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Fluids, Electrolytes, and Acid-Base Disorders

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CONTENTS

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Objectives

Describe factors that influence fluid movement between the intracellular fluid (ICF) and extracellular fluid (ECF) compartments.

Calculate replacement and maintenance fluid requirements for various patient populations.

Recommend appropriate treatment for common electrolyte abnormalities.

Evaluate and treat acid-base disorders based on the clinical presentation and accompanying laboratory data.

Test Your Knowledge Questions

1. The administration of 1 liter 0.9% sodium chloride (NaCl) to a normonatremic patient will increase the intravascular and interstitial fluid compartments by:

A. 1000 mL and 0 mL, respectively

B. 0 mL and 1000 mL, respectively

C. 750 mL and 250 mL, respectively
D. 250 mL and 750 mL, respectively

2. Assuming the same weight and serum sodium concentration, which of the following patients has the greatest free water deficit?

A. A 35-year-old man
B. A 75-year-old man
C. A 35-year-old woman
D. A 75-year-old woman

3. A patient with severe intractable nausea and vomiting is at risk for which of the following acid-base disorders?

A. Hyperchloremic metabolic alkalosis
B. Hyperchloremic metabolic acidosis
C. Hypochloremic metabolic alkalosis
D. Hypochloremic metabolic acidosis

Test Your Knowledge Answers

1) The correct answer is D. A solution of 0.9% NaCl (154 mEq/L) is isotonic and, therefore, does not contribute to an osmotic gradient. Isotonic saline enters and remains in the ECF. Thus, administering 1 liter 0.9% NaCl expands the ECF by 1 liter. The intravascular volume accounts for 25% of the ECF and will expand by 250 mL. The remaining 750 mL will be distributed to the interstitial fluid compartment.
2) The correct answer is A. Free water deficit is calculated as follows:
   Free Water Deficit = TBW × [1 – (140/Serum Sodium)]
   where free water deficit and total body water (TBW) are measured in liters and serum sodium is measured in mEq/L. Given the same body weight and serum sodium concentration, the only variable is the percentage of TBW. The percentage of TBW increases as the proportion of lean body mass (LBM) to adipose tissue increases. In general, the percentage of TBW decreases with age and is lower in females than in males. Younger men would be expected to have the highest proportion of LBM and the highest percentage of TBW and would therefore have the largest free water deficit.
3) The correct answer is C. Gastric fluids contain approximately 130 mEq chloride (Cl^-) per liter and are very acidic (pH 1 to 2). Losing large amounts of gastric fluids via vomiting, especially for a prolonged period of time, can result in a hypochloremic metabolic alkalosis as the loss of acid from the stomach leaves the body with a relative excess of alkali.

Background

Body fluids differ with regard to their distribution and the substances dissolved within them. These substances include electrolytes and nonelectrolytes, such as glucose and proteins. Even with variations in daily intake, fluid and electrolyte balance is achieved through a complex system of regulatory mechanisms that maintain an environment conducive to normal cell function. Because nearly all biochemical reactions are influenced by hydrogen ion concentration, cell function also depends on acid-base homeostasis. In practice, disruptions of fluid, electrolyte, and acid-base homeostasis are common, and the results can profoundly affect organ systems. This chapter discusses normal body requirements, the distribution and homeostasis of water and electrolytes, as well as the evaluation and treatment of common fluid, electrolyte, and acid-base disorders.

Fluid Compartments

Water, the most abundant substance in the body, constitutes approximately 50% to 60% of body weight. TBW is a function of weight, age, sex, and the relative amount of body fat. Of all body tissues, adipose tissue is the least hydrated. Thus, individuals with more body fat have proportionally less TBW content.1

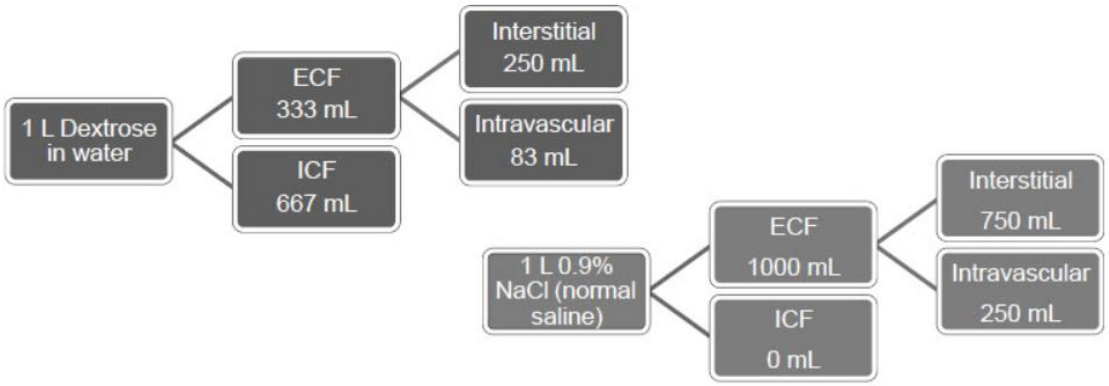
TBW is distributed among the ICF, ECF, and transcellular fluid (TCF) compartments. Approximately two-thirds of TBW is contained in ICF and the remaining one-third is in ECF. The TCF compartment accounts for about 3% of TBW and includes specialized fluids such as cerebrospinal fluid, the aqueous humor of the eye, and secretions of the gastrointestinal (GI) tract. The ECF is the most clinically important fluid compartment because it contains the intravascular and interstitial spaces.2

Osmotic pressure, the pressure required to maintain equilibrium with no net movement of solvent, is of prime importance in determining the distribution of water between the extracellular and intracellular spaces. Each compartment contains a major osmotically active solute that ultimately determines its osmotic pressure. Sodium is the dominant extracellular osmole holding water in the extracellular space, whereas potassium is the primary intracellular osmole holding water within the cells. Activity of cellular sodium-potassium-adenosine triphosphatase (Na+-K+-ATPase) pumps allows for the maintenance of these unique solute compositions of the ECF and ICF and plays a key role in the regulation of cell volume.1

To better illustrate the dynamics of water distribution between the ICF and ECF, consider the exogenous administration of intravenous (IV) fluids. If 1 liter 5% dextrose in water (solute-free water) is infused, the dextrose is metabolized and the resulting water distributes proportionately to all fluid compartments. In other words, two-thirds (667 mL) of the fluid distributes into the ICF and one-third (333 mL) distributes into the ECF. Of the one-third distributed into the ECF, 25% (85 mL) remains in the intravascular space. In contrast, IV administration of 1 liter 0.9% NaCl (isotonic saline) is distributed completely to the ECF where one-quarter (250 mL) remains in the intravascular space. Thus, when choosing IV fluids. isotonic saline is approximately 3 times more efficient than 5% dextrose in water at expanding the intravascular space. Alternatively, the addition of hypertonic fluid (eg, 3% NaCl) to the ECF increases its tonicity, establishing an osmotic gradient that results in the movement of water out of cells and into the ECF until

osmotic equilibrium is attained. The osmolalities of both compartments increases—that of the ECF because of the addition of NaCl and that of the ICF from water loss. The volume change is proportional to the degree of increase in ECF osmolality (Figure 7-1).3

FIGURE 7-1 Water Distribution to the Extracellular Fluid and Intracellular Fluid and Composition of Commonly Used Intravenous Fluids



Solution	Dextrose, g/L	Sodium, mEq/L	Chloride, mEq/L	Tonicity	Free Water, mL/L
D5W (5% dextrose)	50	0	0	Hypotonic	1000
0.45% NaCl (½ normal saline)	0	77	77	Hypotonic	500
0.9% NaCl (normal saline)	0	154	154	Isotonic	0
3% NaCl (hypertonic saline)	0	513	513	Hypertonic	−2331
Lactated Ringer's	0	130	109	Isotonic	0

ECF, extracellular fluid; ICF, intracellular fluid; NaCl, sodium chloride.

