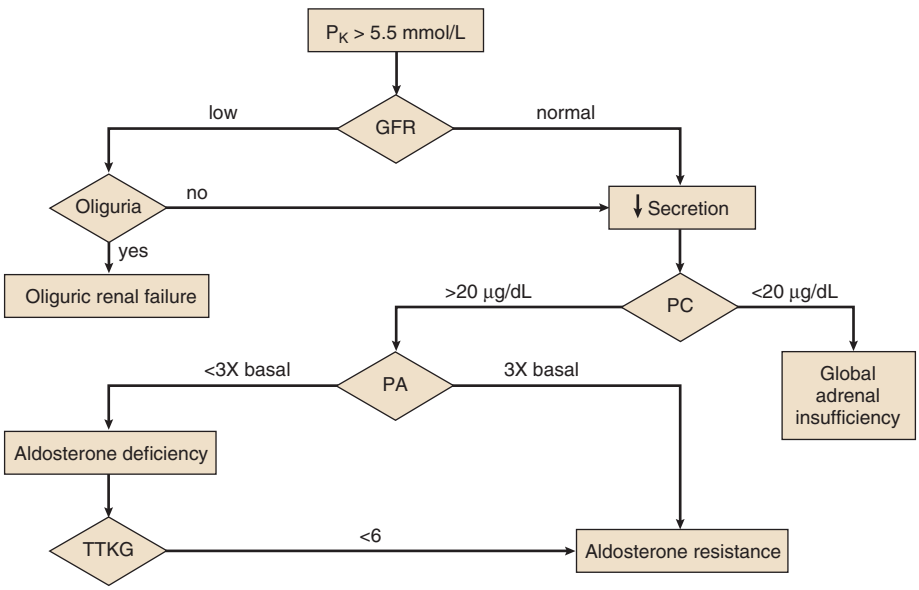


**Figure 57.2** Diagnostic evaluation of chronic hyperkalemia. GFR, glomerular filtration rate; PA, stimulated plasma aldosterone (see text); PC, stimulated plasma cortisol (see Chapter 59); TTKG, transtubular potassium gradient (see text).

obtained and handled properly, especially in patients with leukocytosis, because rapid administration of potassium to a patient with pseudohypokalemia may cause severe hyperkalemia.

The remainder of the evaluation of acute hypokalemia derives mainly from the patient's history, with an emphasis on treatments causing cellular potassium uptake (e.g., insulin, β-adrenergic agonists) or a rapid increase in tissue anabolism, and a history of periodic paralysis. Patients who are hypokalemic upon presentation should be evaluated as though their hypokalemia were acute.

### EVALUATION OF CHRONIC HYPOKALEMIA

Once acute hypokalemia and transient potassium redistribution have been excluded, one should next determine whether the kidney is responding appropriately to the potassium deficit or whether it is contributing to the problem. This is best done by measuring the 24-hour urinary excretion of potassium during potassium repletion (Fig. 57.3). Potassium excretion less than 20 mmol per day suggests appropriate renal potassium conservation and points to extrarenal (lower GI or skin) potassium losses, recovery from diuretic-induced hypokalemia, or chronically potassium-deficient diet. Excretion of greater than 20 mmol per day is evidence of inadequate renal potassium conservation indicating a renal cause of the hypokalemia. Renal potassium losses associated with normal systemic blood pressure are most commonly seen with the use of thiazide or loop diuretics and are accompanied by a metabolic alkalosis. Other causes of hypokalemia with metabolic alkalosis in a normotensive patient include gastric fluid loss and Bartter and Gitelman syndromes. These are separable most often by history, but if not, the urinary chloride measurement will be helpful, being low with gastric fluid losses. Renal hypokalemia may accompany a renal tubular acidosis, in which case the plasma bicarbonate will be low.

Mineralocorticoid excess may be the cause if the renal potassium loss is associated with systemic hypertension, and the renin-aldosterone axis should be studied with basal and saline-suppressed blood hormone measurements. High PRA and aldosterone levels suggest renal artery stenosis, malignant hypertension, or rarely a renin-secreting tumor. Low PRA and high aldosterone levels indicate primary aldosteronism. When both PRA and aldosterone levels are low, one should suspect the syndrome of apparent mineralocorticoid excess, Cushing syndrome, or rarely Liddle syndrome. Note that Cushing syndrome due to ectopic adrenocorticotropic hormone (ACTH) secretion often is not accompanied by typical cushingoid features.[151]

## TREATMENT OF POTASSIUM IMBALANCE

In general, the initial treatment of acute severe potassium imbalance is independent of the cause of the disturbance, whereas the rational therapy for chronic hyper- or hypokalemia depends on an understanding of its pathogenesis.

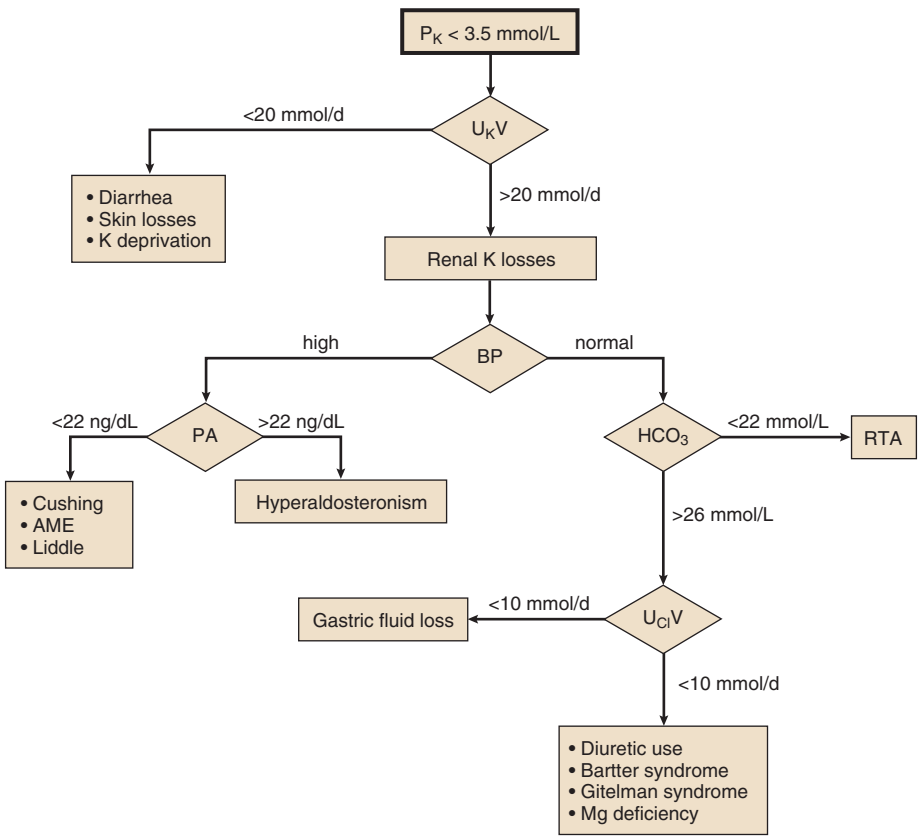


**Figure 57.3** Diagnostic evaluation of chronic hypokalemia. AME, syndrome of apparent mineralocorticoid excess; BP, blood pressure; PA, stimulated plasma aldosterone (see text); RTA, renal tubular acidosis; $U_{Cl}V$, urinary chloride excretion; $U_KV$, urinary potassium excretion.

## TREATMENT OF ACUTE HYPERKALEMIA

In considering when hyperkalemia constitutes an emergency, two points should be kept in mind. First, the electrophysiologic effects of hyperkalemia are directly proportional to both the absolute $P_K$ and its rate of rise.[135] Second, although the ECG manifestations of hyperkalemia are generally progressive and proportional to the $P_K$, ventricular fibrillation may be the first ECG disturbance of hyperkalemia;[138] conversely, a normal ECG may be seen with extreme hyperkalemia.[137] Thus, it is apparent that neither the ECG nor the $P_K$ alone is an adequate index of the urgency of hyperkalemia, and that the clinical context must be considered when assessing a hyperkalemic patient. Because most patients manifest hyperkalemic ECG changes at $P_K$ greater than 6.7 mmol/L,[136] hyperkalemia should be treated emergently for (1) $P_K$ greater than 6.5 mmol/L and (2) ECG manifestations of hyperkalemia regardless of the $P_K$.[152]

Therapy of acute or severe hyperkalemia is directed at preventing or ameliorating its untoward electrophysiologic effects on the myocardium. The goals of therapy, in chronologic order, are as follows (Table 57.2):

1. Antagonize the effect of potassium on excitable cell membranes.
2. Redistribute extracellular potassium into cells.
3. Enhance elimination of potassium from the body.

### Membrane Antagonism

**Calcium.** Calcium directly antagonizes the myocardial effects of hyperkalemia without lowering $P_K$.[153] During treatment with calcium, the ECG should be monitored continuously. The dose may be repeated in 5 minutes if there is no improvement in the ECG, or if the ECG deteriorates after an initial improvement.[152] There are several case reports of sudden death in patients given intravenous calcium while also receiving digitalis glycosides.[154] Although these observations do not provide clear guidance, it may be wise to administer intravenous calcium with caution to patients known or strongly suspected of having toxic levels of digitalis glycosides.

**Hypertonic Saline.** Intravenous hypertonic sodium chloride has been shown to reverse the ECG changes of hyperkalemia in patients with concurrent hyponatremia.[155] Whether hypertonic saline is effective in the treatment of eunatremic patients has not been established. Moreover, the extracellular volume load imposed by hypertonic saline argues against its use.

### Redistribution of Potassium into Cells

**Insulin.** Insulin reliably lowers $P_K$ in a dose-dependent manner. An intravenous dose of 10 units of regular insulin given as a bolus along with an intravenous bolus of dextrose (25-40 g as a 50% solution) to adult patients lowers the $P_K$ by about 1 mmol/L.[156,157] After the initial bolus, a dextrose infusion should be started, because a single bolus of 25 g of dextrose has been shown to be inadequate to prevent hypoglycemia at 60 minutes.[156] There seems to be no advantage of a continuous insulin infusion over a bolus injection.[40] Insulin should be used without dextrose in hyperglycemic patients; indeed, the cause of the hyperkalemia in those patients may be the hyperglycemia itself.[50]

**Albuterol.** $P_K$ has been shown to decline by 0.6 mmol/L after inhalation of 10 mg of albuterol, and by about 1.0 mmol/L after 20 mg in patients with ESRD.[158] The effect of insulin is additive with that of albuterol, with the

**Table 57.2 Emergency Treatment of Hyperkalemia**

| Agent/Intervention | Dose | Onset | Duration | Complications |
|---|---|---|---|---|
| **Membrane Stabilization** | | | | |
| Calcium gluconate (10%) | 10 mL IV over 10 min | Immediate | 30-60 min | Hypercalcemia |
| Hypertonic (3%) sodium chloride | 50 mL IV push | Immediate | Unknown | Volume overload<br>Hypertonicity |
| **Redistribution** | | | | |
| Insulin (short-acting) | 10 units IV push, with 25-40 g dextrose (50% sol'n) | 20 min | 4-6 h | Hypoglycemia |
| Albuterol | 20 mg in 4 mL normal saline solution, nebulized over 10 min | 30 min | 2 h | Tachycardia<br>Inconsistent response |
| **Elimination** | | | | |
| Loop diuretics | | | | |
| Furosemide | 40-80 mg IV | 15 min | 2-3 h | Volume depletion |
| Bumetanide | 2-4 mg IV | | | |
| Sodium bicarbonate | 150 mmol/L IV at variable rate | Hours | Duration of infusion | Metabolic alkalosis<br>Volume overload |
| Sodium polystyrene sulfonate (SPS) (Kayexalate, Kionex) | 15-30 g in 15-30 mL 70% sorbitol PO | >2 h | 4-6 h | Variable effect<br>Intestinal necrosis |
| Hemodialysis | | Immediate | 3 h | Arrhythmias |

combination reported to result in a decline in $P_K$ by about 1.2 mmol/L at 60 minutes.[156] Even among patients not taking beta blockers, as many as 40% appear to be resistant to the hypokalemic effect of albuterol.[156,158] For that reason, albuterol should never be used alone for the treatment of urgent hyperkalemia.

**Bicarbonate.** The putative benefits of a bolus injection of sodium bicarbonate in the emergency treatment of hyperkalemia pervaded the literature until the past decade. Ironically, this dogma was based on studies using a prolonged (4-6 hours) infusion of bicarbonate.[45] It has now been clearly demonstrated that short-term bicarbonate infusion does not reduce $P_K$ in patients with dialysis-dependent kidney failure, implying that it does not cause potassium shift into cells.[46,47,159]

### Elimination of Potassium from the Body

**Enhanced Renal Elimination.** Hyperkalemia occurs most often in patients with renal insufficiency. However, renal potassium excretion may be enhanced even in patients with moderate renal failure by increasing distal nephron flow. This may be accomplished with *saline* or *sodium bicarbonate infusions* and may be enhanced further by the use of *loop diuretics*. Diuretic-induced volume contraction must be avoided because this will lead to decreased distal nephron flow and reduced potassium excretion.[152]

**Exchange Resin.** Sodium polystyrene sulfonate (SPS, Kayexalate, Kionex) is a cation exchange resin that exhanges sodium for secreted potassium in the colon. Each gram of resin binds approximately 0.65 mmol of potassium in vivo, although the effect is highly variable and unpredictable.[40] The resin causes constipation and hence almost always is given with a cathartic. It is more effective when given orally than by retention enema.[40]

There are two concerns with the use of SPS for the treatment of urgent hyperkalemia. The first is its slow effect. When given orally, the onset of action is at least 2 hours and the maximum effect may not be seen for 6 hours or more. One recent study in hemodialysis patients failed to show any effect on $P_K$ after an oral dose of SPS.[160] The second concern with SPS is its possible toxicity. There are numerous case reports of patients who developed intestinal necrosis after exposure to SPS in sorbitol as an enema[161-163] and orally.[164] A retrospective study estimated the incidence of colonic necrosis to be 1.8% among postoperative patients.[164] For these reasons, some authorities consider the use of SPS to be unjustifiable.[165]

**Dialysis.** *Hemodialysis* is the dialytic method of choice for removal of potassium from the body. $P_K$ falls by over 1 mmol/L in the first 60 minutes of hemodialysis and a total of 2 mmol/L by 180 minutes, after which it reaches a plateau.[40] Rebound always occurs after dialysis, with 35% of the reduction abolished after an hour and nearly 70% after 6 hours.[40] There is controversy as to whether dialysis for severe hyperkalemia precipitates serious ventricular arrhythmias. Because of the possibility, patients dialyzed for severe hyperkalemia should have continuous ECG monitoring.[40] The rate of potassium removal with *peritoneal dialysis* is much slower than with hemodialysis.[40]

## TREATMENT OF CHRONIC HYPERKALEMIA

As established previously, chronic hyperkalemia always implies deficient renal potassium excretion. It follows that the therapy of chronic hyperkalemia is primarily directed toward stimulating renal potassium excretion while limiting potassium intake. For all adults with chronic hyperkalemia, daily potassium intake should be restricted to 60 mmol. All drugs known to impair either internal or external potassium balance should be eliminated if possible. Finally, all patients with chronic hyperkalemia should be evaluated for occult urinary tract obstruction.