Although osmotic forces determine the distribution of water between the ICF and ECF spaces, the plasma oncotic and hydrostatic pressures govern the movement of fluid between the plasma and interstitial fluid. These forces are generally balanced, and compartment sizes are therefore maintained in a steady state despite large fluid exchanges between compartments. Disruption in oncotic and/or hydrostatic pressure results in a net flow of fluid from one compartment to another. When these disruptions favor a plasma-to-interstitial fluid shift, third spacing, the accumulation of excess fluid in the interstitial space (edema) or in the potential fluid spaces (effusion),4 occurs. Although the fluid will be absorbed back into the extracellular compartment over a period of days to weeks, the acute reduction in blood volume, if not replaced, can lead to severe volume depletion. This phenomenon is common during critical illness when capillary permeability increases, resulting in the leakage of albumin from the intravascular to the interstitial space and reduced plasma oncotic pressure, which favors the movement of fluid from the intravascular to the interstitial space. Third spacing can occur with intestinal obstruction, severe acute pancreatitis, crush injuries, bleeding, peritonitis, obstruction of a major venous system, and other conditions.

Fluid Balance

After taking into account insensible losses, fluid gains (input) should be in balance with fluid losses (output) over a period of several days. On average, a healthy adult requires 30 to 40 mL of fluid per kg of body weight per day to maintain this balance.5,6 However, weight-based estimates tend to overestimate fluid requirements for large individuals and underestimate them for small people. Water intake is derived primarily from the diet (including water generated from the oxidation of carbohydrates, proteins, and fats), whereas various sources of water loss contribute to total fluid output. In most cases, sensible (easily measurable) losses from the GI tract and kidneys account for most fluid loss, although insensible (not easily measurable) losses from the lungs and skin can contribute up to 1 L/d.1

Calculating Fluid Requirements

Various approaches are used to estimate fluid requirements in adults. Formulas used to calculate daily fluid requirements should account for the patient's weight, age, and clinical status. Water is needed to support an individual's LBM, which fluctuates with weight and decreases with age. Some formulas are energy based (1 mL per kcal consumed7 or 1 mL per kcal required8), and others are weight based, such as the simple calculation of 25 to 35 mL/kg.9 Some weight-based calculations set a minimum of 1500 mL/d.10 For example, the Holliday-Segar formula11 is 1500 mL for the first 20 kg body weight plus 20 mL/kg for the remaining kg of body weight.

Weight-based formulas may lead to fluid overload in patients with severe cardiac issues or kidney distress.8 Fluid-restricted patients whose physical activity is limited may benefit from use of the energy-based formulas to prevent fluid overload.8

To prevent dehydration, some experts discourage the use of energy-based formulas in individuals age 65 years or older and recommend the use of one of the following formulas for the older adult: (1) an adjusted Holliday-Segar formula (1500 mL for the first 20 kg body weight plus 15 mL/kg for remaining body weight) or (2) 30 mL/kg with a minimum of 1500 mL; or (3) 1500 to 2000 mL/d.10,12–14

Nutrition support clinicians must ensure that sufficient fluid is given to individuals who are vulnerable to dehydration, cannot express thirst, or are in a setting where the signs of dehydration are not closely monitored. When patients discharged home or to an alternate care facility receive nutrition support with inadequate fluid, they can become rapidly dehydrated and suffer symptoms such as hypotension, confusion, extreme thirst, and constipation that may not initially be attributed to dehydration.

Some practitioners have found clinical success by calculating fluid needs (mL/d) with the following 2 formulas and then using the average of the results.

Equation 1 (based on body weight and age):9

Ages 18–55 years: 35 mL × Body Weight (kg)

Ages 56–75 years: 30 mL × Body Weight (kg)

Ages >75 years: 25 mL × Body Weight (kg)

Fluid-restricted adults (eg, those with kidney disease, cardiac disease, or fluid overload states): ≤25 mL × Body Weight (kg)

Equation 2 (Holliday-Segar formula adjusted for age):12–14

Ages ≤50 years: 1500 mL for first 20 kg Body Weight + [20 mL × Remaining Body Weight (kg)]

Ages >50 years: 1500 mL for first 20 kg Body Weight + [15 mL × Remaining Body Weight (kg)]

Very muscular, active individuals likely require more water than in the volume estimated by these equations because they have an increased percentage of LBM. Conversely, the use of an obesity-adjusted weight should be used to calculate the fluid needs of obese individuals to account for their increased percentage of body fat. When an individual gains excess weight, about 75% is typically fat tissue and 25% is lean (although the proportions can vary widely among individuals).15 An obesity-adjusted weight is often used when an individual's weight is equal to or greater than 125% ideal body weight (IBW), unless the excess weight is due to muscle mass. For this method, which has not been validated but is in common use, IBW is calculated as follows:

Women: IBW (lb) = 100 lb for 5 ft in height + 5 lb for each inch over 5 ft

Men: IBW (lb) = 106 lb for 5 ft in height + 6 lb for each inch over 5 ft

Then, the obesity-adjusted weight is obtained by subtracting the IBW (± 10%) from the actual weight and adding back one-quarter (25%) of the difference to the IBW:

Obesity-Adjusted Body Weight (lb) = [(Actual Weight – IBW) × 0.25] + IBW

The adjusted weight is then converted to kilograms to perform the fluid calculations. For example, to estimate the fluid requirements for a 61-year-old woman who is 5 feet, 4 inches tall and weighs 160 pounds, the clinician would proceed as follows:

Calculate IBW: 100 lb + (5 × 4 lb) = 120 lb

Calculate obesity-adjusted weight: [(160 lb – 120 lb) × 0.25] + 120 lb = 130 lb (59 kg)

Calculate fluid requirements using Equation 1: 30 mL × 59 kg = 1770 mL/d

requirements using Equation 2: 1500 mL + [15 × (59 kg –20 kg)] = 2085 mL/d

Calculate fluid Calculate the mean of the results from steps 3 and 4: (1770 mL/d + 2085 mL/d)/2 = ~1900 mL/d

For obese, chronically inactive individuals, an additional approach is to calculate both energy and fluid requirements using IBW instead of an obesity-adjusted weight.

Additional fluid must be provided for patients with severe diarrhea or emesis; large draining wounds; excessive diaphoresis; constant drooling; paracentesis losses; drains; high gastric, fistula, and ostomy outputs; or persistent fevers. Fluid needs increase by 7% for each °F above normal (13% for each °C above normal). Women who are lactating also have increased fluid requirements.

Fluid losses should be measured when possible, but outputs are not always collectable. Weighing wound dressings before and after placement may help determine the fluid loss from open wounds. Excessive diaphoresis that soaks bed linens is usually equal to at least 1 liter of fluid.16

Fluids in the Nutrition Support Prescription

Parenteral nutrition (PN) formulas can usually meet a patient's calculated fluid needs. For patients receiving enteral tube feedings, the tube feeding formula provides a portion of the fluid needs, but additional water is usually required. Enteral tube feeding formulas are 67% to 87% water (approximately 160 to 210 mL water per 8-oz container). The remainder is solids consisting of macro- and micronutrients (see Chapter 11). The more energy-dense a formula is, the lower the percentage of water volume is. Manufacturers do not usually list water content on the formula label, although the information is available elsewhere in product documentation. After accounting for the water in the parenteral or enteral formula, the patient's remaining fluid needs are provided with water flushes (if enteral nutrition support), oral fluid (if allowed), or additional IV fluids. When parenteral or enteral formulas are held, it is important to continue to provide the fluids needed by some other means to prevent dehydration.

Regardless of the method used to determine the initial fluid prescription, the fluid volume must be adjusted regularly based on fluctuations in intake and output as well as patient clinical status (eg, organ/system function). Fluid imbalances can occur quickly; therefore, patients receiving nutrition support and their caregivers must be educated on the signs and symptoms of under- and overhydration. See Practice Scenario 7-1 for a discussion of maintenance fluids in a common clinical condition.1,17–20

Practice Scenario 7-1

Question: How would you manage maintenance fluids for a patient with heart failure?

Scenario: RA is a 65-year-old man weighing 75 kg with an ideal body weight of 66 kg. His past medical history is significant for heart failure and diabetes, and he was admitted to your hospital for heart failure exacerbation. Physical examination revealed jugular venous distention, rales, and 3+ pitting edema in bilateral lower extremities. On admission, RA was receiving oxygen therapy at 8 L/min via a nasal cannula and was unable to tolerate an oral diet. An intravenous (IV) solution with 0.9% sodium chloride was initiated at 125 mL/h. On hospital Day 3, RA's oxygen requirements increased, necessitating noninvasive positive pressure ventilation and transfer to the intensive care unit (ICU).

Intervention: Upon transfer to the ICU, the intensivist started a continuous IV furosemide infusion and changed IV fluids to 0.45% sodium chloride at 10 mL/h to maintain IV access.