Further therapy of the persistently hyperkalemic patient should be guided by the diagnostic evaluation outlined in Figure 57.2. In cases of mineralocorticoid unresponsiveness or when mineralocorticoid treatment is complicated by fluid overload, a *thiazide* or *loop diuretic* can be added to the regimen. This will restore normal volume status and enhance renal tubular potassium secretion in many mineralocorticoid-resistant patients. It is crucial to avoid diuretic-induced volume depletion, however, because this will exacerbate the renal potassium secretory defect.

Patients who fail to respond to the previously mentioned measures with an increase in TTKG or urine potassium : creatinine ratio and a decrease in $P_K$ may be given sodium bicarbonate, which will stimulate renal potassium secretion. This is especially appropriate for patients whose chronic hyperkalemia is accompanied by a renal tubular acidosis (type IV RTA). The usual dose is 1 to 2 mmol bicarbonate per kg body weight per day in three or four divided doses.[152]

## TREATMENT OF ACUTE HYPOKALEMIA

A low $P_K$ almost always indicates a large total body potassium deficit. In fact, $P_K$ decreases by approximately 0.3 mmol/L for each decrement of 100 mmol total body potassium.[166] But if potassium is replenished too quickly, the homeostatic mechanisms that defend $P_K$ will be overwhelmed and $P_K$ will rise abruptly. The rate of rise of $P_K$ with potassium administration can be greatly altered by factors that affect internal potassium balance. For example, during treatment of DKA with insulin, cellular uptake of potassium may be massive, obligating enormous replacement doses of potassium. Conversely, insulin deficiency markedly impairs tolerance to a potassium load.[61]

See "Evaluation of Acute Hypokalemia" for definitions of urgent hypokalemia. Limited information exists on which to base a rational prescription of KCl in an emergency.[61,167,168]

Based on the available literature, we can estimate that nondiabetic patients with normal renal function should respond well to a 1- to 2-hour infusion of KCl at 0.6 mmol/kg/hour given intravenously in saline. In patients with renal failure of any degree, the infusion rate should be halved (0.3 mmol/kg/hour). Patients with diabetes mellitus not being treated for DKA or hyperglycemia should receive no more than 0.2 mmol/kg/hour, or about 0.1 mmol/kg/hour in the setting of renal failure. For severe hypokalemia, the ECG should be monitored continuously and the infusion stopped immediately if signs of hyperkalemia develop. The maximum increase in $P_K$ is seen at the end of the infusion, and about 50% of the increase is lost over the next 2 to 3 hours when a new steady state is achieved. Thus, $P_K$

should be measured at the end of the infusion. If the patient is still dangerously hypokalemic at this point, additional potassium may be given. If at the end of the infusion $P_K$ is in an acceptable range, the measurement should be repeated 2 to 3 hours later when disposal of potassium load is complete in order to determine the need for further treatment.[152]

Hypokalemia in the setting of aggressive "refeeding," and especially in the treatment of severe DKA, should be treated initially as described earlier. Frequent monitoring of $P_K$ with rapid laboratory turnaround time is critical for proper management.

Hypokalemia that is not life threatening is best treated with oral potassium replacement. It is important to recognize that GI absorption of an oral dose of KCl elixir is essentially complete. Dangerous hyperkalemia can occur in entirely normal individuals following KCl ingestion.[169] The maximum increase in $P_K$ is seen 1.5 to 2 hours after an oral potassium load. Thus, a sensible oral dose of KCl in moderate hypokalemia should probably not exceed the hourly intravenous doses proposed earlier. There is no reason to give a simultaneous oral and intravenous potassium dose; serious hyperkalemia may ensue.

### TREATMENT OF CHRONIC HYPOKALEMIA

The treatment of chronic hypokalemia depends entirely on identifying and, if possible, remediating the cause (see Fig. 57.3). When the cause of the excessive potassium loss cannot be treated specifically, maintenance potassium supplementation is needed.

## WATER HOMEOSTASIS

Hyponatremia and hypernatremia reflect disorders of water homeostasis. They are common disorders in critically ill patients and are associated with increased morbidity and mortality rates.[170,171]

### PHYSIOLOGY OF WATER HOMEOSTASIS

Normal plasma sodium concentration varies very little, even less than the "normal" range of clinical laboratories (135-145 mmol/L). This tight regulation depends on the following elements: (1) pituitary secretion of arginine vasopressin (AVP; also known as antidiuretic hormone, or ADH) that varies over a wide range in response to physiologic stimuli; (2) kidneys that are capable of responding to circulating vasopressin by varying the urine concentration; (3) intact thirst; and (4) access to water.

*Tonicity* or *effective osmolality* describes the capacity of particles in solution to effect water movement across a semipermeable membrane such as the cell membrane. The normal response to water ingestion (of sufficient magnitude to lower the plasma osmolality even slightly) is the excretion of maximally dilute urine (urine osmolality <100 mOsm/kg). The underlying physiologic sequence is as follows: The plasma *hypotonicity* is sensed by the cells making up the hypothalamic osmostat. These hypothalamic nuclei then proportionately reduce their synthesis of AVP, also known as ADH, leading to diminished AVP release into the circulation by the posterior pituitary. The lower circulating AVP concentration, in turn, results in the insertion of proportionately fewer water channels into the collecting duct of the kidney. This, in turn, creates a more water-impermeable conduit, preventing water reabsorption and allowing excretion of the dilute urine elaborated by the more proximal segments of the nephron.[172]

Conversely, plasma hypertonicity leads to higher circulating AVP concentration and proportionately higher water permeability of the collecting duct, and the excretion of a concentrated urine.[172]

Figure 57.4 shows the relationship between plasma osmolality, plasma AVP concentration, and urine osmolality. The normal "set point" is a plasma osmolality of about 285 mOsm/kg. Notice that the minimum urine osmolality is about 50 mOsm/kg, and the maximum is about 1200 mOsm/kg.[173]

When plasma osmolality rises beyond 290 to 295 mOsm/kg, the *thirst* center of the hypothalamus is stimulated. At that point, neurologically intact individuals with access to water will drink until the plasma osmolality returns to normal.[173]

### NONOSMOTIC VASOPRESSIN RELEASE

It is important to recognize that plasma osmolality is not the only determinant of AVP synthesis and release. Low arterial blood pressure and low effective arterial volume powerfully stimulate AVP release.[173] This baroreceptor-mediated AVP release is teleologic, because water retention is an important component in the defense against hypovolemia. So primal is this circulatory defense that the baroreceptor stimulation predominates over any osmolal effect on AVP release.[173] Thus, a volume-contracted or hypotensive individual will have high circulating AVP levels even if his plasma osmolality is low. In addition, circulating AVP levels rise with pain, stress, nausea, hypoxia, hypercapnia, and a variety of medications, most notably epinephrine and high doses of narcotic analgesics.[173]

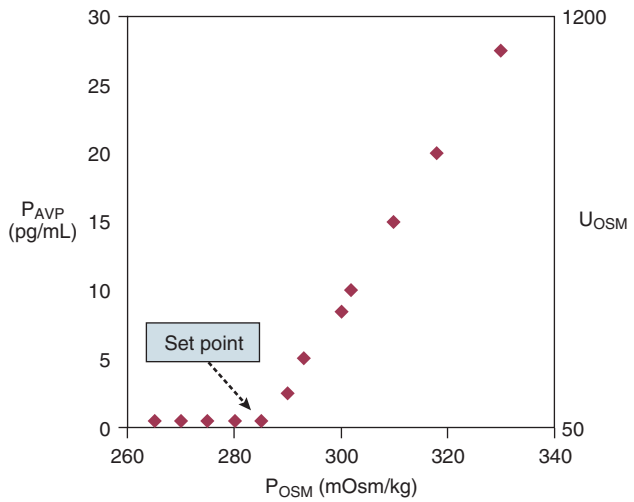


**Figure 57.4** Typical example of the relationship between plasma osmolality ($P_{osm}$), plasma vasopressin concentration ($P_{AVP}$), and urine osmolality ($U_{osm}$). $P_{AVP}$ and $U_{osm}$ vary around the *set point* to maintain $P_{osm}$ within the range of normal.

## HYPONATREMIA

### EPIDEMOLOGY AND CLINICAL MANIFESTATIONS

Hyponatremia (plasma sodium concentration < 135 mmol/L) is one of the most common electrolyte disorders, found in approximately 3% of hospitalized patients and as many as 30% of patients in ICUs.[170]

The clinical manifestations of hyponatremia are largely attributed to intracellular volume expansion (cellular edema), which occurs only when hyponatremia is associated with hypotonicity. Intracellular volume expansion is of greatest consequence in the brain, where it is translated into increased intracranial pressure because of the rigid calvarium.[174]

### PATHOPHYSIOLOGY

The pathophysiology of hypotonic hyponatremia has important implications for its management. Most cells—especially brain cells—have adaptive mechanisms for mitigating tonicity-related volume changes.[174] Cell volume peaks 1 to 2 hours after the onset of acute hypotonicity. Thereafter, solute and water are lost from cells, and cell volume returns toward normal. After several days of sustained hypotonicity, cell volume is restored nearly to normal.[174]

The morbidity and mortality risks associated with hypotonic hyponatremia are influenced by several factors, including the magnitude and rate of development of the hyponatremia, the patient's age and gender, and the nature and severity of any underlying diseases.[174] The very young and very old, women, and alcoholics appear to be at particular risk.[175] Cell-volume adaptation to hypotonicity may be deficient in premenopausal women, who suffer more frequent and more severe neurologic consequences than men with equivalent degrees of hypotonicity.[176]

Neurologic symptoms usually do not occur until the plasma sodium concentration falls below 125 mmol/L, at which point the patient may complain of anorexia, nausea, and malaise. Between 120 and 110 mmol/L, headache, lethargy, confusion, agitation, and obtundation may be seen. More severe symptoms (seizures, coma) may occur with levels below 110 mmol/L.[177] Focal neurologic findings are unusual but do occur, and transtentorial cerebral herniation has been described in severe cases, especially in young women following surgery.[176] In that setting, hypoxemia is common and often is associated with noncardiogenic pulmonary edema.[178] Hypoxia appears to exacerbate the cerebral damage in hyponatremia.[179]

Although symptoms generally resolve with correction of the hypotonicity, permanent neurologic deficits may occur, particularly in acute severe hypotonicity, when the brain's volume-regulatory defenses may be overwhelmed.[176] Profound hypotonicity that develops in less than 24 hours may be associated with residual neurologic deficits and has a 50% mortality rate in some populations.[176] In contrast, when hypotonicity develops more gradually, symptoms are both less common and less severe. Indeed, patients with chronic hyponatremia, even in the range of 115 to 120 mmol/L, may be completely asymptomatic.[174]

### DIFFERENTIAL DIAGNOSIS

Hyponatremia may coexist with a normal, high, or low plasma osmolality. Thus, the diagnostic algorithm for hyponatremia (see Fig. 57.2) begins with an assessment of the plasma osmolality ($P_{osm}$). This may be estimated by the following formula:

$$\text{estimated } P_{osm} = (2 \times P_{Na}) + \frac{P_{gluc}}{18} + \frac{BUN}{2.8}$$

where $P_{gluc}$ is the plasma glucose concentration and BUN is blood urea nitrogen concentration, both in mg/dL. If there is a suspicion that an unmeasured, osmotically effective solute may be implicated (e.g., mannitol or glycerol), the $P_{osm}$ should be measured directly.

Isotonic hyponatremia (also known as *factitious hyponatremia* or *pseudohyponatremia*) is a laboratory artifact seen with analytic techniques that measure the mass of sodium per unit volume of plasma sampled.[180] It is seen in the presence of marked hypertriglyceridemia or paraproteinemia, when the measurement method involves a predilution step. Direct potentiometry (which uses an ion-selective electrode in undiluted plasma) avoids this problem.[180]

*Hypertonic hyponatremia* results from the presence in ECF of abnormal amounts of osmotically effective solutes other than sodium (e.g., glucose, mannitol, or glycerol). The osmotic pressure exerted by the nonsodium solute leads to redistribution of water from the intracellular to the ECF compartment, resulting in cellular dehydration and hyponatremia. The hyponatremia is real (not *pseudo-*), but it is accompanied by *hyper*tonicity and a *decrease* in cellular volume.

*Hypotonic hyponatremia* is almost always caused by an inability of the kidney to excrete sufficient electrolyte-free water to match water intake. This may occur either because the normal diluting capacity of the kidney is overwhelmed by excessive water intake or because the diluting capacity of the kidney is impaired. These alternatives usually can be distinguished by measuring the urine osmolality. A urine osmolality less than 100 mOsm/kg in a patient with hypotonic hyponatremia points to excessive water intake as the cause (Fig. 57.5). It is a prodigious feat for an individual eating a normal diet to overwhelm the normal diluting capacity of the kidney. Estimates are that one can ingest (and excrete) about 20 L of water a day without affecting the plasma osmolality appreciably.[173] Thus, patients who develop hyponatremia from so-called *psychogenic* or *primary polydipsia*—usually patients with obsessive-compulsive disorder or psychosis—typically have concurrent urinary diluting defects, either in association with the underlying mental illness or perhaps as a side effect of psychotropic or anticonvulsant medications.[181]

Not all patients with hypotonic hyponatremia and a dilute urine have primary polydipsia. The patient may be ingesting a diet so deficient in protein and salt that he excretes very little solute in the urine. In that situation (called *beer potomania* for obvious reasons,[182] although the syndrome has been seen in other patients with very low daily solute intake[183]) the low daily solute excretion limits the total amount of water that can be eliminated even with a maximally dilute urine (i.e., maximum urine volume = solute excretion ÷ minimum $U_{osm}$). This might reduce the maximum water excretion to only 3 to 4 L/day, a quantity easily exceeded by an enthusiastic beer drinker.