Answer: Maintenance fluid requirements for a healthy 75-kg man would be 25 to 35 mL/kg/d (1875 to 2625 mL/d). However, patients who present with fluid overload secondary to heart failure exacerbations cannot tolerate normal maintenance fluid requirements. For patients with heart failure, daily fluid intake should be approximately 20 to 25 mL per kg of estimated dry weight and calculated fluid requirements should take into account clinical symptoms (ie, edema, fatigue, shortness of breath). Additionally, sodium should be restricted to less than 2000 mg (87 mEq) per day.17,18 Because RA has a history of heart failure and was admitted with fluid overload and shortness of breath, 3 liters of maintenance IV fluids per day contributed to further respiratory decompensation, requiring aggressive diuresis and ICU transfer. The restriction of IV fluids and sodium along with diuresis resulted in decreased oxygen requirements and improvement in other clinical symptoms associated with fluid overload.

Rationale: Heart failure patients with evidence of significant fluid overload should initially be treated with loop diuretics and sodium and fluid restriction. Therapy for hospitalized patients with decompensated heart failure should begin as soon as possible because early interventions have been associated with better outcomes.19,20 After admission to the hospital, patients should be carefully monitored in accordance with the severity of their symptoms and the results of initial findings on the physical examination and laboratory assessment.

Serum osmolality (water balance) is maintained within the normal range of 280 to 295 mOsm/kg. This point is essential because imbalances of only 1% to 2% initiate mechanisms to return the serum osmolality to normal.1 Two mechanisms regulate water balance: (1) the thirst sensation, and (2) control of renal water excretion by antidiuretic hormone (ADH). The body responds to a water load by suppressing ADH secretion, resulting in decreased collecting tubule water reabsorption and excretion of excess water. The correction of a water deficit requires the intake and retention of exogenous water achieved by increases in thirst and ADH release. Efficiency of this regulatory system is incomplete if the patient has any renal impairment or abnormality in the thirst mechanism (eg, lack of access to water for a mechanically ventilated patient).

Fluid and Electrolyte Disorders

Terminology

Disorders of fluid balance can be classified as disturbances of volume, concentration, or composition. These disturbances often occur simultaneously in clinical practice. Excessive gain of fluid (ie, water and solute such as sodium) is referred to as volume overload or hypervolemia. Conversely, excessive fluid loss is known as volume depletion or hypovolemia. Volume depletion often follows GI hemorrhage, vomiting, diarrhea, and diuresis.21 Overhydration refers to the gain of water alone, whereas dehydration is the loss of water only. These 2 conditions are recognized by a change in serum sodium concentration and plasma osmolality.2 A disturbance of composition refers to a gain or loss of potassium, magnesium, calcium, phosphate, chloride, bicarbonate, or hydrogen ions.

General Management Principles

Some fluid losses contain significant amounts of electrolytes, minerals, or proteins that require replacement along with water. Knowledge of the composition of specific body fluids is therefore useful. Table 7-1 shows the volume of fluid secreted and its electrolyte content throughout the GI tract.5 Abnormalities in renal excretion and excessive losses from the GI tract (eg, vomiting, nasogastric suctioning, diarrhea) are often primary contributors to electrolyte imbalances. Identifying the etiology of the electrolyte imbalance is essential to providing safe and effective treatment.

TABLE 7-1 Volume and Average Electrolyte Content of Gastrointestinal Secretions

		Electrolyte Concentration, mEq/L			
Source/Type of Secretion	Volume, L/d	Na^+	K^+	Cl^-	HCO_3^-
Saliva	1.5	10	26	10	30
Stomach	1.5	60	10	130	0
Duodenum	Variable	140	5	80	0
Ileum	3	140	5	104	30
Colon	Variable	60	30	40	0
Pancreas	Variable	140	5	75	115
Bile	Variable	145	5	100	35

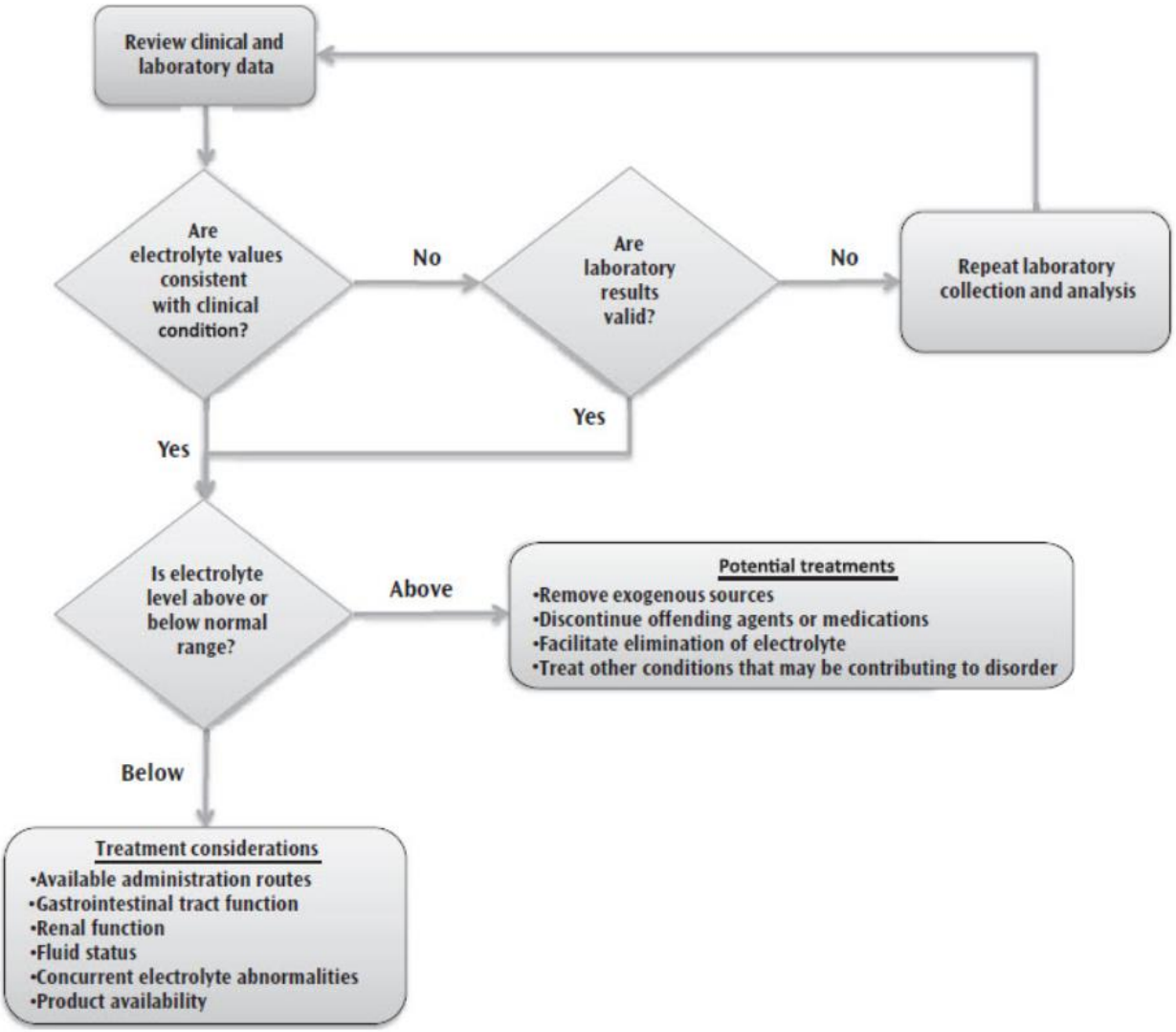
Cl–, chloride; HCO3–, bicarbonate; K+, potassium; Na+, sodium.Source: Adapted with permission from reference 5: Whitmire SJ. Fluids and electrolytes. In: Matarese LE, Gottschlich MM, eds. Contemporary Nutrition Support Practice: A Clinical Guide. Philadelphia, PA: Saunders: 1998:130. Copyright © Laura E. Matarese and Michele M. Gottschlich.

The therapeutic approach to fluid and electrolyte disorders requires clinicians to determine the time frame in which the abnormality occurred. Generally, the development of an acute abnormality (less than 48 hours) is associated with symptoms that require immediate treatment (eg, altered mental status with acute hyponatremia). The development of a chronic electrolyte disorder is often asymptomatic, and the patient may be harmed if the disorder is corrected too rapidly, as in the case of chronic hyponatremia. In the absence of symptoms, the chronologic trends in electrolyte values are generally more important than the absolute value on any given day.2 Clinicians should review all available electrolyte values because patients often have multiple electrolyte abnormalities.