A urine osmolality above 100 mOsm/kg in the face of hypotonic hyponatremia signifies impaired urinary diluting

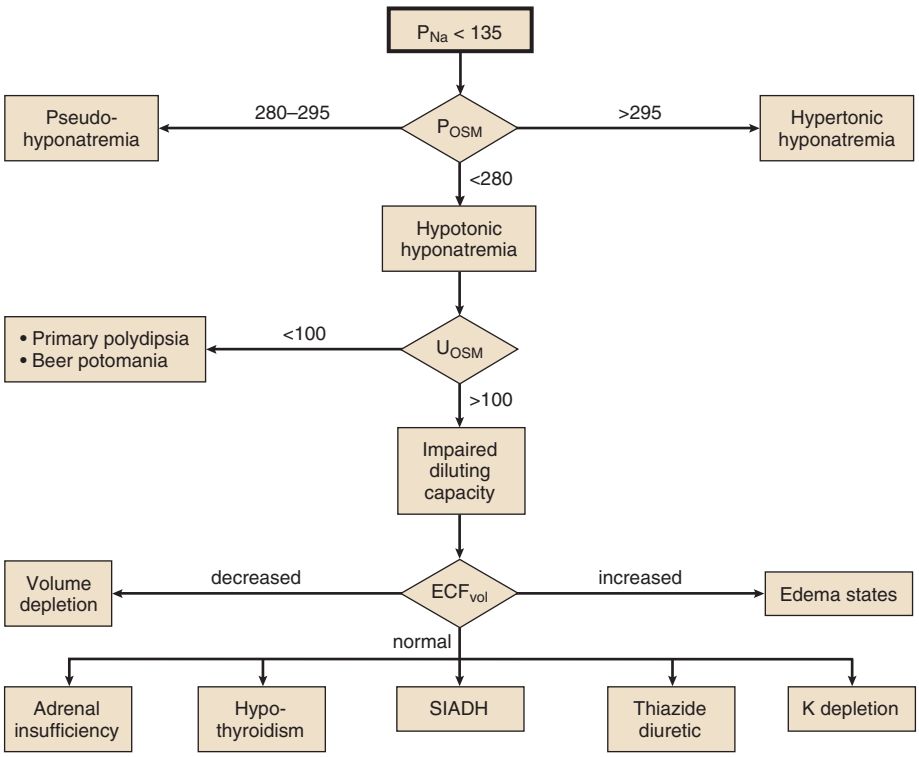


**Figure 57.5** Diagnostic evaluation of hyponatremia. $ECF_{vol}$, extracellular fluid volume status; $P_{Na}$, plasma sodium concentration; $P_{osm}$, plasma osmolality (mOsm/kg); SIADH, syndrome of inappropriate antidiuretic hormone secretion; $U_{osm}$, urine osmolality (mOsm/kg).

capacity. The concentrated urine usually reflects a high circulating AVP level. Because circulating AVP is affected by systemic hemodynamics as well as osmolality, assessment of the patient's ECF volume status and hemodynamics is crucial at this juncture. Hypotonic hyponatremia may be associated with normal, decreased, or increased extracellular volume.

### Euvolemic Hyponatremia

Patients with pure water excess appear clinically euvolemic because excess water distributes throughout the total body water space; only one third of total body water is extracellular (and only one twelfth is intravascular). The only evidence of the slight intravascular volume expansion is low BUN and plasma uric acid concentration.[184] The paradigm of euvolemic hyponatremia with a concentrated urine is the syndrome of inappropriate antidiuretic hormone secretion (SIADH). It is characterized by elevated circulating AVP (ADH) levels that are inappropriate to vasopressin's two physiologic stimuli (i.e., osmotic or hemodynamic).[185] Hypotonic hyponatremia in patients with SIADH develops to the extent that water ingestion exceeds water eliminated by insensible, GI, and renal routes. Because the normal response to extracellular hypotonicity is the elaboration of maximally dilute urine (urine osmolality < 100 mOsm/kg), the urine need only be inappropriately concentrated (i.e., >100 mOsm/kg) to be compatible with a diagnosis of SIADH.

Because hypothyroidism[186] and glucocorticoid insufficiency[187] may impair urinary dilution, patients in whom a diagnosis of SIADH is entertained should undergo appropriate tests of thyroid and adrenocortical function. (see Chapter 59.)

Once a diagnosis of SIADH is made, its cause must be established, because the cause may have important implications in its own right and may be easily remediable. Box 57.8 lists important causes of SIADH. They fall into five major categories: intracranial abnormalities, intrathoracic abnormalities, tumors, drugs, and idiopathic. An important variant of SIADH is the *reset osmostat syndrome*,[188] in which vasopressin levels are regulated normally by tonicity but around a lower "set point" than normal. This syndrome is seen most often in patients who are severely debilitated (e.g., malnutrition, metastatic cancer, advanced tuberculosis) and may account for up to one third of cases of SIADH. The diagnosis of reset osmostat syndrome has important therapeutic implications, as will be discussed later.

### Hypovolemic Hyponatremia

The urinary diluting impairment in hypovolemia is mediated both by decreased delivery of fluid to the diluting segments of the nephron and by hemodynamically stimulated vasopressin release. Thus, the volume-contracted patient cannot excrete electrolyte-free water normally, and even in the face of modest water ingestion readily may become hyponatremic.

The cause of the volume contraction usually is obvious (e.g., hemorrhage, vomiting, diarrhea, diuretics). When it is not, the urine sodium concentration can be helpful in distinguishing between renal and extrarenal solute losses. Renal losses (e.g., as a result of diuretic medications) are usually reflected by sodium wasting, and extrarenal losses

**Box 57.8 Causes of Syndrome of Inappropriate Antidiuretic Hormone Secretion**

**Intracranial Abnormalities**

Infection
Stroke
Hemorrhage
Tumor

**Intrathoracic Abnormalities**

Malignancy
Pulmonary abscess
Pneumonia
Pleural effusion
Pneumothorax
Chest wall deformity

**Drugs**

Antidiuretic drugs (vasopressin, 1-deamino-8-D-arginine vasopressin [DDAVP], oxytocin)
Narcotic analgesics
Antidepressant medications
Amiodarone
Major antipsychotic medications
Chlorpropamide and other sulfonylurea drugs
Carbamazepine
Cyclophosphamide
Methotrexate
Interferon-α
Vinca alkaloids
Platinum compounds
Melphalan
Isofosfamide
MDMA (Ecstasy)

**Extracranial Tumors**

Small cell lung carcinoma
Pancreatic cancer
Others

**HIV/AIDS**

**Hereditary**

Gain-of-function mutation of vasopressin-2 receptor

**Miscellaneous**

Guillain-Barré syndrome
Nausea
Stress
Pain
Acute psychosis
*Legionella* infection

**Idiopathic**

AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

are usually accompanied by sodium conservation (urine sodium concentration < 10 mM). Exceptions occur in the recovery phase after diuretic therapy and in metabolic alkalosis due to vomiting. In the latter situation, the urine chloride concentration tends to be very low and is the best indicator of extracellular volume depletion.[189,190]

*Cerebral salt wasting* may be responsible for hypovolemic hyponatremia in patients with intracranial pathology (e.g., tumors, hemorrhage). The pathogenesis of the urinary salt wasting is incompletely understood. The mechanism of hyponatremia in this setting is similar to that of other hypovolemic states. As a hyponatremic syndrome in patients with central nervous system disease, cerebral salt wasting is often difficult to distinguish from SIADH because urinary sodium excretion tends to be high. Particularly confusing in patients with cerebral salt wasting is the finding of *hypo*uricemia, which is thought to reflect impaired solute reabsorption in the proximal tubule.[191] The key features that distinguish cerebral salt wasting from SIADH are volume depletion and urinary sodium excretion inappropriate to the patient's volume status.[191]

The hyponatremia associated with *diuretic treatment* is multifactorial in origin. Insofar as diuretics produce overt volume depletion, they can cause hyponatremia by the mechanisms discussed previously. Thiazides have been associated with the development of acute severe, symptomatic hyponatremia, particularly in small, elderly women, in the absence of overt signs of volume depletion.[192] The cause of this often precipitous syndrome remains uncertain.[193]

### Hypervolemic Hyponatremia

Hypervolemic hyponatremia generally is seen in patients who cannot excrete sodium normally because they have either severe renal failure or one of the pathologic edema-forming states (e.g., congestive heart failure, hepatic cirrhosis, nephrotic syndrome). Patients with advanced chronic kidney disease are predisposed to hyponatremia.[194] Acute oliguric renal failure or end-stage (dialysis-dependent) renal failure will be accompanied by hyponatremia to the extent that water intake exceeds insensible and GI water elimination (see Chapter 55).

Hyponatremia is seen in over 20% of patients presenting with decompensated congestive heart failure and over 30% of patients admitted to hospital with complications of hepatic cirrhosis.[195] The hormonal milieu of such patients is typical of intravascular volume depletion, even though the absolute intravascular volume typically is increased. Thus, these disorders are said to be characterized by *reduced effective circulating volume*.[196] Because of the perceived intravascular volume depletion, renal diluting ability is compromised for reasons similar to those in hypovolemic hyponatremia.

### Hyponatremia in Endurance-Sports Athletes

The incidence of hyponatremia, with serum sodium less than 135 mmol/L, is approximately 15% in marathon and triathalon athletes; 0.6% of runners develop severe hyponatremia with serum sodium levels less than 120 mEq/L.[195] The three major risk factors associated with hyponatremia in this setting includes body mass index (BMI) less than 20, racing time more than 4 hours, and weight gain related to excessive fluid intake during the race. Fluid overload is the most important factor in the development of hyponatremia for runners.[195]

## MANAGEMENT AND COMPLICATIONS

Hyponatremia per se requires treatment only when it is associated with hypotonicity. Hypertonic hyponatremia responds to the treatment of the underlying disorder,

most commonly a hyperosmolar hyperglycemic state (see Chapter 58).

The therapy of hypotonic hyponatremia must be tailored to (1) the patient's signs and symptoms, and (2) the duration of the disorder.[175] Severe hyponatremia (plasma sodium concentration < 115 mmol/L) can be life threatening, especially if it develops rapidly.[177,197] The therapy of symptomatic hyponatremia, irrespective of cause, is directed at raising ECF tonicity to shift water out of the intracellular space, thereby ameliorating cerebral edema. The rate of correction, however, must be carefully regulated. Overly rapid correction, particularly in patients with chronic hyponatremia, in whom cell volume adaptations may be complete, can produce *osmotic demyelination syndrome*.[198,199] Osmotic demyelination syndrome is associated with a variety of sometimes irreversible neurologic deficits (e.g., dysarthria, dysphagia, behavioral disturbances, ataxia, quadriplegia, coma), which typically develop 3 to 10 days after treatment.[200] Additional risk factors for osmotic demyelination include hypokalemia, malnutrition, alcoholism, advanced age, female gender, and the postoperative state, particularly after orthotopic liver transplantation.[201-203]

For patients with chronic hyponatremia (>48 hours duration) or hyponatremia of unknown duration, the plasma sodium concentration should be raised by a maximum of 0.5 mmol/L/hour, 8 to 10 mmol/L in the first 24 hours[199] and 20 mmol/L over the first 48 hours. Care should be taken to avoid *over*correcting the plasma sodium concentration.[187,200] In grave situations (plasma sodium concentration < 105 mmol/L or in the presence of seizure or coma), initial therapy can be more aggressive (targeting a change in the plasma sodium concentration of 1 to 2 mmol/L/hour for the first few hours), but the recommended daily target should not be exceeded.[187,200]

Correction of severe symptomatic hypotonic hyponatremia, regardless of cause, should be accomplished with hypertonic (3%) saline (sodium concentration 513 mmol/L). The volume of 3% saline required can be estimated by the following formula:

$$\text{volume of 3\% saline (L/24 hours)} = \text{target change } P_{Na} \text{ (mmol/L/24 hours)} \times \text{TBW (L)} \div 513$$

For example, in a 70-kg man with a plasma sodium concentration of 105 mmol/L and total body water (TBW) of 42 L (60% of body weight), the amount of sodium needed to raise the plasma sodium concentration by 10 mmol/L is 10 × 42, or 420 mmol. Therefore, 420 ÷ 513 or 0.82 L of 3% saline would be required in the first 24 hours, or 34 mL/hour. It is important to recognize that the calculation provides only a very rough guideline. The plasma sodium concentration must be monitored frequently during treatment to adjust the rate of correction. If the rate of correction begins to exceed the target rate, the hypertonic saline infusion should be stopped; rarely, it may be necessary to administer water (enterally or intravenously) or even desmopressin[204] in order to prevent overly rapid correction or overcorrection. Rapid extracellular volume expansion with hypertonic saline may precipitate pulmonary edema, particularly in patients with underlying heart disease. Thus, patients receiving 3% saline should be assessed frequently for evidence of volume overload. One may administer a loop diuretic if necessary, recognizing that this will enhance electrolyte-free water clearance and accelerate the correction. Rarely, administration of isotonic (normal) saline to patients with SIADH paradoxically may *lower* the plasma sodium concentration if the urine osmolality remains high—a process that has been called *desalination*.[205]

The treatment of chronic asymptomatic hypotonicity should be directed at correcting the pathophysiologic mechanisms involved in generating the hypotonic state. Because euvolemic hyponatremia represents pure water excess, treatment depends on restricting water intake to less than the daily water output. Patients with SIADH excrete little or no electrolyte-free water in the urine. Therefore, if water intake is limited to less than the amount of insensible water losses (approximately 10 mL/kg/day), the plasma sodium concentration will slowly rise. Patients with the reset osmostat variant of SIADH characteristically do not develop progressive hypotonicity, and therapy is rarely required.

If the cause of SIADH cannot be corrected and if water restriction is poorly tolerated or ineffective, a specific vasopressin ($V_2$) receptor antagonist (VRA) can be used.[206] Conivaptan (parenteral) and tolvaptan (oral) were the first VRAs to be approved by the U.S. Food and Drug Administration for clinical use. These agents have changed the management of patients with SIADH.[207] Tolvaptan reliably increases $P_{Na}$ concentration, but hyponatremia recurs within 1 week after the medication is discontinued.[208] For patients admitted with hyponatremia related to decompensated congestive heart failure, tolvaptan along with diuretic therapy improves most signs and symptoms of heart failure within 1 week,[209] although no effect on 24-month mortality rate or heart failure morbidity has been demonstrated.[210] Before the introduction of VRAs, demeclocycline (a tetracycline antibiotic that increases electrolyte-free water excretion by inhibiting vasopressin-mediated water reabsorption in the collecting duct) was commonly used to treat patients with SIADH. Demeclocycline is contraindicated in patients with renal disease, hepatic cirrhosis, or congestive heart failure because drug-related renal insufficiency has been described in these situations.[206] Neither VRAs nor demeclocycline are indicated for the treatment of acute, severe hyponatremia.

Therapy of hypovolemic hyponatremia should be directed at restoring intravascular volume with intravenous isotonic saline while identifying and correcting the cause of the excessive solute loss. Volume repletion readily elicits a water diuresis by increasing the delivery of fluid to the renal diluting segments and suppressing vasopressin release. As with all categories of hypotonic hyponatremia, the rate of correction must be carefully controlled.

The treatment of diuretic-induced hyponatremia is straightforward: Withdrawing the offending drug, liberalizing salt intake, and replenishing body potassium stores usually correct the disorder. Severe symptomatic hyponatremia in this setting should be treated with hypertonic saline as detailed earlier. Patients must be watched carefully after correction of the hyponatremia because relapse may occur for up to a week.[193]

Resolution of the hyponatremia associated with any of the pathologic edematous disorders ultimately depends on effective treatment of the underlying disease. Regardless of the specific therapy of the underlying disorder, the mainstay

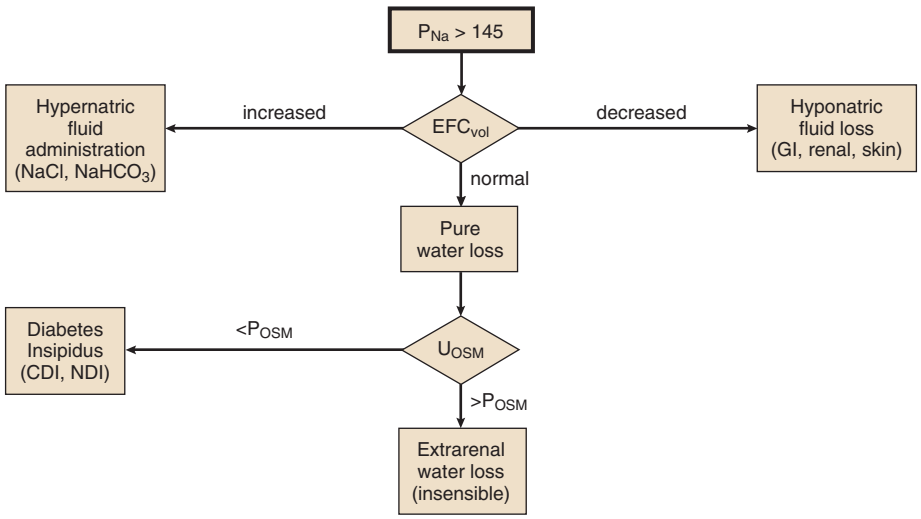


**Figure 57.6** Diagnostic evaluation of hypernatremia. See Figure 57.3 legend for abbreviations. CDI, central diabetes insipidus; GI, gastrointestinal; NDI, nephrogenic diabetes insipidus.

of therapy for the hyponatremic edematous patient remains salt and water restriction. Diuretics are often a double-edged sword in the hyponatremic edematous patient: They may be needed to treat pulmonary vascular congestion, peripheral edema, and ascites but if used to excess can produce further decrements in effective arterial blood volume and exacerbate water retention. Strategies directed at increasing effective arterial blood volume (e.g., afterload reduction with angiotensin-converting enzyme inhibitors[211,212]) have had some success in increasing electrolyte-free water excretion and ameliorating hyponatremia in patients with congestive heart failure. VRAs are likely to facilitate treatment of hypervolemic hyponatremia (see earlier).[207]

## HYPERNATREMIA

### EPIDEMIOLOGY AND CLINICAL MANIFESTATIONS

Hypernatremia is common in critically ill patients, being present on admission in about 9% of patients and developing during the course of the ICU stay in another 6%.[213] It is associated with a significantly higher mortality rate than is seen in patients without hypernatremia.[213]

Sustained hypernatremia develops in patients whose water output exceeds their input. Water ingestion can defend against the development of hypernatremia even when water losses are prodigious. For that reason, hypernatremia upon presentation to the hospital occurs most commonly in patients who are incapacitated: those who have impaired thirst sensation, who cannot access water, or who cannot express their need for water (e.g., infants and patients with neurologic impairments). Similar predispositions prevail among critically ill patients. Thus, the development of hypernatremia in hospitalized patients is considered to be iatrogenic, reflecting an incomplete understanding of the factors that lead to hypernatremia.[213] The increased mortality rate seen in patients with hypernatremia probably is due to their underlying vulnerabilities rather than an effect of the hypernatremia itself.[214]

The clinical manifestations of hypernatremia are proportional to the magnitude and rate of rise of the plasma sodium concentration and are attributable to intracellular volume contraction. To counteract cellular volume contraction, cells begin to adapt within minutes by allowing the influx of electrolytes, thus mitigating cell shrinkage. When hypernatremia lasts more than a few hours, brain cells generate new *organic osmolytes*. This leads to further water movement back into brain cells, restoring cell volume nearly to normal after about 3 days.[215] Thus, chronic progressive hypernatremia is associated with fewer and milder symptoms than acute severe hypernatremia. Most often, patients with longstanding hypernatremia present with weakness, lethargy, and confusion. Seizure and coma may supervene. Acute severe hypernatremia in infants and small children is associated with intracranial bleeding,[216] presumably caused by brain shrinkage and traction on the penetrating vessels. There is some controversy, however, as to whether the hypernatremia in that situation is the cause or the effect of the intracranial hemorrhage.[217]

### DIFFERENTIAL DIAGNOSIS

The plasma sodium concentration reflects the ratio of body sodium content to total body water. Thus, hypernatremia (plasma sodium concentration > 145 mmol/L) can result from loss of pure water alone, loss of *hyponatric** fluid, or a gain of sodium or *hypernatric* fluid. It is important to distinguish among these paths to hypernatremia because they have diagnostic and therapeutic implications (Fig. 57.6).

#### Euvolemic Hypernatremia

Hypernatremic patients who appear euvolemic most likely have pure water loss as an explanation for their hypernatremia. This is because the water is lost from all body compartments proportionately; only one twelfth of the water loss is intravascular. For example, a 60-kg woman with a 3 L pure

**Hyponatric* and *hypernatric* are used here to refer to a fluid with a sodium concentration less than (or greater than) that of plasma.*

water loss would experience an intravascular loss of only 250 mL (clinically imperceptible) but would develop a plasma sodium concentration of 155 mmol/L.* Pure water can be lost either through the skin and respiratory tract (so-called *insensible* losses) or in urine.

Insensible losses amount to about 10 mL/kg/day under normal environmental conditions in an afebrile individual with a normal respiratory rate. A hot environment, fever, or rapid respiratory rate may double that rate.[173] Note that a patient on a mechanical ventilator using humidified gas will lose no water through the respiratory tract.

The loss of large amounts of dilute, electrolyte-free water in the urine is typical of *diabetes insipidus* (DI). DI may be central (CDI) or nephrogenic (NDI) depending on whether the defect is in vasopressin release from the posterior pituitary or in renal response to circulating vasopressin, respectively. The causes of DI are shown in Box 57.9. Most cases of CDI, especially those following trauma or intracranial surgery, are self-limited, lasting 3 to 5 days. Of special interest to intensivists is a classic triphasic syndrome that may be seen following severe head trauma:

1. Initially, there is abrupt cessation of vasopressin release from the posterior pituitary, accompanied by polyuria.
2. About a week later, an antidiuretic phase ensues, characterized by urinary concentration and water retention with a tendency toward hyponatremia, lasting 5 to 6 days. This appears to result from the release of stored vasopressin from the degenerating hypothalamic neurons.
3. Persistent CDI recurs when the vasopressin stores are depleted.[218]

Regardless of the cause, patients with DI of either type usually have a plasma sodium concentration within the normal range because their water ingestion matches their urinary water output. They develop hypernatremia only with water deprivation due to mental or physical incapacity or neglect. An awareness of the causes of DI, a careful history, and familiarity with the differential diagnosis of polyuria will prevent hypernatremia in these circumstances.

### Box 57.9 Causes of Diabetes Insipidus

**Central Diabetes Insipidus**

- Posthypophysectomy
- Posttraumatic
- Granulomatous diseases
  - Histiocytosis
  - Sarcoidosis
- Infections
  - Meningitis
  - Encephalitis
- Inflammatory/autoimmune hypophysitis
- Vascular
  - Hypoxia
  - Thrombotic or embolic stroke
  - Hemorrhagic stroke
- Neoplastic
  - Craniopharyngioma
  - Pituitary adenoma
  - Lymphoma
  - Meningioma
- Drugs or toxins
  - Ethanol
  - Snake venom
- Congenital/hereditary

**Nephrogenic Diabetes Insipidus**

- Drug-induced
  - Lithium
  - Demeclocycline
  - Cisplatin
  - Ethanol
- Hypokalemia
- Hypercalcemia
- Vascular
  - Sickle cell anemia
- Infiltrating lesions
  - Sarcoidosis
  - Multiple myeloma
  - Amyloidosis
  - Sjögren syndrome
- Congenital
  - Autosomal recessive: aquaporin-2 water channel gene mutations
  - X-linked recessive: arginine vasopressin (AVP) $V_2$ receptor gene mutations

### Hypovolemic Hypernatremia

The loss of salt and water, with the water loss greater than the sodium loss, will lead to hypernatremia and volume depletion, manifested by orthostatic or persistent hypotension and tachycardia and evidence of organ underperfusion (e.g., acute renal failure, lactic acidosis). For example, if the 60-kg woman whose plasma sodium concentration rose to 155 mmol/L (see earlier) had lost the equivalent of half-isotonic saline instead of pure water, her intravascular volume would have contracted by 750 mL, enough to cause at least orthostatic hypotension and tachycardia.

A common cause of hypovolemic hypernatremia is the loss of GI fluids.[219] Most GI fluids have an electrolyte concentration below that of plasma: The concentration of sodium plus potassium in stool is roughly constant at 110 to 120 mmol/L over a wide range of stool volume.[125] Gastric fluid has an even lower electrolyte concentration: about 40 to 50 mmol/L total cation concentration.[220] Diuresis, either osmotic (glucose-, mannitol-, or urea-induced) or medication-induced, causes the loss of urine with an electrolyte concentration less than that of plasma, leading to volume contraction and hypernatremia. The loss of sweat, which contains some sodium, can cause hypovolemic hypernatremia in individuals who exercise vigorously in a hot environment. If the cause of the fluid loss is not apparent from the history or the physical examination, a urinary chloride concentration less than 10 mmol/L in the face of hypovolemic hypernatremia suggests that the electrolyte loss is extrarenal (cutaneous or GI).

*The expected change in the serum sodium concentration is calculated as follows: [initial total body water volume] × [serum sodium concentration initial] ÷ [final total body water volume]; 30 L × 140 mmol/L ÷ 27 L = 155 mmol/L.

### Hypervolemic Hypernatremia

Hypervolemic hypernatremia is relatively uncommon. It results most often from the administration of hypertonic sodium salts to patients without free access to water.[219] Patients show signs of extracellular volume expansion (e.g., hypertension, edema, congestive heart failure, and pulmonary edema). In infants, this syndrome has been caused by erroneous preparation of dietary formula using salt instead of sugar; in adult outpatients, it may be caused by ingestion of a concentrated salt solution, usually for its emetic effect.[221] The risk of death is substantial and seems to be proportional to the plasma sodium concentration.[221]

In hospitalized adults, hypervolemic hypernatremia it is most often iatrogenic, caused by intravenous administration of undiluted sodium bicarbonate (formulated at 1 mEq/mL or 1000 mmol/L) or sodium chloride (3% [513 mmol/L] or 23.5% [4019 mmol/L]). Not all hypervolemic hypernatremia results from the administration of hypertonic fluids. It may be seen in a volume-expanded patient who then loses hypotonic fluid.[222]

## TREATMENT

The initial treatment of the hypernatremic patient depends on his or her volume status. For patients with pure water losses (euvolemic), therapy has two goals: (1) reduction or replacement of ongoing water losses, and (2) replacement of the existing water deficit.

If the water losses are urinary (see Fig. 57.6) and due to CDI, ADH should be administered. Several formulations are available (Table 57.3). In the acute (postsurgical or posttraumatic) setting, L-arginine vasopressin may be used either subcutaneously or intravenously, although the latter route may be associated with hypertension and coronary spasm and should therefore be used with extreme caution.[223] The advantage of vasopressin in this setting is its short half-life, which allows the physician to repeatedly assess the need for continued hormone replacement, especially when the disorder may be self-limited. Desmopressin (DDAVP) is a synthetic analog of vasopressin that has no vasoconstrictor properties, thus avoiding the risks of hypertension and myocardial ischemia. The treatment of the urinary water losses associated with NDI are best treated with thiazide diuretics with or without COX inhibitors. Because most of these agents are orally administered, treatment of NDI in the critically ill patient often consists of urinary water replacement until he or she is able to take medications by mouth.

The current body water deficit can be estimated by the following formula:

$$\text{Water deficit (liters)} = \text{TBW}\,(1 - [140 \div \text{current } P_{Na}])$$

where TBW is total body water in liters (estimated as about 0.5 × lean body weight [kg] in women and 0.6 × lean body weight in men). For example, a 60-kg woman presenting with a plasma sodium concentration of 160 mmol/L is estimated to have a total body water deficit of 30 (1 – 0.875), or 3.75 L. This formula provides only a rough estimate of the water deficit.

The rate of water replacement should be proportional to the rapidity with which the hypernatremia developed.[215] Thus, if the hypernatremia had developed over only a few hours (such as in postsurgical or posttraumatic DI), it can be corrected just as quickly. On the other hand, hypernatremia of more than a day's duration, or of unknown duration, must be correctly slowly in order to avoid cerebral edema. In general, one should aim to correct half the water deficit in the first 24 hours and the remainder over the next 24 to 48 hours.

Water is best administered enterally, as tap water. If that route is unavailable, 5% dextrose in water ($D_5W$) may be used, with the understanding that the capacity to metabolize glucose is limited to about 15 g/hour in a critically ill adult.[224] Thus, even in nondiabetic patients, the administration of more than 300 mL/hour of $D_5W$ is likely to result in hyperglycemia, which may be relatively resistant to insulin administration. Hyperglycemia will exacerbate urinary water losses by causing an osmotic diuresis. Half-normal (0.45%) saline may be a good alternative, as long as one recognizes that only half the administered volume is electrolyte-free water and that the sodium load may cause unwanted volume expansion.

Regardless of the degree of hypernatremia, normal (.9%) saline should be given intravenously to patients who present with obvious volume depletion, manifested by hypotension, tachycardia, and evidence of impaired tissue perfusion. This is consistent with the first principles of emergency and critical care, prioritizing the adequacy of the circulation. Only

**Table 57.3 Pharmacologic Treatment of Central Diabetes Insipidus**

| Agent | Total Daily Dose | Frequency of Administration | Time to Onset (h) | Duration of Action (h) | Comments |
|---|---|---|---|---|---|
| Arginine vasopressin, 20 units/mL | 5-10 units subcutaneous | q2-4h | 1-2 | 2-6 | Intravenous route may cause vasoconstriction and coronary spasm |
| Desmopressin acetate (DDAVP) | | | | | |
| 10 µg/0.1 mL intranasal | 10-40 µg intranasal | Daily or bid | 1-2 | 8-12 | |
| 4 µg/mL injection | 2-4 µg IV or subcutaneous | Daily or bid | 1-2 | 8-12 | |

Adapted from Singer I, Oster JR, Fishman LM: The management of diabetes insipidus in adults. Arch Intern Med 1997;157(12):1293-1301.

after the extracellular volume deficits have been largely corrected may the physician direct his or her attention to the total body water deficit (see earlier).