Figure 7-2 illustrates several key principles that warrant consideration when evaluating and treating electrolyte disorders in clinical practice. Upon initial review of laboratory data, clinicians should first determine whether the reported electrolyte levels are consistent with the patient's clinical condition. If

laboratory results are inconsistent, the accuracy of the specimen collection should be validated before further treatment is considered. This step is crucial to prevent inappropriately treating electrolyte values that may be caused by errors in sample collection or handling. If a collection error or specimen mishandling is confirmed, a new specimen should be collected and further analyzed. If the laboratory result is valid, clinicians should then develop a treatment regimen based on the aberrant electrolyte level.

FIGURE 7-2 Algorithm for the Management of Electrolyte Disorders



If an electrolyte level is above the normal range, therapy should be directed toward the removal of exogenous sources of the electrolyte or facilitating its elimination. The most appropriate treatment regimen often depends on the severity of the electrolyte disorder and the presence or absence of symptoms. Potential treatments to consider include removing electrolyte supplementation from IV

fluids or PN, changing an enteral nutrition formulation that contains the electrolyte(s) to another product, discontinuing medications that could be contributing to the electrolyte disorder, management of acid-base abnormalities (eg, metabolic acidosis), and/or inducing renal or GI elimination of the electrolyte.

Electrolyte replacement is the treatment for electrolyte levels below the normal range. To determine whether oral or IV electrolyte replacement is appropriate, patient-specific factors should be considered. IV electrolyte replacement is preferred for patients with impaired GI tract function (eg, diarrhea, malabsorption), those with difficulty swallowing, those who are nil per os status, and those who have critically low electrolyte levels. Conservative electrolyte replacement is often indicated for patients with impaired renal function unless they are actively receiving renal replacement therapy. Patients with volume overload should receive volume-restricted electrolyte replacement or oral therapy whenever possible. When considering IV electrolyte replacement, the options for IV access (peripheral vs central) should be identified. Peripheral administration has limits for volume and the rate of administration, especially for potassium and calcium, and exceeding these limits can result in tissue damage and potential patient harm.

To optimize and minimize electrolyte replacement, clinicians should assess the presence of concurrent electrolyte abnormalities. For example, to optimize replacement in a patient with hypomagnesemia and hypokalemia, magnesium should be repleted before potassium because potassium levels are rarely corrected unless the magnesium deficit is corrected first. The use of potassium phosphate to correct concurrent hypokalemia and hypophosphatemia is an example of minimizing electrolyte replacement.

Sodium

At its normal serum concentration of 135 to 145 mEq/L, sodium (Na^+) is the principal cation in the ECF. Sodium functions as the major osmotic determinant in regulating ECF volume and water distribution in the body. Other functions of sodium include determining the membrane potential of cells and the active transport of molecules across cell membranes.

Hyponatremia

Hyponatremia (serum sodium concentration less than 135 mEq/L) occurs in 25% of hospitalized patients.22 Symptoms include headache, nausea, vomiting, muscle cramps, lethargy, restlessness, disorientation, depressed reflexes, seizures, and coma. Clinical manifestations related to central nervous system (CNS) dysfunction are more likely when the serum sodium concentration drops rapidly and when it falls below 125 mEq/L.2 Mortality rates are increased significantly when serum sodium drops below 120 mEq/L.23

The hyponatremic patient requires a systematic assessment. Upon recognition of clinically relevant hyponatremia (serum sodium less than 130 mEq/L), clinicians should determine the patient's serum sodium concentration and volume status to identify the etiology of the hyponatremia and appropriate treatment options.

Serum osmolality can be directly measured, or it can be calculated with the following equation:

Serum Osmolality = 2 × {[(Serum Na+) + (Serum Glucose)/18] + [BUN/2.8]}

where serum osmolality is measured in mOsm/kg, serum sodium is measured in mEq/L, and serum glucose and blood urea nitrogen (BUN) are measured in mg/dL.

Serum and calculated osmolalities should be relatively close in value. If there is a difference between the 2 values, the patient should be assessed for possible ingestion of toxic substances (ethylene glycol, propylene glycol) that can cause a gap between serum and calculated osmolality. Such a gap is referred to as an osmolar gap when the difference is more than 10 mOsm/kg.

Hypertonic hyponatremia (serum osmolarity greater than 290 mOsm/L) is caused by the presence of osmotically active substances other than sodium in the ECF. Common causes include hyperglycemia and mannitol administration. The correction of serum sodium related to hyperglycemia can be estimated with the following equation:

Corrected Na+ = Serum Na+ + [0.016 × (Serum Glucose) – 100]

where sodium is measured in mEq/L and serum glucose is measured in mg/dL.

Isotonic hyponatremia (serum osmolarity within the normal range, approximately 275 to 300 mOsm/L) occurs when the fraction of serum that is composed of water is reduced (indicating an excess of plasma proteins or lipids). With recent advances in laboratory analysis, isotonic hyponatremia is rarely observed.

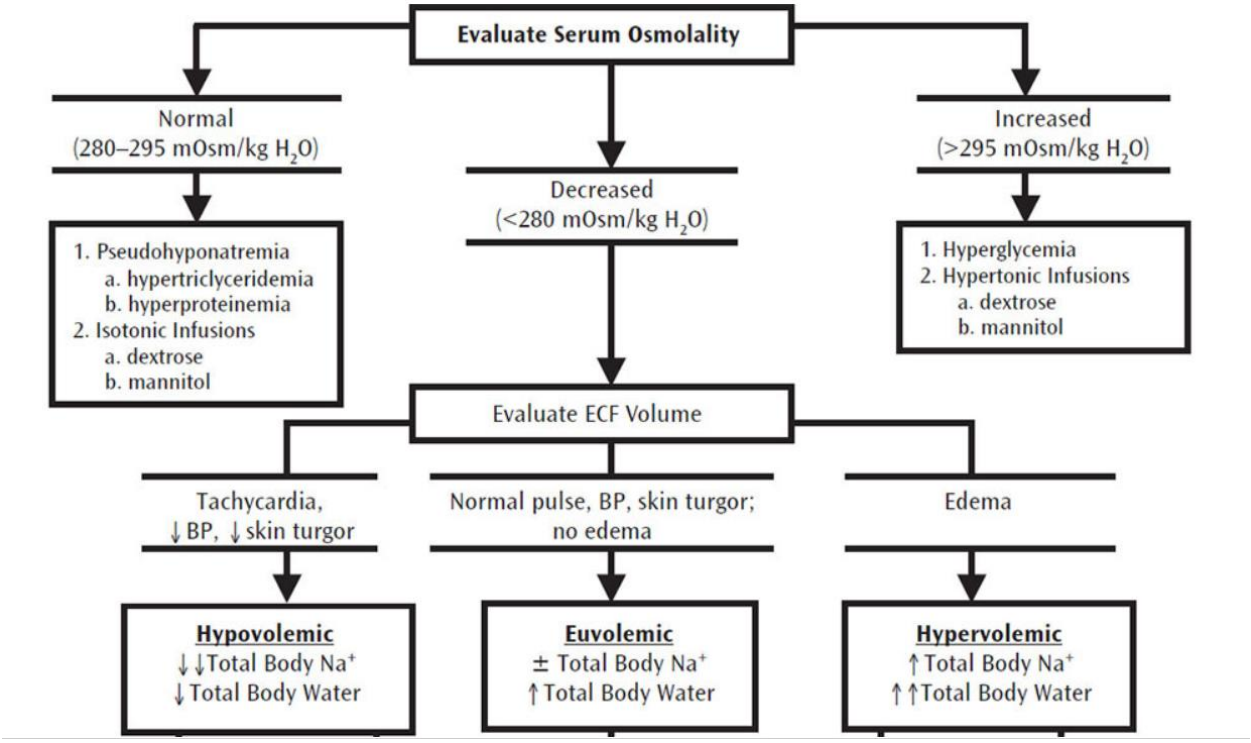
Hypotonic hyponatremia (serum osmolarity less than 275 mOsm/L) warrants a detailed assessment of volume status and urine sodium osmolality. In hypovolemic hypotonic hyponatremia, patients lose more sodium in relation to water. Therefore, it is critical to determine the source of fluid loss. Urine osmolality in these patients is always greater than serum osmolality, which indicates concentrated urine and the body's attempt to retain fluid. Renal losses are usually caused by diuretic use and identified by urine sodium less than 20 mEq/L. Extrarenal losses can be caused by diarrhea, GI fistula output, excessive sweating, burns, open wounds, and fluid drains (eg, peritoneal, pleural, biliary, or pancreatic drains) and may be associated with urine sodium greater than 20 mEq/L. Cerebral salt wasting, which is associated with subarachnoid hemorrhage, may also result in hypovolemic hyponatremia. Both renal and extrarenal fluid losses associated with hyponatremia are treated with isotonic fluids to expand the ECF volume.

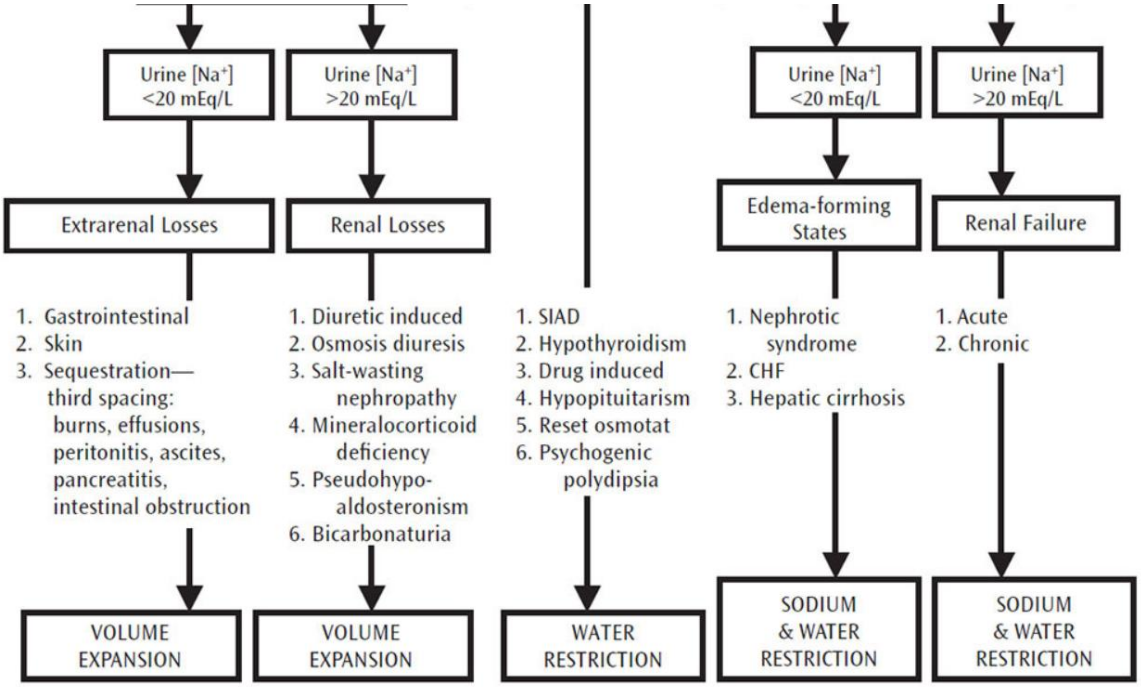
Patients with hypervolemic hypotonic hyponatremia have some element of end-organ damage (renal failure, hepatic failure with ascites, heart failure), resulting in fluid retention or third spacing. These patients retain more water than sodium, and treatment involves both fluid and sodium restriction. Sodium restriction may seem counterintuitive for hyponatremia; however, increased sodium intake increases fluid retention.

Euvolemic hypotonic hyponatremia is commonly associated with the syndrome of inappropriate antidiuresis (SIAD). Patients with SIAD have stable sodium intake/output but retain additional amounts of water because of excessive levels of ADH (which is released from the pituitary gland and, in small amounts, from lung alveoli). Common causes of SIAD include brain or CNS malignancies, head trauma, lung malignancies, and pneumonia. With euvolemic hypotonic hyponatremia, urine osmolality is always greater than serum osmolality and urine sodium is greater than 20 mEq/L, indicating that the kidneys are inappropriately concentrating urine and volume status is adequate, thus differentiating this condition from hypovolemic hypotonic hyponatremia. The mainstay of treatment for SIAD is to restrict fluids to 500 to 1000 mL/d; if the patient is symptomatic, exogenous salt is also administered. SIAD refractory to conventional treatment may require pharmacologic therapy with loop diuretics and/or vasopressin-2 receptor antagonists such as conivaptan or tolvaptan. Other causes of euvolemic hypotonic hyponatremia are psychogenic polydipsia (the ingestion of large amounts of free water), hypothyroidism, and reset osmostat. Treatment revolves around correcting the underlying disorder and fluid restriction.

Figure 7-3 presents an algorithm for the evaluation, etiology, and treatment of hyponatremia.5 To prevent osmotic demyelination, the targeted rate of sodium correction for hyponatremia should not exceed 10 to 12 mEq/L/d if the condition is acute or 6 to 8 mEq/L/d if the condition is chronic or of unknown duration.24

FIGURE 7-3 Evaluation of Hyponatremia





BP, blood pressure; CHF, congestive heart failure; ECF, extracellular fluid; H2O, water; Na+, sodium; SIAD, syndrome of inappropriate antidiuresis.

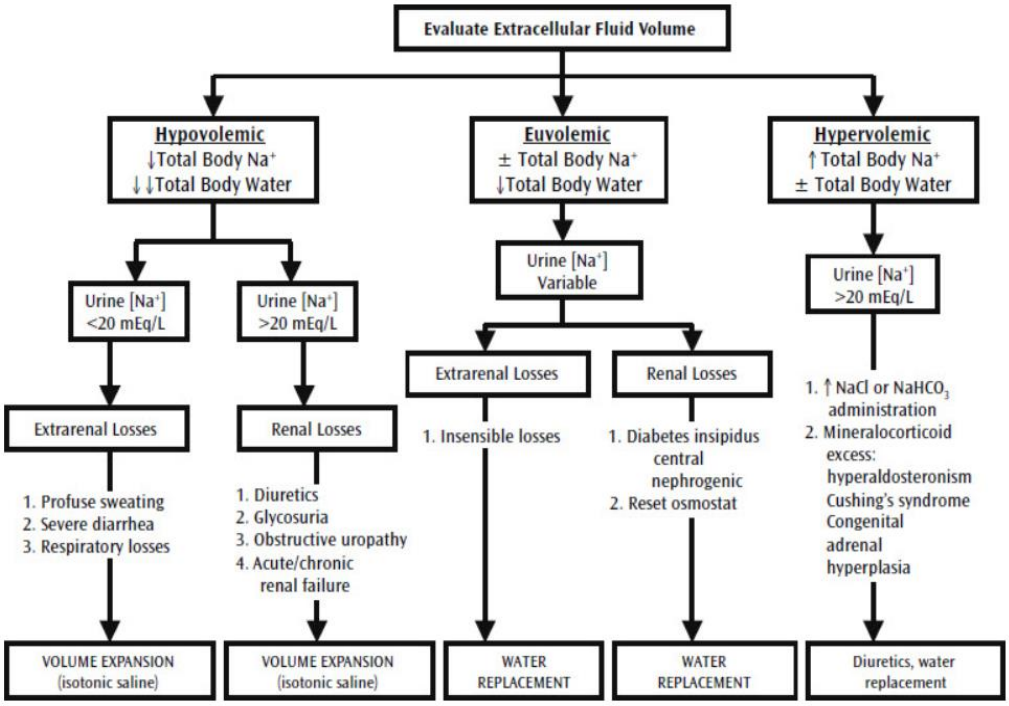
Source: Adapted with permission from reference 5: Whitmire SJ. Fluids and electrolytes. In: Matarese LE, Gottschlich MM, eds. Contemporary Nutrition Support Practice: A Clinical Guide. Philadelphia, PA: Saunders: 1998:129. Copyright © Laura E. Matarese and Michele M. Gottschlich.

Hypernatremia

Hypernatremia (serum sodium greater than 145 mEq/L) occurs in approximately 2% of hospitalized patients, and serum sodium levels greater than 160 mEq/L are associated with a significant increase in mortality.25,26 Clinical manifestations of hypernatremia are associated with neurologic sequelae that range from mild (headache, dizziness, confusion) to severe (seizures, coma, and death). The approach to determine the etiology of hypernatremia is similar to the method used to identify causes of hyponatremia.