Patients with hypervolemic hypernatremia need reduction in their extracellular and intravascular volume before their water deficit can be corrected. Failure to do so will exacerbate the volume overload. For patients with adequate renal function, this may be accomplished with the use of diuretic drugs. Loop diuretics tend to cause the excretion of an isotonic urine. Replacement of that urine volume with pure water will allow correction of the hypervolemia and the hypernatremia simultaneously.

Because of the imprecision of the estimation formulas and the failure of the foregoing analysis to take account of other fluids and electrolytes both administered and lost, it is crucial that the plasma electrolytes be monitored frequently during the correction of hypernatremia, especially in view of the dire consequences of overly rapid correction.

## CALCIUM HOMEOSTASIS

Calcium (Ca) is required for bone mineralization, muscle contraction, nerve conduction, and blood coagulation. It is required for cell division, hormone secretion, phagocytosis, chemotaxis, and activation of numerous intracellular second messengers.[225] Calcium is also responsible for activation of calcium-dependent phospholipases and proteases, generation of free radicals, release of cytokines, and inhibition of adenosine triphosphate (ATP) production in the face of ischemic injury. Thus calcium plays a central role in physiologic as well as pathologic conditions.[226]

### NORMAL CALCIUM PHYSIOLOGY

Calcium is the most abundant cation in the body. The total body calcium content of an average adult is approximately 1 kg, 99% of which is found in bones and teeth, with only 1% in plasma and soft tissues.[227] Calcium homeostasis is achieved with the cooperation of several organs, including the skeleton, the gut, and the kidney, under the influence of several hormones, mainly vitamin D, parathyroid hormone (PTH), and calcitonin.

#### CALCIUM INTAKE AND ABSORPTION

The typical daily dietary intake of calcium for an average adult in North America is 800 to 1000 mg. The main dietary source of calcium is milk and other dairy products; it is also available in the form of fortified food and calcium-containing supplements. Approximately 20% of dietary calcium is absorbed by intestine. Intestinal absorptive capacity increases with calcium deprivation and under certain physiologic conditions such as growth spurt in children, pregnancy, and lactation.[228] Intestinal absorption occurs via both passive paracellular and active transcellular pathways. Vitamin D increases the active transport of calcium across the intestinal membranes.[227]

#### RENAL HANDLING OF CALCIUM

The filtered load of calcium (the product of glomerular filtration rate and the plasma concentration of ultrafilterable calcium) is about 10 g/day. Calcium balance is maintained when the kidneys excrete about 200 mg/day (the intestinal absorptive load). Thus, the fractional excretion of calcium is only about 2%.[227,228] Of the 98% of filtered calcium reabsorbed along the nephron, 60% is reabsorbed in the proximal tubule. Approximately 15% of the filtered calcium is reabsorbed in the thick ascending limb of loop of Henle (TAL). The reabsorption of calcium in TAL is mostly passive and proportional to the lumen-positive voltage generated by the furosemide-inhibitable Na-K-Cl cotransporter (NKCC2) channel and potassium recycling via renal outer medullary potassium (ROMK) channels. There is also some active transcellular transport, which is under the influence of PTH and calcitonin.[227,228] In the distal tubule, approximately 10% to 15% of filtered calcium is reabsorbed via active transcellular pathways. The apical membranes of distal convoluted tubules (DCT) and connecting tubules (CNT) contain highly selective epithelial calcium channels (TRPV-5)[227,228] that facilitate calcium entry into the cells. PTH increases the density and open probability of TRPV-5 channels.[229]

Volume expansion, hypercalcemia, acute and chronic acidosis, and loop diuretics reduce the renal calcium reabsorption and result in hypercalciuria. Conversely, hypocalcemia, alkalosis, PTH, calcitriol, and thiazide diuretics enhance renal calcium reabsorption and cause hypocalciuria.

#### REGULATION OF PLASMA CALCIUM

Normal plasma calcium concentration is 8.8 to 10.4 mg/dL. In plasma, calcium exists in two forms: protein-bound and *ultrafilterable* (permeant across the glomerular filtration barrier). Approximately 40% of plasma calcium is bound to plasma proteins (predominantly albumin), cannot cross the biologic membranes, and is thus physiologically inert. The ultrafilterable portion of plasma calcium makes up the remaining 60% of plasma calcium and consists of calcium complexed with various anions like citrate, phosphate, and lactate (about 10%) and free, ionized calcium ($Ca^{2+}$)—the biologically active form—accounting for about 50% of plasma levels.[230]

Plasma $Ca^{2+}$ concentration is tightly regulated. Several factors play an important role in maintaining plasma $Ca^{2+}$ concentration within a narrow range (about 4.4-5.2 mg/dL or 1.1-1.3 mmol/L). The principal regulators are PTH, vitamin $D_3$, and $Ca^{2+}$ itself.

$Ca^{2+}$ acts as a ligand for calcium-sensing receptors (CaSR) present on the chief cells of the parathyroid glands. A rise in plasma $Ca^{2+}$ concentration results in activation of CaSR, which in turn inhibits PTH secretion. Conversely, a fall in $Ca^{2+}$ concentration inhibits CaSR, increasing PTH secretion. PTH mobilizes the calcium from bone stores, stimulates renal calcium reabsorption, and increases the conversion of $25(OH)D_3$ to $1,25(OH)_2D_3$, the most active form of vitamin $D_3$. Activated vitamin $D_3$ increases intestinal calcium absorption. All these systems work in concert to keep the $Ca^{2+}$ levels within physiologic levels.[225]

### PLASMA CALCIUM MEASUREMENT

$Ca^{2+}$ is the physiologically important moiety, yet total calcium is most often measured in clinical laboratories. Under normal circumstances, there is a fairly constant relationship

between total and ionized calcium (see earlier), but in critically ill patients, this relationship may be disturbed such that total calcium no longer provides a reliable index of the physiologically important calcium concentration. The two major factors affecting the ratio of ionized to total calcium are acid-base status and plasma protein concentration.

Acidemia causes displacement of calcium ions from albumin by protons and results in a relative increase in $Ca^{2+}$. Conversely, alkalemia increases calcium binding to albumin, causing a relative fall in $Ca^{2+}$ levels while total plasma calcium concentration remains unchanged.[225,227]

Changes in the concentration of plasma protein, especially albumin, result in alterations in total calcium concentration: Hypoalbuminemia, common in critically ill patients, causes a reduction in total calcium concentration; hyperalbuminemia (e.g., in states of severe volume contraction) tends to cause an increase in total plasma Ca. Numerous formulas have been proposed to adjust the total calcium concentration for changes in plasma albumin concentration.[231] The most commonly used formula is based on the observation that each gram of albumin binds about 0.8 mg calcium at physiologic pH:

$$Ca_{corrected} = Ca_{observed} + (0.8 \cdot [4.0 - albumin])$$

Unfortunately, the corrected calcium correlates very poorly with $Ca^{2+}$ in various critically ill populations, typically with a very low sensitivity for diagnosis of true hypocalcemia.[231-233]

The reasons for this discrepancy are manifold, including concurrent acid-base disorders, high circulating concentrations of free fatty acids,[234] and infusions of heparin, citrate, and bicarbonate.[233] Therefore, in critically ill patients, direct measurement of $Ca^{2+}$ is recommended for assessing physiologic calcium concentration.

## HYPOCALCEMIA

### EPIDEMIOLOGY

Hypocalcemia is extremely common in critically ill patients. The prevalence of ionized hypocalcemia is reported to be 60% to 85% among medical, surgical, and trauma ICU patients.[235-238] Risk factors for the development of hypocalcemia in critically ill patients include advanced age, sepsis, acute renal failure, multiple blood transfusion, malnutrition, magnesium deficiency, severe shock, and colloid volume resuscitation.[238,239] Mortality rate is higher in hypocalcemic patients[236,240,241] but does not appear to be independently associated with hypocalcemia.[237,238]

### CAUSES OF HYPOCALCEMIA

Causes of hypocalcemia are shown in Box 57.10. Hypocalcemia may be caused by disorders involving the hormonal regulators of calcium homeostasis, PTH, and vitamin D; redistribution of calcium; drugs; and miscellaneous influences. We will discuss causes of particular relevance to the critical care setting.

#### Hypoparathyroidism

Parathyriodectomy, for hyperparathyroidism or "incidentally" with thyroidectomy, may cause postoperative hypocalcemia. Risk factors for developing hypocalcemia include subtotal parathyroidectomy and simultaneous thyroidectomy. Profound, long-lasting hypocalcemia may develop as part of the "hungry bone" syndrome, in which calcium is sequestered into the rapidly remineralizing bone.[242] Hypomagnesemia may contribute to the hypocalcemia (see discussion under "Magnesium Homeostasis").

#### Vitamin D Deficiency

Vitamin D deficiency is common in elderly, institutionalized patients due to poor dietary intake and inadequate sunlight exposure. Diseases involving liver and small intestine may result in poor absorption of vitamin D. For conversion to its most active form, vitamin D requires hydroxylation in liver and kidney. Frequently, critically ill patients suffer from liver and kidney dysfunction, which results in impaired vitamin D synthesis and predisposes to hypocalcemia.[226] Vitamin D deficiency (level <20 ng/dL) upon admission to a medical ICU has been associated with increased mortality rate.[243] Whether vitamin D supplementation to critically ill patients will reduce mortality rate remains to be determined.

**Box 57.10 Causes of Hypocalcemia**

**Hypoparathyroidism**

Acquired
- Parathyroidectomy
- Infiltrative or malignant disease

Congenital
Idiopathic

**Vitamin D Deficiency**

Malnutrition
Malabsorption
Liver disease
Kidney disease

**Redistribution**

Tissue sequestration
- Acute pancreatitis
- Rhabdomyolysis

Complexation
- Alkali
- Citrated blood-product transfusions
- Citrate anticoagulation in continuous renal replacement therapy
- Plasmapheresis
- Bicarbonate infusion for metabolic acidosis
- Phosphate
- Tumor lysis syndrome
- Fleet enemas and phosphate-containing laxatives
- Rhabdomyolysis

Ethylenediamine tetra-acetic acid (EDTA)

**Drugs**

Cisplatin
Bisphosphonates
Plicamycin

**Miscellaneous**

Sepsis/systemic inflammatory response syndrome
Hypomagnesemia
Acute renal failure

### Redistribution

*Citrate* is useful as a preservative and anticoagulant for blood components precisely because it chelates calcium and thereby inhibits the coagulation cascade. The calcium citrate complex is then metabolized in liver, where citrate is converted into bicarbonate, and ionized calcium is released into the circulation. Massive blood transfusion may result in ionized hypocalcemia due to chelation of calcium by citrate. However, hypocalcemia is transient in patients with normal liver function and ionized calcium levels return to normal levels within 15 minutes of transfusion.[244] Citrate also may be used for anticoagulation of the dialysis circuit for continuous renal replacement therapy (CVVHD and variants). Under those conditions, calcium typically is infused through a central venous line to prevent hypocalcemia. Inadequate calcium replacement or concomitant liver failure may result in clinically significant hypocalcemia. In the latter case, with citrate accumulation, the total calcium may be misleadingly normal, but the $Ca^{2+}$ is low.[245,246] Hypocalcemia is frequently reported with plasmapheresis where citrate is used for anticoagulation.[247] Sodium *bicarbonate* to treat metabolic acidosis may cause hypocalcemia from calcium binding to albumin and formation of carbonate complexes. Similarly, abrupt alkalinization from hemodialysis against a bicarbonate bath may precipitate symptomatic hypocalcemia.

*Phosphate* binds with calcium to form insoluble calcium phosphate complexes. Under normal physiologic conditions, calcium and phosphorus levels are tightly regulated, preventing significant complexation. Any condition that causes acute increase in phosphate levels, however, can cause complexation and resultant ionized hypocalcemia. Examples include endogenous phosphorus overload as in the tumor lysis syndrome[72] and exogenous phosphorus overload from laxatives and cathartics.[248-251] Patients with impaired renal function are at particular risk.[249] (See discussion under "Phosphorus Homeostasis.")

Hypocalcemia in *rhabdomyolysis* is multifactorial and involves calcium deposition in injured muscles, formation of calcium-phosphate complex due to hyperphosphatemia, and acute renal failure causing decreased synthesis of vitamin D.[252]

Ionized hypocalcemia is reported in up to 85% of patients suffering from acute severe *pancreatitis*.[253] The cause of hypocalcemia in this setting us unclear. Calcium has been shown to accumulate in pancreas, liver, and skeletal muscle in an animal model of acute pancreatitis.[254] Low[255] and high[256,257] levels of PTH have been reported. Experimental elevation in free fatty acids, both circulating[258] (as might be seen in the hypertriglyceridemia of acute pancreatitis) and intraperitoneal,[259] have been associated with the hypocalcemia of acute pancreatitis. Finally, high circulating endotoxin levels may have a role.[253]

### Drugs

*Bisphosphonates* are used for the treatment of osteoporosis and hypercalcemia. They act by impairing osteoclast function and reducing osteoclast numbers. Bisphosphonate-induced hypocalcemia has been reported in patients with renal failure, hypoparathyroidism, or vitamin D deficiency.[260] Other drugs such as colchicine, plicamycin (formerly mithramycin), and calcitonin also decrease bone release of calcium.[227]

### Sepsis/Systemic Inflammatory Response Syndrome

Hypocalcemia is common in patients suffering from sepsis or systemic inflammatory response syndrome.[236,240] The cause probably is multifactorial.[261] Among the proposed mechanisms are calcium sequestration,[262,263] an effect of inflammatory cytokines,[264] calcitonin precursors,[264,265] hypomagnesemia[266] with inappropriate hypoparathyroidism,[261] and probable PTH resistance.[264,267] Vitamin D deficiency, from malnutrition and inability to hydroxylate vitamin D due to coexisting liver and kidney dysfunction, also has been implicated.[261] The hypocalcemia may serve to protect vulnerable cells from the deleterious effects of calcium during sepsis. Indeed, calcium administration in this setting may be detrimental.[261]

## CLINICAL MANIFESTATIONS

Hypocalcemia affects predominantly the neuromuscular and cardiovascular systems. Neuromuscular manifestations include paraesthesias (perioral and acral), hyperactive reflexes, tetany (carpopedal spasm and other muscle spasm), and seizures.[227] Laryngospasm and bronchospasm may supervene, leading to respiratory arrest.[225] Tetany may be provoked by tapping over the facial nerve and noting ipsilateral facial muscle twitching (Chvostek sign) and transiently occluding the brachial artery with a tourniquet and noting carpal spasm (Trousseau sign), although neither of these signs is specific for hypocalcemia. Prolonged hypocalcemia lasting more than 36 hours has been associated with the development of critical illness polyneuropathy and myopathy.[268] Psychiatric manifestations include anxiety, irritability, confusion, and psychosis.[225]

Cardiovascular findings include a prolonged QT interval and, in severe hypocalcemia, bradycardia, hypotension refractory to fluids and pressors, heart block, heart failure, and cardiac arrest.[226]

Symptoms and signs of hypocalcemia depend on the degree of depression of ionized calcium levels and the rate of decline.[227] Mild hypocalcemia (ionized calcium > 3.2 mg/dL) usually is well tolerated.