An assessment of volume status is the first step in diagnosing hypernatremia. In hypovolemic hypernatremia, patients have above-normal serum osmolality. In hypovolemic patients, it is important to determine the source of fluid loss. Renal losses are commonly caused by diuretic use, solute diuresis associated with hyperglycemia or azotemia, or acute tubular necrosis. Extrarenal losses (diarrhea, excessive sweating) can also lead to hypovolemic hypernatremia. Treatment of hypovolemic hypernatremia involves replacing hypotonic fluids via an enteral or parenteral route (see Figure 7-4).5

FIGURE 7-4 Evaluation of Hypernatremia



Na+, sodium; NaCl, sodium chloride; NaHCO3, sodium bicarbonate.

Source: Adapted with permission from reference 5: Whitmire SJ. Fluids and electrolytes. In: Matarese LE, Gottschlich MM, eds. Contemporary Nutrition Support Practice: A Clinical Guide. Philadelphia, PA: Saunders: 1998:130. Copyright © Laura E. Matarese and Michele M. Gottschlich.

Euvolemic hypernatremia is commonly caused by diabetes insipidus. These patients have water losses that exceed sodium losses. Diabetes insipidus can be either central or nephrogenic in etiology (Table 7-2). Central diabetes insipidus is an impairment of ADH secretion, whereas the nephrogenic condition occurs when the kidneys cannot respond to ADH circulating in the serum. Both types of diabetes insipidus lead to excessive water losses via urine. Treatment differs for the 2 disorders, but both conditions require the replacement of water via the enteral or parenteral route and normalization of serum calcium and potassium (Figure 7-4).5

TABLE 7-2 Causes of Diabetes Insipidus

Nephrogenic causes
• Hypokalemia • Hypercalcemia • Lithium toxicity • Polycystic kidney disease

- Advanced renal disease
- Drugs:

– Amphotericin B

– Cidofovir

– Foscarnet

– Osmotic diuretics

– Demeclocycline

Central causes

- Cerebral hemorrhage
- Head trauma
- Neurosurgery (pituitary)
- CNS infection
- CNS malignancy

CNS, central nervous system.

Hypervolemic hypernatremia can be iatrogenic in nature (excessive administration of isotonic or hypertonic sodium) or related to mineralocorticoid excess (from exogenous administration, Cushing's syndrome, or adrenal malignancy). Treatment involves correcting the underlying disorder, administering diuretics, and replacing water (Figure 7-4).5

When treating hypernatremia, the following equation may be used to calculate the free water deficit for the initial replacement volume:

Free Water Deficit = TBW × [1 – (140/Serum Na+)]

where free water deficit and TBW are measured in liters and serum sodium is measured in mEq/L.

However, the use of this equation has been shown to underestimate free water losses by 1 to 2.5 liters; thus, clinical monitoring is required to normalize the serum sodium concentration.27 Because of the risk for cerebral edema and neurologic impairment, sodium correction should not exceed 10 mEq/L/d when hypernatremia is chronic or of an unknown duration.24 Acute hypernatremia may be corrected at a rate of 2 mEq sodium per liter per hour until the serum sodium reaches 145 mEq/L.24

Potassium

At its normal serum concentration of 3.5 to 5 mEq/L, potassium (K+) is the major intracellular cation. In contrast to sodium, which is restricted primarily to the ECF, 98% of total body potassium is located within cells. Potassium plays a critical role in cell metabolism, including protein and glycogen synthesis. Additionally, the ratio of potassium concentrations in the cell and the ECF is vital to maintaining resting

membrane potential and therefore crucial for normal neural and muscular function. Normal daily potassium requirements range from 0.5 to 2 mEq/kg.6

Regulation of the internal distribution of potassium seems to be extremely efficient, as the movement of only 1.5% to 2% of cellular potassium to the ECF can result in a potentially fatal increase in the plasma potassium concentration to levels as high as 8 mEq/L or more.1 Of all the factors that influence this distribution, the Na+-K+-ATPase pump and the plasma potassium concentration are the most important in the daily regulation of potassium balance.28 Other factors affecting potassium distribution include those regulating the activity of the Na+-K+-ATPase pump—specifically insulin and catecholamines—as well as exercise, extracellular pH, and cellular breakdown.

Hypokalemia

Hypokalemia is a common electrolyte abnormality. When defined as a serum potassium concentration less than 3.6 mEq/L, it is found in over 20% of hospitalized patients.29 Clinical manifestations vary among individuals and are influenced by the rapidity of onset and the degree of hypokalemia. Patients are typically asymptomatic when the disorder is mild (serum potassium 3.0 to 3.5 mEq/L); with lower serum potassium concentrations, nonspecific symptoms such as generalized weakness, lethargy, and constipation are more likely. More severe consequences of hypokalemia can include muscle necrosis, ascending paralysis, arrhythmias, and death.30

Hypokalemia is often the result of abnormal potassium losses via the urine or stool. It can also develop from a transcellular shift of potassium from the ECF into cells or inadequate dietary intake. Metabolic alkalosis and increases in insulin and catecholamines (ie, epinephrine or norepinephrine) are potential causes of transcellular shifts of potassium into the cells. As shown in Table 7-3, many medications can also cause hypokalemia. The table lists drugs associated with magnesium depletion because hypokalemia is often refractory to treatment in the setting of hypomagnesemia.

TABLE 7-3 Causes of Drug-Induced Hypokalemia

Mechanism	Examples
Increased renal potassium loss	• Diuretics: – Acetazolamide – Thiazides – Indapamide – Metolazone – Bumetanide – Furosemide – Torsemide • Fludrocortisone • Hydrocortisone • Drugs associated with magnesium depletion: – Aminoglycosides – Cisplatin – Foscarnet – Amphotericin B – Posaconazole
Excess potassium loss in stool	• Patiromer • Phenolphthalein • Sodium polystyrene sulfonate • Sorbitol
Potassium shift from ECF to ICF	• B_2-adrenergic agonists: – Epinephrine – Albuterol – Terbutaline – Pirbuterol – Salmeterol – Isoproterenol – Ephedrine – Pseudoephedrine • Theophylline • Caffeine • Verapamil intoxication • Insulin (all types)

ECF, extracellular fluid; ICF, intracellular fluid.

Goals of therapy for hypokalemia include avoidance or resolution of symptoms, restoring the serum potassium concentration to normal, and preventing hyperkalemia. Hypokalemia is treated by administration of oral or IV potassium supplements. Commonly used oral and enteral potassium supplements are listed in Table 7-4. IV potassium supplements are available as chloride, acetate, and phosphate salts. Potassium acetate is used as an alternative to potassium chloride in the presence of a metabolic acidosis because acetate is converted to bicarbonate by a normally functioning liver. Potassium phosphate is used to correct coexisting hypokalemia and hypophosphatemia.

TABLE 7-4 Commonly Used Oral Potassium Replacement Products

Dosage Form	Brand Names	Strength	Clinical Considerations
Enteral or oral administration			
Potassium bicarbonate: effervescent tablet for solution	Klor-Con/EF, K-Lyte	25 mEq	Dissolve in 90 mL water; orange flavor
Potassium chloride:			
• Effervescent tablet for solution	K-Lor, Klor-Con	20 mEq/packet	Dissolve in 120 mL water; fruit flavor
• Powder for solution	Klor-Con/25	25 mEq/packet	Dilute in 120 mL cold water or juice for administration; contains sorbitol, which may cause diarrhea
• Solution		20 mEq/15 mL 40 mEq/15 mL	
Potassium phosphate:			
• Tablet for solution	K-Phos	500 mg (3.7 mEq potassium)	Dissolve in 90 mL water
• Powder for solution	Phos-NaK	250 mg (7.1 mEq potassium, 8 mmol phosphorus) per packet	Dilute in 75 mL water; fruit flavor
• Tablet	K-Phos No. 2	2.3 mEq potassium, 8 mmol phosphorus per tablet	
Oral administration only			
Potassium chloride:			
• Capsule, extended-release, microencapsulated	Micro K	8 mEq/600 mg 10 mEq/750 mg	Swallow whole; capsules may be opened and contents sprinkled on applesauce and swallowed immediately without chewing
• Tablet, extended-release	Micro K	8 mEq/600 mg 10 mEq/750 mg 20 mEq/1500 mg	Swallow whole; do not crush or chew; larger tablet size with higher doses; difficult to swallow; potential noncompliance issues
• Tablet, extended-release, microencapsulated	Klor-ConM10 Klor-ConM15 Klor-ConM20	10 mEq/750 mg 15 mEq/1125 mg 20 mEq/1500 mg	Tablet may be broken in half; whole tablet may be dissolved in 120 mL water or ½ tablet in 60 mL water
• Tablet, extended-release, wax matrix	Klor-Con	8 mEq/600 mg 10 mEq/750 mg	Do not crush or chew; swallow whole

Potassium supplements are best administered orally in a moderate dosage over a period of several days to 1 week to achieve complete potassium repletion. An oral potassium dosage of 10 to 30 mEq/d is generally sufficient to prevent hypokalemia, whereas dosages of 40 to 100 mEq/d may be required for treatment.

Oral correction of hypokalemia is generally safer and reduces the risk of overcorrection and rebound hyperkalemia. Potassium chloride can be given in a capsule, tablet, or liquid formulation. Although several liquid preparations are available and less expensive than capsules and tablets, they often have an unpleasant taste and are poorly tolerated. The slow-release tablets are well tolerated but have been associated with ulceration and bleeding of the GI tract.31 Oral potassium dosages of 40 to 100 mEq/d divided into 2 to 4 doses are usually sufficient to correct hypokalemia.32,33

IV potassium supplementation is reserved for the treatment of severe hypokalemia or when the condition of the GI tract precludes the use of oral agents. Recommendations for IV potassium replacement doses vary according to the severity of hypokalemia and the presence of renal insufficiency (Table 7-5).32–36 Infusion rates should generally not exceed 10 to 20 mEq/h; however, infusion rates as high as 40 mEq/h have been used for emergent cases or severely symptomatic patients. If an infusion rate exceeding 10 mEq/h is required, continuous cardiac monitoring is recommended to detect any signs of hyperkalemia. Administration via a central venous catheter is recommended to minimize phlebitis and burning. Total daily potassium supplementation, in most cases, should not exceed 40 to 100 mEq/d (or 0.5 to 1.2 mEq/kg/d). However, some patients with severe potassium wasting may require doses of 200 mEq/d (1.5 mEq/kg/d) or higher with additional cardiac monitoring.

TABLE 7-5 Empirical Treatment of Hypokalemia

Serum Potassium Concentration, mEq/L	Intravenous Potassium Dose, mEq[a]
3–3.4	20–40
2.5–2.9	40–80
<2.5	80–120

[a]These dosing guidelines are recommended for patients with normal renal function. Patients with renal impairment should receive 50% of the initial empirical dose. Rate of infusion: 10 to 20 mEq potassium per hour; maximum infusion rate: 40 mEq/h. Continuous cardiac monitoring and infusion via a central venous catheter are recommended for infusion rates >10 mEq potassium per hour.

Additional caveats to consider when replacing a potassium deficit include the diluent (dextrose vs saline) and the presence of hypomagnesemia. When possible, dextrose solutions should be avoided because they may worsen the hypokalemia by stimulating insulin release that promotes an intracellular shift of potassium.37 A magnesium deficit should be corrected because hypomagnesemia may result in refractory hypokalemia related to accelerated renal potassium loss or the impairment of Na+-K+-ATPase pump activity.38

Hyperkalemia

Because of the body's effective regulatory mechanisms, hyperkalemia (serum potassium greater than 5.0 mEq/L) rarely occurs in healthy individuals. In contrast to the relatively large decrease in total body potassium needed to cause a slight decrease in serum potassium, even a small excess of total body potassium will elicit a sharp increase in the serum concentration.39 Clinical manifestations of hyperkalemia are related to changes in neuromuscular and cardiac function. Patients are often asymptomatic until the serum potassium concentration exceeds 5.5 mEq/L.32 Signs and symptoms of hyperkalemia include muscle twitching, cramping, weakness, ascending paralysis, electrocardiogram changes (eg, tall, peaked T-waves; prolonged PR-interval; widened QRS complex; shortened QT interval), and arrhythmias (eg, bradyarrhythmias, ventricular fibrillation, asystole).

Although hyperkalemia can be caused by extracellular shifts of potassium and increased potassium ingestion, it most often occurs in the setting of chronic kidney disease (CKD). Increased potassium intake alone rarely causes hyperkalemia. Extracellular shifts of potassium are relatively common and are often a result of metabolic acidosis, tissue catabolism, and pseudohyperkalemia. Metabolic acidosis results in an extracellular potassium shift to maintain electroneutrality because some of the excess hydrogen ions are buffered intracellularly.40 In general, for every 0.1 decrease in pH, potassium will increase by an average of 0.6 mEq/L but the increase can range from 0.3 to 1.3 mEq/L. Tissue destruction or breakdown causes the release of intracellular potassium into the ECF. Pseudohyperkalemia signifies an artifactual increase in serum potassium related to the release of intracellular potassium during or after blood sampling. This finding is most commonly associated with trauma during venipuncture, but it can also occur with the measurement of serum potassium in patients with marked leukocytosis

(100,000/mm3) or thrombocytosis (400,000/mm3) or when the blood sample is contaminated with infused potassium or hydrolyzed. Therefore, if a serum potassium level is inappropriately elevated for the clinical situation, a repeat potassium level should be obtained to confirm the diagnosis and avoid unwarranted treatment. Drug-induced causes of hyperkalemia are listed in Table 7-6.41

TABLE 7-6 Causes of Drug-Induced Hyperkalemia

Mechanism	Examples
Impaired renal potassium excretion	• Potassium-sparing diuretics (spironolactone, eplerenone, triamterene, amiloride) • Nonsteroidal anti-inflammatory agents • ACE-inhibitors • Angiotensin-II receptor blockers • Aliskiren • Trimethoprim • Pentamidine • Cyclosporine • Tacrolimus • Everolimus • Heparin • Aripiprazole • Canagliflozin
Increased potassium input	• Potassium supplements • Salt substitutes • Stored packed red blood cells • Penicillin G potassium
Potassium shift from ICF to ECF	• Beta blockers • Succinylcholine • Digoxin intoxication

ACE, angiotensin-converting-enzyme; ECF, extracellular fluid; ICF, intracellular fluid.

Table 7-7 lists therapies for the treatment of hyperkalemia.42–44 The choice of treatment depends on the degree of hyperkalemia and the severity of symptoms. Goals of therapy include antagonizing the cardiac effects of potassium, reversing symptoms (if present), and returning the serum potassium concentration to normal. If feasible, all sources of exogenous potassium and other medications that can cause hyperkalemia should be discontinued or dosages should be decreased. IV calcium gluconate should be given to symptomatic patients and those with electrocardiogram changes to restore membrane excitability to normal. Insulin and dextrose, sodium bicarbonate, and beta2-adrenergic agonists cause potassium to move intracellularly. Loop and thiazide diuretics, cation-exchange resins (eg, sodium polystyrene sulfonate), and dialysis facilitate potassium removal. Serum potassium should be monitored frequently during the treatment of symptomatic patients because many of the therapies employed for acute hyperkalemia redistribute potassium and do not remove it from the body. Upon symptom resolution, continued potassium monitoring is recommended every 4 to 12 hours after therapeutic interventions until potassium levels return to normal.

TABLE 7-7 Treatment of Hyperkalemia

Treatment	Dose	Onset	Duration	Action
Calcium gluconate[a,b]	1–2 g (4.65–9.3 mEq) intravenously over 10 min	1–2 min	10–30 min	Antagonizes cardiac conduction abnormalities
Sodium bicarbonate[a]	50–100 mEq intravenously over 2–5 min	30 min	2–6 h	Shifts potassium intracellularly
Regular insulin with dextrose	5–20 units intravenously with 50–120 mL of 50% dextrose injection	15–45 min	2–4 h	Shifts potassium intracellularly
Albuterol	10–20 mg nebulized	30 min	1–2 h	Shifts potassium intracellularly
Furosemide	20–80 mg intravenous push	5–15 min	4–6 h	Promotes renal potassium loss
Patiromer sorbitex calcium	8.4 g/d; may adjust in increments of 8.4 g at weekly intervals up to 25.2 g/d	4-7 h	≥24 h	Nonabsorbable cation-exchange polymer that increases fecal potassium excretion
Sodium polystyrene sulfonate	15–60 g orally or rectally	1 h	4–6 h	Increases fecal potassium elimination
Hemodialysis	Variable	Immediate	Variable	Removes potassium from plasma

[a]First-line therapies in hyperkalemic emergencies.

bRepeat dose in 5 minutes if abnormal electrocardiogram persists. Calcium chloride may be used, but calcium gluconate is preferred for peripheral administration (less venous irritation). Calcium chloride (1 g = 13.6 mEq) provides 3 times more calcium than calcium gluconate (1 g = 4.65 mEq).