## DIAGNOSIS

When hypocalcemia is suspected in a critically ill patient, the diagnosis should be established by direct measurement of ionized calcium levels (see "Plasma Calcium Measurement"). If ionized hypocalcemia is confirmed, plasma magnesium and phosphorus should be measured. Further diagnostic evaluation derives from the differential diagnosis (see Box 57.10). Without PTH levels and vitamin D levels, the diagnosis of hypocalcemia remains obscure in the majority of critically ill patients.[236]

## TREATMENT

Therapy of hypocalcemia depends on its severity. Hypocalcemia (ionized Ca < 3.2 mg/dL) accompanied by serious cardiovascular or neuromuscular signs should be treated urgently. Calcium gluconate (10% in 10 mL containing 90 mg elemental calcium) can be given over 5 to 10 minutes, followed by calcium gluconate infusion (500-1000 mg in 500 mL 5% dextrose) over 6 hours.[227] Calcium chloride (10% in 10 mL containing 272 mg elemental calcium) contains more calcium and can rapidly increase plasma calcium

levels, however, it is more irritating to the veins and must be given by a central venous catheter. Patients with renal failure, hyperphosphatemia, and serious hypocalcemia may require dialysis.

Patients receiving intravenous calcium should have frequent measurement of the ionized calcium. They should be monitored for side effects of calcium administration including hypertension, skin flushing, nausea, vomiting, and chest pain.

Intravenous calcium should be reserved for patients who have severe hypocalcemia or who are incapable of taking calcium orally. Administration of intravenous calcium can cause complexing with phosphorus and ectopic calcification.

Critically ill patients with mild hypocalcemia (iCa > 3.2 mg/dL) tend to have few if any manifestations. Patients with longstanding or chronic hypocalcemia (e.g., due to vitamin D deficiency or hypoparathyroidism) should receive oral calcium supplementation. Calcium is available as carbonate, citrate, phosphate, and lactate salt. Calcium requirement varies between 1 and 4 g elemental calcium daily and must be given in divided doses. Vitamin D can be added with calcium to enhance intestinal absorption.

Several points in the management of hypocalcemia should be borne in mind. First, in cases of concomitant mild hypocalcemia with hyperphosphatemia (e.g., renal failure), the hyperphosphatemia should be corrected using phosphate binders because that alone will often lead to correction of the hypocalcemia. Second, magnesium deficits should be corrected because that may restore normal calcium physiology even without calcium supplementation (see discussion under "Magnesium Homeostasis"). Finally, concurrent severe metabolic acidosis should await correction of the hypocalcemia, because correction of the acidosis will be likely to worsen the ionized hypocalcemia and precipitate tetany.

## HYPERCALCEMIA

Hypercalcemia has been reported in 15% to 30% of critically ill patients, [267,269] and thus appears to be less common than hypocalcemia. It is more common in patients with higher severity of illness and in those with concurrent renal failure.[267,269]

### CAUSES OF HYPERCALCEMIA

Box 57.11 lists causes of hypercalcemia. About 90% of hypercalcemia in ambulatory and non-ICU patients is caused by only two entities: primary hyperparathyroidism and malignancy.[225] The spectrum is a bit broader in critically ill patients.

#### Primary Hyperparathyroidism

*Primary hyperparathyroidism* is the most common cause of hypercalcemia, accounting for more than 50% of cases in ambulatory patients. Specific causes include benign adenoma (80-90%), hyperplasia (10-20%), and carcinoma (1%). Biochemical abnormalities include elevated circulating intact PTH, hypercalcemia, and hypophosphatemia.[225]

**Box 57.11 Causes of Hypercalcemia**

- Primary hyperparathyroidism
- Malignancy
  - Parathyroid hormone related peptide (PTHrP)
  - Ectopic parathyroid hormone
  - Vitamin D mediated
  - Lytic bone lesions
- Vitamin D
  - Exogenous
  - Endogenous
- Hyperthyroidism
- Adrenal insufficiency
- Rhabdomyolysis, recovery
- Immobilization
- Drugs
  - Thiazide
  - Lithium
  - Vitamin D/calcium supplements
  - Vitamin A

#### Malignancies

Hypercalcemia is rarely the presenting sign of a malignancy; most malignancies are advanced at the time hypercalcemia develops. About 40% of hypercalcemia in hospitalized patients has been associated with cancer.[270] Almost 80% of malignancy-related hypercalcemia is secondary to the secretion of *parathyroid hormone-related peptide* (PTHrP) by the malignant cells.[270] PTHrP is not detected by clinical laboratory assays for PTH. Numerous types of malignancies are associated with PTHrP-mediated hypercalcemia including breast,[271] renal cell, and ovarian carcinomas[225] and hematologic malignancies.[272]

Increased production of 1,25-$(OH)_2D_3$ by malignant cells is one of the causes of hypercalcemia in patients with lymphomas.[273,274] Finally, osteolytic bone lesions from advanced cancers such as breast, lung, and multiple myeloma frequently result in hypercalcemia.[225]

#### Rhabdomyolysis

Rhabdomyolysis associated with acute renal failure commonly produces hypocalcemia during the initial phase (see "Hypocalcemia"). Approximately 30% of patients, mostly young men, develop hypercalcemia during resolution of the acute renal failure.[275] Release from injured muscles of previously sequestered calcium appears to be the basis for the hypercalcemia.[275,276] PTH is appropriately suppressed according to most[277,278] but not all[279] studies. Vitamin D levels may be elevated[277,279] or suppressed;[252,278] its contribution to the syndrome is unclear. Whatever the underlying mechanism, the hypercalcemia is usually mild and self-limited.[275]

#### Immobilization

Immobilization is associated with hypercalcemia due to increased bone resorption. Risk factors include duration of bed rest, spinal cord injury, multiple skeletal fractures, and underlying disorders leading to increased bone resorption (e.g., Paget disease, malignancy).[280,281] Although

hypercalcemia is usually modest and completely reversible with activity, calcitonin and bisphosphonates can be used with success if treatment is required.[280]

### Medications

A small percentage (5-10%) of patients treated with *lithium* develop hypercalcemia due to lithium-induced hyperparathyroidism.[225] Hyperparathyroidism may or may not be reversible on discontinuation of therapy. *Thiazide diuretics* increase tubular reabsorption of calcium and are well known to cause modest hypercalcemia, which reverts back to normal upon discontinuation of therapy. More severe hypercalcemia should prompt an evaluation for occult hyperparathyroidism. *Vitamin A* may increase osteoclast-mediated bone resorption and cause hypercalcemia.

### Milk-Alkali Syndrome

This syndrome comprises hypercalcemia (often extreme), metabolic alkalosis, and acute renal failure. It is seen in patients who ingest large quantities of alkaline calcium salts (e.g., calcium carbonate), often with vitamin D preparations.[282] Because of the increasing use of these medications to prevent or treat osteoporosis, the incidence of this syndrome, once considered rare, appears to be increasing.[283]

## CLINICAL MANIFESTATIONS

Clinical manifestations of hypercalcemia depend on the rate of increase and absolute level of plasma calcium. The most serious manifestations are *neurologic* and *cardiovascular*. Patients may experience muscle weakness, fatigue, depression, and altered mental status. At extremely high levels, stupor and coma may ensue.[225,230] Prolonged hypercalcemia lasting longer than 36 hours has been associated with the development of critical illness polyneuropathy and myopathy.[268] Hypercalcemia causes an increased rate of cardiac repolarization and results in shortened QT interval. Conduction disturbances and malignant arrhythmias have been reported with hypercalcemia.[284,285]

Hypercalcemia may lead to acute renal failure from volume depletion and renal vasoconstriction and polyuria and polydipsia due to NDI.[225,230] GI symptoms include anorexia, nausea, vomiting, and constipation. Peptic ulcer disease and acute pancreatitis are exceedingly rare, especially in the acute setting.[225]

## DIAGNOSIS

The diagnosis of hypercalcemia often is apparent from the history, with an understanding of the differential diagnosis (see Box 57.11). In cases of sustained or unexplained hypercalcemia, assays for intact PTH and vitamin D metabolites are of great value. An assay for PTHrP rarely is necessary in the evaluation of hypercalcemia in a critically ill patient, because in most patients with hypercalcemia of malignancy, the cancer is advanced and the diagnosis will be obvious when the PTH and vitamin D levels are shown to be suppressed.

## TREATMENT

The treatment strategy for hypercalcemia depends on the severity of the disturbance and on its underlying cause. Identification of the probable cause of the hypercalcemia is important both for the immediate and long-term management.

Mild hypercalcemia (total Ca ≤ 12 mg/dL or 3 mmol/L) is usually caused by primary hyperparathyroidism, thiazide diuretics, calcium and vitamin D supplements, lithium, and immobilization. Treatment should begin with withdrawal of the offending agent (if possible). Volume deficits should be replaced orally if possible. Early mobilization should be encouraged. Loop diuretics should be avoided in patients with mild asymptomatic hypercalcemia as they may exacerbate the volume depletion, leading to increased renal calcium reabsorption.

The immediate treatment of moderate hypercalcemia (total Ca > 12 mg/dL or 3 mmol/L, and ≤ 14 mg/dL or 3.5 mmol/L) includes the measures discussed earlier, as well as intravenous volume expansion with isotonic saline. A loop diuretic will enhance renal excretion of calcium, but care must be taken to avoid volume depletion.

Severe hypercalcemia (total Ca >14 mg/dL or 3.5 mmol/L), even in the absence of signs and symptoms, should be treated as an emergency. Strategies for treatment include (1) enhanced calcium elimination; (2) reduced bone resorption; (3) decreased gut absorption of Ca; and (4) identification and treatment of the underlying cause.

### Enhanced Calcium Elimination

Forced diuresis is the mainstay of treatment. *Volume expansion* with normal saline should be instituted immediately at a rate of 200 to 300 mL/hour. The net fluid balance in adults should be positive approximately 2 L in 24 hours. Caution must be taken to avoid symptomatic volume overload in patients with impaired myocardial performance and/or renal insufficiency.

Once the volume deficit is adequately replaced, *loop diuretics* should be added to enhance renal calcium excretion. A dose of loop diuretic that at least doubles the rate of urine output can be given as often as every 8 hours.

For patients with congestive heart failure unresponsive to diuretics, or with advanced kidney failure, *dialysis* should be considered. Hemodialysis against a solution containing 2.0 mEq/L calcium is very effective in decreasing plasma calcium levels. Lower calcium baths are likely to cause hypotension[286] and precipitate tetany.

### Reduced Bone Resorption

Several agents are available for the management of hypercalcemia. *Bisphosphonates* inhibit the osteoclast functions and number and inhibit bone turnover. They are well tolerated, although nephrotoxicity may develop if administered too quickly.[230] Pamidronate (60-90 mg intravenously) reduces the plasma calcium in 48 to 72 hours and the effect may last for a month.[230] Zoledronic acid may be even more efficacious.[287] With the advent of bisphosphonates, two older agents have fallen into disfavor: *Calcitonin* has rapid onset of action but tachyphylaxis occurs within 48 to 72 hours. *Plicamycin* (formerly mithramycin) has unacceptable liver, renal, and bone marrow toxicity.

### Decreased Gut Calcium Absorption

If endogenous vitamin D overproduction is implicated in the hypercalcemia (e.g., lymphoma, sarcoidosis),

corticosteroids will lower the plasma calcium, at least partly by decreasing gut calcium absorption.

## MAGNESIUM HOMEOSTASIS

Disorders of magnesium balance may be the most commonly seen electrolyte abnormalities in the ICU. Hypomagnesemia, the more common disorder, is seen in 12% of hospitalized patients and up to 65% of critically ill patients.[288-290] Because of magnesium's involvement in a host of critical physiologic functions,[291] its derangement can be expected to result in a variety of manifestations.

### NORMAL MAGNESIUM PHYSIOLOGY

The normal adult total body magnesium content is approximately 24 g or 2000 mEq, 50% to 60% of which is found in bones and 40% to 50% in the intracellular compartment, mainly in the muscles and soft tissues. Only about 1% of total body magnesium is in the extracellular space, the normal concentration range being 1.8 to 2.3 mg/dL (1.5-1.9 mEq/L or about 0.7-1.0 mmol/L).[228] In plasma, 20% to 30% of magnesium is bound to protein, mainly albumin, with the rest (70-80%) in a form that is filterable across the glomerulus.[228] Magnesium is taken up slowly into cells, under no known hormonal control.

Magnesium is a major constituent of chlorophyll, and therefore green vegetables are a good dietary source. Also, magnesium is found in grains, cereals, meat, and seafood.[228,292] The normal adult diet contains about 300 mg of magnesium.[293] Under normal circumstances, about one third of that is absorbed in the small bowel; there is some obligatory secretion in that segment as well, along with some minor reabsorption downstream in the colon.[288] This results in net absorption of about 100 mg/day. (Magnesium absorption is highly dependent on dietary magnesium content, however, and can increase to up to 70-80% of dietary intake under conditions of magnesium deprivation.[228]) Unlike calcium absorption, magnesium absorption from the intestine does not seem to depend significantly on vitamin D.[228,294] The small intestinal secretion of magnesium normally amounts to a loss of only about 20 mg a day. With acute or chronic diarrhea, however, GI losses can be substantial.[228]

The filtered load of magnesium (the product of the glomerular filtration rate and the plasma concentration of ultrafilterable magnesium) is about 2500 mg/day. In order to maintain external magnesium balance, the renal excretion of magnesium must equal the intestinal absorption, or about 100 mg/day. Thus, the fractional excretion of magnesium ($Mg_{excreted} \div Mg_{filtered}$) is about 4% under normal conditions.[228] With magnesium depletion, the fractional excretion of magnesium can fall to less than 1%, and with magnesium loading, it can rise to match the excess in the filtered load.[228] This modulation in magnesium excretion is largely due to changes in plasma magnesium concentration.

The major site of renal magnesium reabsorption (60-70% of the filtered load) is the TAL. This tubular segment is responsible for most of the modulation in magnesium excretion. Magnesium reabsorption here is largely passive and depends on a lumen-positive voltage generated by the (diuretic-inhibitable) NKCC2 channel and potassium recycling via the ROMK channels.[228] This explains why loop diuretics increase urinary magnesium excretion and tend to cause hypomagnesemia. Other factors that inhibit magnesium reabsorption in the TAL include volume expansion, hypercalcemia, hypophosphatemia, and to a lesser extent metabolic acidosis. Conversely, volume depletion, hypocalcemia, and metabolic alkalosis increase magnesium reabsorption. About 10% of filtered magnesium is reabsorbed in the distal convoluted tubule. Reabsorption at this site is stimulated by potassium-sparing diuretics like amiloride.[288]

Magnesium plays a vital role in cellular physiology. It catalyzes over 300 enzymatic reactions and is an integral part of all ATP-dependent reactions.[291] It is involved in synthesis of proteins, energy-rich compounds, and electron and proton transporters; DNA and RNA transcription; translation of mRNA; and regulation of mitochondrial function.[291,295] There is evidence that magnesium helps regulate intracellular calcium concentration, especially in vascular smooth muscle, and thereby affects vascular tone.[295] In vitro studies suggest a role for magnesium in inflammation and immunity, though clinical confirmation is lacking.[295]

### ASSESSMENT OF BODY MAGNESIUM STATUS

Because extracellular magnesium accounts for only about 1% of total body magnesium, plasma magnesium is a poor reflection of body magnesium status. Nonetheless, magnesium status is most commonly assessed by measuring plasma magnesium levels. Like calcium, magnesium circulates in the plasma in bound and free (ionized) forms, the latter being the metabolically active form. Determination of $Mg^{2+}$ is clinically impractical, and there is no reliable correlation with serum albumin concentration. Moreover, the relationship between low $Mg^{2+}$ concentration and increased morbidity and mortality rate in critically ill patients has yet to be clearly established.[296-298] Thus, the available literature does not support the superiority of the measurement of $Mg^{2+}$ over the cheaper and widely available total serum magnesium levels.

The magnesium loading test has been proposed as a more sensitive measure of total body magnesium stores than the plasma magnesium concentration. In theory, magnesium-depleted individuals will translocate more of the administered magnesium load into cells and excrete a lower proportion in the urine over 24 hours.[266,288,295] Because the test requires a 24-hour urine collection, and must be limited to patients who have normal renal function and who are not on medications that affect magnesium excretion (see later), the test is impractical.

### HYPOMAGNESEMIA

#### EPIDEMIOLOGY

Patients with malnutrition, chronic alcoholism, or congestive heart failure on loop diuretics; patients in the postoperative period (especially after open heart surgery); and patients with cancer are at higher risk than general ICU population.[288-290,299]

## CAUSES

The causes of hypomagnesemia can be divided into four main categories: (1) insufficient intake, (2) renal loss, (3) extrarenal loss, and (4) redistribution (Box 57.12).

The renal causes can be distinguished from the others by measuring 24-hour urinary magnesium excretion or, more practically, the fractional excretion of magnesium ($FE_{Mg}$), calculated as follows:[288]

$$FE_{Mg} = \frac{U_{Mg} \times P_{Cr}}{(0.7 \times P_{Mg}) \times U_{Cr}} \times 100$$

where $U_{Mg}$ and $P_{Mg}$ are the urine and plasma concentrations of Mg, respectively, and $U_{Cr}$ and $P_{Cr}$ are the urine and plasma concentrations of creatinine, respectively. ($P_{Mg}$ is multiplied by 0.7, which represents the ultrafilterable fraction of magnesium.) A 24-hour urinary magnesium excretion of more than about 25 mg, or $FE_{Mg}$ greater than 2%, is consistent with renal hypomagnesemia.[225,288] Most hypomagnesemia in critically ill patients is multifactorial.

**Box 57.12 Causes of Hypomagnesemia**

**Deficient Intake**

Magnesium-deficient parenteral nutrition
Protein-calorie malnutrition
Alcoholism

**Renal Loss**

Drug induced
- Loop diuretics
- Thiazide diuretics
- Aminoglycosides
- Amphotericin B
- Cisplatin
- Cetuximab
- Foscarnet
- Pentamidine

Volume expansion
Osmotic diuresis (e.g., hyperglycemia)
Alcohol
Hypercalcemia
Tubular dysfunction
- Recovery from acute tubular necrosis
- Bartter syndrome
- Gitelman syndrome

**Gastrointestinal**

Small intestine resection
Inflammatory bowel disease
Jejunoileal bypass surgery
Diarrhea
Steatorrhea
Malabsorption syndromes
Proton pump inhibitors

**Redistribution**

Acute pancreatitis
"Hungry bone" syndrome

### Deficient Intake

The prevalence of hypomagnesemia is chronic alcoholics is approximately 20% to 30%. Hypomagnesemia in alcoholics is multifactorial and results from decreased dietary intake, increased renal loss, and acute pancreatitis.[288] Parenteral nutrition is an important cause of hypomagnesemia in the ICU. Patients receiving parenteral nutrition have a higher daily magnesium requirement for unknown reasons.[225]

### Gastrointestinal Losses

Diarrheal fluid contains high concentration of magnesium, up to 16 mg/dL,[225,295] and hypomagnesemia is a common finding in patients suffering from acute or chronic diarrhea from any cause. Because intestinal absorption of magnesium occurs primarily in jejunum and ileum, conditions such as celiac disease, inflammatory bowel disease, extensive small bowel resection, and jejunoileal bypass surgery for obesity are frequently associated with intestinal magnesium wasting.[288]

### Renal Losses

Medications are perhaps the most important cause of renal magnesium wasting in critically ill patients. Loop diuretics are commonly used at high doses. Aminoglycosides may cause asymptomatic hypomagnesemia 3 to 4 days after initiation of therapy; typically it resolves after cessation of therapy.[225,300] Almost all patients who receive cisplatin develop renal magnesium wasting and hypomagnesemia, which may persist for months after discontinuation of therapy.[301] Most of the patients who receive intravenous pentamidine therapy develop renal magnesium wasting and hypomagnesemia that may last for 1 to 2 months after cessation of the therapy.[225] The renal magnesium wasting associated with chronic alcohol use may take up to a month to resolve with abstinence.[288]

### Redistribution

Hypomagnesemia is reported in up to 20% of patients with acute pancreatitis.[290,295] The proposed mechanism is saponification of necrotic fat with magnesium and calcium. The mechanism of hypomagnesemia with the "hungry bone" syndrome (following parathyroidectomy for hyperparathyroidism) is rapid bone uptake of magnesium during remineralization.

## CLINICAL MANIFESTATIONS

Hypomagnesemia in critically ill patients has been associated with a twofold increase in mortality rate, even after adjustment for severity of illness.[302] (The observation that magnesium supplementation has not been shown to improve outcome[288] suggests that hypomagnesemia may be a marker for pejorative conditions not captured by severity of illness scores.)

The signs and symptoms of hypomagnesemia are cardiovascular, neuromuscular, and metabolic, and are shown in Box 57.13.[225,288,291,295] There is little evidence that hypomagnesemia is associated with arrhythmias in otherwise healthy individuals. In the setting of acute myocardial ischemia, however, even mild hypomagnesemia has been associated with increased frequency of ventricular arrythmias.[288] Results of recent large clinical trials, however, have shown no benefit to magnesium supplementation in this setting in the absence

**Box 57.13 Clinical Manifestations of Hypomagnesemia**

**Cardiovascular**

Ventricular arrhythmias
- Torsades de pointes
- Ventricular fibrillation; premature ventricular contractions
- Increased digitalis toxicity

Conduction disturbances
- Prolonged QT interval
- Prolonged QRS duration
- ST-segment depression
- Peaked T wave

**Neuromuscular**

Muscle weakness
Tetany
Horizontal and vertical nystagmus
Choreoathetoid movements
Seizures

**Metabolic**

Hypokalemia, refractory
Hypocalcemia, refractory

**Box 57.14 Causes of Hypermagnesemia**

**Patients with Renal Insufficiency**

Magnesium-containing antacids (e.g., magnesium aluminum hydroxide)
Magnesium-containing laxatives or enemas (e.g., magnesium citrate)

**Patients with Normal Renal Function**

Treatment of preeclampsia or eclampsia
Treatment of hypomagnesemia

**Miscellaneous**

Hypothyroidism
Hyperparathyroidism
Addison's disease
Lithium treatment

of overt hypomagnesemia.[295] Torsades de pointes is a malignant ventricular arrhythmia associated with magnesium deficiency or drugs that prolong the QT interval. Magnesium is the treatment of choice. Magnesium supplementation after cardiopulmonary bypass may reduce the frequency of ventricular ectopy.

The hypocalcemia associated with hypomagnesemia is caused by both hypoparathyroidism and bone resistance to PTH. The hypokalemia is caused by renal potassium wasting and will not resolve until the hypomagnesemia is corrected.[303,304]

### TREATMENT

In patients who have malignant cardiac arrhythmias (ventricular fibrillation or torsades de pointes) or seizure attributed to hypomagnesemia, intravenous magnesium (2 g of magnesium sulfate over minutes) must be given immediately (see Chapter 31 for details).

Less urgent cases, but those in which signs and symptoms are present, may be treated with magnesium sulfate 6 g intravenously in the first 24 hours followed by 3 to 4 g daily for the next 2 to 6 days.[225,288,295] Because translocation of magnesium into cells is a slow process, and because urinary excretion is proportional to the plasma magnesium level, more rapid infusion rates are associated with urinary magnesium wasting that defeats the purpose of the therapy. Effective intravenous infusions should be given over 8 to 12 hours.[288] For patients with impaired renal function, the dose should be reduced by 50% to 75% and serum magnesium levels should be monitored frequently. Patients should be monitored closely for symptoms and signs of hypermagnesemia (see later).

Patients with refractory hypokalemia in the setting of hypomagnesemia, who are receiving high doses of potassium, must be monitored closely for the development of hyperkalemia once the magnesium is being replenished.

For mild asymptomatic hypomagnesemia, patients who can tolerate oral medication should receive oral magnesium salts (e.g., magnesium chloride, 500 mg slow release tablets, 10-12 per day in divided doses). High doses of oral magnesium salts may cause diarrhea.

## HYPERMAGNESEMIA

### CAUSES

Hypermagnesemia is much less common than hypomagnesemia. Patients with normal renal function have prodigious capacity to excrete excess magnesium through the kidneys.[225] Thus, hypermagnesemia is seen only in patients with compromised renal function receiving enteral or parenteral Mg or in patients with normal renal function receiving massive exogenous magnesium (e.g., treatment for preeclampsia and eclampsia).[225] The causes of hypermagnesemia are shown in Box 57.14.

### CLINICAL MANIFESTATIONS

The clinical manifestations of hypermagnesemia (Box 57.15) are largely due to the effects on the heart, nerve, and smooth muscle. Initial manifestations, with plasma concentrations of 4 to 6 mg/dL, include nausea and vomiting, hypotension, and flushing. More severe effects, including death,[305] are seen with levels exceeding 6 mg/dL.

### TREATMENT

Treatment of hypermagnesemia depends on severity of symptoms and the patient's renal function. Patients with adequate renal function and mild asymptomatic hypermagnesemia require no treatment except to remove all sources of exogenous magnesium. The half-time of elimination of magnesium is about 28 hours.[225] Magnesium excretion may be enhanced by saline infusion and the use of loop diuretics.[225] (Care must be taken to prevent hypokalemia and metabolic alkalosis.) Patients with symptomatic hypermagnesemia, especially with cardiovascular manifestations, require urgent treatment. The recommended therapy is calcium gluconate 1 g intravenously over 5 minutes.

Patients with acute or chronic renal failure and symptomatic hypermagnesemia will require dialysis to remove excess

**Box 57.15 Clinical Manifestations of Hypermagnesemia**

Cardiovascular
- Hypotension
- Facial flushing
- Bradycardia
- Sinoatrial or atrioventricular heart block
- Asystole

Gastrointestinal
- Nausea and vomiting
- Ileus

Neuromuscular
- Hyporeflexia
- Flaccid skeletal muscle paralysis
- Respiratory muscle weakness and paralysis
- Lethargy
- Coma

Urinary retention

magnesium. Hemodialysis removes magnesium efficiently, yielding a 30% to 50% reduction in predialysis serum magnesium levels after a 3- to 4-hour treatment.[225]

## PHOSPHORUS HOMEOSTASIS

Phosphorus has an essential role in normal physiology. It is necessary for skeletal integrity; energy economy (formation of high-energy phosphate bonds); nucleic acid, lipid, and protein structure; cell signaling; and buffering.[228] It is not surprising, therefore, that disorders of phosphorus homeostasis have diverse manifestations.[306-308] Hypophosphatemia is considerably more common in hospitalized and critically ill patients than hyperphosphatemia.

### NORMAL PHOSPHORUS HOMEOSTASIS

Total body phosphorus amounts to about 700 g in an adult. About 85% resides in the skeleton, about 15% in soft tissues, and only about 1% in blood.[227] Circulating phosphorus is mostly in the form of inorganic phosphates. The normal plasma concentration of phosphorus is 2.5 to 4.5 mg/dL, also expressed as a phosphate concentration of 0.9 to 1.45 mmol/L. (Phosphate concentration should not be expressed in mEq/L because the average valence of plasma phosphates—a mixture of $HPO_4^{2-}$ and $H_2PO_4^-$—changes with pH.[309]) Of that circulating phosphorus, about 75% is free and ultrafilterable; 25% being protein bound.[228]

A normal adult diet includes about 1000 mg of phosphorus per day. Stool contains about 300 mg, so the net absorption (mostly in the small intestine under the influence of vitamin D) is about 70%. The dietary and secreted phosphorus may be bound into insoluble, nonabsorbable salts by cations such as $Al^{3+}$, $Ca^{2+}$, and $Mg^{2+}$. Thus, the kidney is responsible for excreting about 700 mg phosphorus per day. Almost all phosphorus reabsorption takes place in the proximal tubule. The most important regulators of renal phosphorus excretion are PTH, fibroblast growth factor (FGF)-23, and dietary phosphorus content. PTH increases phosphorus excretion.[227] FGF-23, a phosphotonin released by osteocytes and osteoblasts in bone, increases urinary phosphorus excretion.[310] Renal excretion of phosphorus is proportional to the dietary intake. Other factors that increase renal phosphorus excretion include extracellular volume expansion, acute hypercalcemia, diuretics, and glucocorticoids.[227,228] Acid-base disorders have a variable effect on phosphorus reabsorption depending on their direction and duration,[227,228] with one exception: Respiratory alkalosis causes a marked decrease in renal phosphorus excretion by causing redistributive hypophosphatemia[307] (see later).

Phosphorus homeostasis depends on PTH, FGF-23, and vitamin D. PTH and FGF-23 cause phosphaturia by decreasing renal proximal tubule reabsorption. Active vitamin D inhibits PTH release. Vitamin D activation (1-α-hydroxylation) in the kidney is inhibited by FGF-23 and hyperphosphatemia. This, in turn, reduces intestinal phosphorus absorption and allows increased PTH secretion, causing phosphaturia and returning plasma phosphorus toward normal. Hypophosphatemia reverses this physiology, allowing increased gut absorption and reduced renal excretion of phosphorus.

### HYPOPHOSPHATEMIA

Hypophosphatemia is common in critically ill patients. It has been reported in 29% of adult surgical patients (and 45% of patients with one or more risk factors for hypophosphatemia) and—liberally defined—in 76% of pediatric ICU patients.[311] Patients with malnutrition, uncontrolled diabetes mellitus, sepsis, and chronic alcoholism are at high risk for hypophosphatemia.[312] It is associated with a marked increase in mortality rate in patients with sepsis,[313] and serum phosphorus concentration is inversely correlated with APACHE II after liver resection.[314] In these situations, the serum phosphorus concentration probably is a marker of severity of illness. If severe, however, hypophosphatemia itself may cause serious complications.

#### CAUSES OF HYPOPHOSPHATEMIA

The causes of hypophosphatemia classically are divided into three general categories: (1) redistribution from the extracellular to the intracellular space, (2) increased renal excretion, and (3) decreased intestinal absorption (Box 57.16). It is important to recognize that many factors have several different effects on phosphorus homeostasis.

##### Redistribution

*Respiratory alkalosis* causes intracellular phosphate shift (by stimulating glycolysis) and can cause severe symptomatic hypophosphatemia. Respiratory alkalosis is commonly encountered in ICU patients because of sepsis or liver failure and is seen in patients requiring mechanical ventilation; in the latter case, the degree of hypophosphatemia is proportional to the pH.[225,315] *Sepsis* is commonly associated with hypophosphatemia, probably due to hyperventilation and respiratory alkalosis. Rapid *refeeding* of patients with malnutrition may result in significant hypophosphatemia due to insulin-mediated intracellular phosphate shift. In one study of ICU patients, refeeding hypophosphatemia developed in 34% of patients after 48 hours of starvation and was predicted by the prealbumin concentration. Profound hypophosphatemia (<1 mmol/dL) occurred in 10%

**Box 57.16 Cause of Hypophosphatemia**

**Redistribution**

Acute respiratory alkalosis
Refeeding syndrome
Treatment of diabetic ketoacidosis
"Hungry bone" syndrome—postparathyroidectomy
Leukemia

**Increased Renal Excretion**

Hyperparathyroidism
Vitamin D deficiency or resistance
Volume expansion
Postobstructive diuresis
Recovery from acute tubular necrosis
Fanconi syndrome
Postrenal transplantation
Drugs
  Acetazolamide
  Corticosteroids
Inherited disorders
Tumor-induced osteomalacia

**Decreased Intestinal Absorption**

Malnutrition
Phosphate-binding medications
Chronic diarrhea
Chronic alcoholism

**Box 57.17 Clinical Manifestations of Hypophosphatemia**

Skeletal muscle
  Weakness
  Rhabdomyolysis
Decreased cardiac output
Hematologic
  Erythrocytes
  Decreased 2,3-DPG (2,3-diphosphoglycerate)
  Decreased tissue oxygen delivery
  Spherocytosis
  Hemolysis
  Impaired leukocyte function
  Impaired platelet function
Neurologic
  Anorexia
  Irritability
  Confusion
  Paresthesias
  Ataxia
  Seizure
  Coma
Skeletal
  Bone pain
  Pseudofractures
  Osteomalacia
Insulin resistance

of patients.[316] Patients with anorexia nervosa, uncontrolled diabetes mellitus, chronic malnutrition, and chronic alcoholism are at a particularly high risk of developing refeeding syndrome. *Leukemia* in the leukemic phase[317] and with rapid leukocyte reconstitution after bone marrow transplant[318] has been reported to cause severe redistributive hypophosphatemia.

*DKA* is associated with phosphorus efflux from cells and increased urinary phosphate excretion, resulting in severe total body phosphorus depletion (often with a deceptively normal presenting serum phosphorus concentration).[307] Initiation of insulin therapy in such patients results in intracellular phosphate shift and can result in profound, symptomatic hypophosphatemia.[307]

### Increased Renal Excretion

Any cause of *primary hyperparathyroidism* will cause phosphaturia and tend to cause hypophosphatemia. Hyperparathyroidism due to hypocalcemia or *vitamin D deficiency* or *resistance* is similarly associated with hypophosphatemia. The exception is the secondary hyperparathyroidism of chronic kidney disease, in which hyperphosphatemia due to decreased renal phosphorus elimination is characteristic. Vitamin D deficiency or resistance also causes hypophosphatemia from decreased intestinal phosphate absorption. Extracellular volume expansion increases the filtered phosphorus load and dilutes the luminal concentration of phosphorus, resulting in phosphaturia. *Ethanol* and *glycosuria* both decrease proximal tubule phosphate reabsorption.[225,307] All *diuretic drugs*, but particularly those with proximal tubular effects such as acetazolamide and, to a lesser degree, thiazides, cause phosphaturia.

### Decreased Intestinal Absorption

Salts of $Al^{3+}$ and $Ca^{2+}$, formulated for oral administration as antacids or as phosphate-binding medications, can cause malabsorptive hypophosphatemia. Chronic diarrhea and steatorrhea may cause reduced intestinal phosphate absorption directly and by way of vitamin D deficiency and cause hypophosphatemia.

The hypophosphatemia commonly associated with *chronic alcohol ingestion* is multifactorial. Dietary phosphorus deficiency, malabsorption, antacid ingestion, hypocalcemia, secondary hyperparathyroidism, hypomagnesemia, and an ethanol-induced renal tubular defect all have been implicated.[307]

## CLINICAL MANIFESTATIONS

Important clinical manifestations of hypophosphatemia are shown in Box 57.17. Most patients are asymptomatic until plasma phosphorus falls below 1.5 mg/dL or about 0.5 mmol/L. The most severe manifestations, such as hemolysis, spontaneous rhabdomyolysis, seizure, or coma, are not commonly seen with phosphorus above 1 mg/dL (0.3 mmol/L). Acute clinical manifestations are thought to be largely due to altered cellular energy economy.[225,227,306,307]

## TREATMENT

The therapy of hypophosphatemia starts with its prevention. In critically ill patients, this depends on recognition and correction of the factors that lead to hypophosphatemia. The astute clinician will be able to anticipate the development of hypophosphatemia (in refeeding, for example), monitor the patient appropriately, and supplement phosphorus accordingly. Patients on total parenteral nutrition

should receive adequate phosphorus for their level of renal function (see Chapter 82).[309]

The exact method of phosphorus supplementation in hypophosphatemia depends on the severity of the disturbance and the patient's underlying condition. In mild to moderate hypophosphatemia (>1.5 mg/dL or about 0.5 mmol/L) oral replacement is usually sufficient. Skim milk is an excellent source of phosphorus and provides 900 mg/L of inorganic phosphate. In patients who cannot tolerate milk, oral sodium phosphate, formulated to provide 250 mg of phosphate in each tablet, can be used. Alternatively, Fleet Phospho-soda can be give to provide 60 mmol of phosphorus per day, divided into three doses of 5 mL each.[227] Supplementation should continue for several days in order to replenish phosphorus deficits adequately. Administration of sufficient doses of oral phosphorus preparations very commonly causes diarrhea, limiting its usefulness.

Patients with severe hyperphosphatemia (<1.5 mg/dL), or those for whom the enteral route is not an option, require intravenous phosphorus repletion. In such patients, the recommended dose is 2.5 to 5.0 mg (0.08-0.16 mmol) per kg body weight over 6 hours, doses at the higher end of the range being reserved for profound, symptomatic hypophosphatemia.[227,309] A recent study used a more aggressive, weight-based protocol in critically ill patients and found it to be safe and effective.[319] Clinicians should recognize that the administered intravenous phosphorus can complex with circulating calcium, leading to a decrease in $Ca^{2+}$ (with attendant hypotension and tetany) and metastatic calcification. The use of potassium salts of phosphate for repletion of phosphorus deficits has been associated with dangerous hyperkalemia. For that reason, potassium deficits and phosphorus deficits should be treated separately.[309]

## HYPERPHOSPHATEMIA

Hyperphosphatemia (plasma phosphorus > 5.0 mg/dL or a phosphate concentration > 1.6 mmol/L) most often is associated with renal dysfunction. Massive influx of phosphorus into the extracellular space, however, either from endogenous sources or exogenous, can overwhelm normal renal excretory mechanisms and lead to severe hyperphosphatemia.

### CAUSES OF HYPERPHOSPHATEMIA

Hyperphosphatemia may be caused by (1) redistribution of phosphorus from the intracellular to the extracellular space, (2) increased phosphorus intake, and (3) decreased renal excretion of phosphorus (Box 57.18). It is important to recognize that most hyperphosphatemia is multifactorial.

#### Redistribution

Hyperphosphatemia is a common complication of the *tumor lysis syndrome.*[72] Similarly, rhabdomyolysis often is associated with hyperphosphatemia, especially when it is complicated by acute renal failure.[74,320] Less commonly recognized causes of redistributive hyperphosphatemia include acute and chronic respiratory acidosis, acute pancreatitis,[321] DKA,[322] and lactic acidosis.[323]

**Box 57.18 Causes of Hyperphosphatemia**

- Redistribution
  - Tumor lysis syndrome
  - Rhabdomyolysis
  - Pancreatitis
  - Respiratory acidosis
  - Lactic acidosis
  - Diabetic ketoacidosis
- Increased intake
  - Phosphate-containing enemas and laxatives
  - Intravenous phosphate
  - Hypervitaminosis D
- Decreased renal excretion
  - Acute renal failure
  - Chronic kidney disease
  - Hypoparathyroidism
- Pseudohyperphosphatemia

#### Increased Intake

Exogenous administration of phosphorus is unlikely to cause hyperphosphatemia unless renal function is compromised. Several cases have been reported of potentially life-threatening hyperphosphatemia and hypocalcemia after the use of phosphate-containing laxatives and enemas, especially in children and elderly.* Overly aggressive parenteral phosphorus supplementation can cause hyperphosphatemia. Hypervitaminosis D causes increased intestinal uptake of phosphorus and a decrease in PTH, both of which predispose to hyperphosphatemia.

#### Decreased Renal Excretion

Acute renal failure is associated with elevated phosphate levels due to inability of kidneys to excrete phosphate load. This is particularly pronounced in patients in whom acute renal failure is caused by the tumor lysis syndrome or rhabdomyolysis. Advanced chronic kidney disease (GFR < 25 mL/minute) commonly is associated with hyperphosphatemia. Such patients are particularly susceptible to developing severe and life-threatening hyperphosphatemia if they are exposed to acute increase in serum phosphate levels. Hypoparathyroidism of any cause is associated with impaired renal phosphorus excretion.

#### Pseudohyperphosphatemia

Spurious increases in the measured plasma phosphorus concentration are reported to be caused by contamination of the blood sample with phosphate-buffered saline as a diluent for heparin[326] or during sample processing by the laboratory.[327] Even microliter volumes of the contaminant can cause significant elevations in the measured phosphorus.[326] Paraproteinemia can also cause pseudohyperphosphatemia.

### CLINICAL MANIFESTATIONS OF HYPERPHOSPHATEMIA

Phosphate complexes with circulating calcium, reducing the concentration of $Ca^{2+}$. Thus, most of the clinical

*248, 250, 251, 324, 325.

consequences of hyperphosphatemia are the same as those of hypocalcemia (see earlier). In addition, ectopic deposition of calcium phosphate salts can occur, especially when the calcium-phosphorus product exceeds 70 mg/dL.[227] Such ectopic calcification in the heart can cause conduction and rhythm disturbances.[328]

Because phosphate is an "unmeasured ion," hyperphosphatemia causes increases in the anion gap. Extreme hyperphosphatemia can cause shocking elevations in the anion gap. One case of hyperphosphatemia from Phospho-soda intoxication (serum phosphorus 62.5 mg/dL) was associated with an anion gap of 51 mmol/L.[329] In order to estimate the contribution of phosphorus to the anion gap, one must know not only the plasma concentration of phosphorus but the pH, because the valence of phosphate varies with pH, from 1.8 mEq/mmol at pH 7.4 to 1.6 mEq/L at pH 7.0.[309] Because extreme hyperphosphatemia can be caused by lactic or ketoacidosis (see earlier), an elevated anion gap in the setting of hyperphosphatemia should never be attributed to the hyperphosphatemia itself without further investigation.

### TREATMENT OF HYPERPHOSPHATEMIA

Treatment of hyperphosphatemia consists of reducing the phosphate intake and enhancing the removal of excess phosphate. If the patient is taking oral diet, dietary phosphate should be restricted to less than 800 mg/day. Oral phosphate binders can be added with meals to decrease intestinal phosphate absorption.

Patients with normal renal function can be treated with saline diuresis to increase renal phosphate excretion. Acetazolamide can be added to enhance phosphaturia, taking care to avoid a metabolic acidosis. Patients with severe hyperphosphatemia with coexisting renal failure may require renal replacement therapy in the form of intermittent or continuous hemodialysis.

## KEY POINTS

- Acid-base disorders often provide a window into underlying pathology. Optimal diagnosis of acid-base disorders requires familiarity with the rules of normal compensation and the pitfalls characteristic of critical illness.
- Acute hyperkalemia may result from exogenous potassium administration or redistribution from cells. Acute hypokalemia always is caused by redistribution.
- Patients, particularly women, are predisposed to catastrophic hyponatremia if hypotonic fluids are administered in the postoperative period.
- The treatment of acute symptomatic hyponatremia is largely independent of its cause, whereas the treatment of chronic hyponatremia depends critically on the underlying pathophysiology.

## KEY POINTS (Continued)

- Hypernatremia in hospitalized patients should be considered iatrogenic, reflecting insufficient recognition of the causes of water loss and inadequate water replacement in vulnerable patients.
- Plasma calcium concentration, corrected for the plasma albumin concentration, correlates poorly with $Ca^{2+}$ in critically ill patients. If possible, $Ca^{2+}$ should be directly measured when considering disorders of calcium homeostasis.
- The clinical manifestations of many metabolic disorders have common features (e.g., hypocalcemia, hypomagnesemia, hyperphosphatemia, metabolic alkalosis) relating to their overlapping pathophysiology.

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