Magnesium

At its normal serum concentration of 1.8 to 2.8 mg/dL, magnesium (Mg^{2+}) is mostly found in the ICF.45 Total body magnesium content is approximately 25 g (2000 mEq), of which 50% to 60% is in bone.46 The rest is located in cardiac muscle, skeletal muscle, and the liver, with about 2% in the ECF. Magnesium is essential in the activation of more than 300 enzymatic reactions, including those involved in glucose metabolism, fatty acid synthesis and breakdown, and DNA and protein metabolism.47 Magnesium is also required for the maintenance of the Na^+-K^+-ATPase pump and, hence, cell membrane action potential. It is a structural component of bone and a factor in parathyroid hormone (PTH) secretion, neuromuscular transmission, cardiovascular excitability, vasomotor tone, and muscle contraction.

Cellular and extracellular magnesium concentrations are carefully regulated by the GI tract, kidney, and bone. Healthy people absorb approximately 30% to 40% of ingested magnesium. Magnesium absorption occurs primarily in the distal jejunum and ileum and varies inversely with intake. Renal elimination normally accounts for approximately one-third of absorbed magnesium. However, with increased magnesium intake, renal magnesium excretion increases to maintain normal serum concentrations.48

Hypomagnesemia

Hypomagnesemia (serum magnesium less than 1.8 mg/dL), has been reported in 6.9% to 47% of hospitalized patients,49–52 and in as many as 65% of patients in ICUs.53 Neuromuscular hyperexcitability is the primary symptom of magnesium deficiency.54 Latent tetany, as elicited by positive Chvostek and Trousseau signs, may be present. Frank, generalized seizures may also occur in severe cases. Concomitant electrolyte abnormalities in the setting of magnesium deficiency include

hypokalemia and hypocalcemia. Both are refractory to treatment until the magnesium deficit is corrected. Hypomagnesemia occurs in approximately 38% to 61% of patients with hypokalemia and 22% to 28% of patients with hypocalcemia.52,55,56 Magnesium depletion is also associated with cardiac complications, including electrocardiogram changes, arrhythmias, and increased sensitivity to cardiac glycosides (digoxin).57 Additionally, hypomagnesemia may reduce insulin sensitivity and glucose cellular uptake, impair insulin secretion, and reduce lipoprotein lipase.58

Hypomagnesemia can occur with decreased intake or absorption, excessive losses, or redistribution into the ICF. Common causes of reduced magnesium intake or absorption include protein-energy malnutrition, prolonged administration of magnesium-free IV fluids or PN, alcoholism, presence of an ileostomy or colostomy, malabsorption syndromes, short bowel syndrome, and intestinal bypass operations. Magnesium losses can occur via the GI tract or the kidneys. Renal losses may be caused by acute tubular necrosis, renal tubular acidosis, Bartter syndrome, hyperaldosteronism, or they may be induced by drugs such as thiazide and loop diuretics, cisplatin, cyclosporine, amphotericin B, aminoglycosides, and foscarnet.59 Intracellular shifts of magnesium may be seen during refeeding, diabetic ketoacidosis, hyperthyroidism, and myocardial infarction.

Because only about 1% to 2% of total body magnesium is located in the ECF, serum levels may not correlate with intracellular concentrations or total body magnesium levels. Therefore, treatment of hypomagnesemia is largely empirical. Both oral and IV formulations of magnesium are available to replace estimated deficits. Table 7-8 lists commonly used oral and enteral magnesium supplements. The IV route of administration is often preferred because issues with administration, slow onset of action, and GI intolerance limit the use of oral supplements. Table 7-9 provides recommended dosing regimens for the treatment of hypomagnesemia according to severity.60–63 Maximal magnesium infusion rates should not exceed 1 g/h (8 mEq/h) in asymptomatic patients because more than 50% of the dose may be lost in the urine as renal magnesium reabsorption is exceeded.61,63 Similarly, recommended empirical doses should be reduced by approximately 50% or more when administered to patients with renal impairment to reduce the risk of hypermagnesemia. IV treatment of hypomagnesemia can be generally expected to produce a serum magnesium change of 0.1 mg/dL for each gram (8 mEq) administered, although the plasma concentration typically takes up to 48 hours after the bolus to equilibrate.64,65 Additionally, replacing magnesium concurrently with potassium reduces renal potassium excretion and cardiac dysrhythmias observed clinically.66

TABLE 7-8 Commonly Used Oral Magnesium Replacement Products

Dosage Form	Brand Names	Strength	Clinical Considerations
Enteral or oral administration			
Magnesium gluconate: solution	Magonate	4.8 mEq/5 mL (1000 mg/5 mL)	
Magnesium sulfate: solution		4 mEq/mL (500 mg/mL)	
Oral administration only			
Magnesium chloride:			
• Tablet, enteric-coated	Slow-Mag	5 mEq	Do not crush or chew; swallow whole; contains 106 mg elemental calcium
• Tablet, delayed-release	Mag 64	5 mEq	Do not crush or chew; swallow whole; contains 110 mg elemental calcium
Magnesium gluconate tablet	Mag G Magtrate	2.4 mEq/500 mg 2.4 mEq/500 mg	
Magnesium lactate: caplet, sustained-release	Mag-Tab SR	7 mEq	Do not crush or chew; swallow whole
Magnesium oxide:			
• Capsule	Mag-Caps Uro-Mag	7 mEq 7 mEq/140 mg	
• Capsule, soft gel	MagGel	28.6 mEq/600 mg	
• Tablet	Mag-Ox 400 MG Plus Protein	20 mEq/500 mg 11 mEq	Large tablet size; potential noncompliance issues Chelated to soy protein; reduced gastrointestinal side effects

TABLE 7-9 Empirical Treatment of Hypomagnesemia

Severity	Serum Magnesium Concentration, mg/dL	Intravenous Magnesium Dose[a]
Mild to moderate	1–1.5	16–32 mEq (2–4 g) magnesium sulfate; ≤1 mEq/kg
Severe	<1	32–80 mEq (4–10 g) magnesium sulfate; ≤1.5 mEq/kg

[a]These dosing guidelines are recommended for patients with normal renal function. Patients with renal impairment should receive 50% of the initial empirical dose. If hypomagnesemia is asymptomatic, the maximum rate of infusion is 8 mEq (1 g) magnesium sulfate per hour, ≤96 mEq (12 g) magnesium sulfate over 12 hours. Up to 32 mEq (4 g) magnesium sulfate may be infused over 4 to 5 minutes in severe symptomatic hypomagnesemia.

Hypermagnesemia

Hypermagnesemia (serum magnesium greater than 2.8 mg/dL) occurs primarily in the setting of CKD in combination with magnesium intake. Hypermagnesemia is generally well tolerated, but it can affect neurologic, neuromuscular, and cardiac function when magnesium levels exceed 4.8 mg/dL.50 Physical findings include nausea, vomiting, diaphoresis, flushing, sensation of heat, depressed mental functioning, drowsiness, muscular weakness, loss of deep tendon reflexes, hypotension, and bradycardia.

IV calcium (chloride or gluconate) should be administered to patients with symptomatic severe hypermagnesemia to reverse the cardiac and neuromuscular effects.46,67 Therapy for patients with asymptomatic hypermagnesemia includes the removal of exogenous sources of magnesium (eg, PN, IV fluids), magnesium restriction, and loop diuretics.

Calcium

Normal total serum calcium (Ca^{2+}) concentrations range from 8.6 to 10.2 mg/dL. Calcium is one of the most abundant cations in the body and accounts for 1% to 2% of adult human body weight.46 It is essential to many physiological functions, including the preservation of cell membrane integrity,

neuromuscular activity, regulation of endocrine secretory activities, blood coagulation, activation of the complement system, and bone metabolism.68 Serum calcium concentrations are under hormonal control primarily mediated by PTH, vitamin D, and calcitonin.1 Low serum calcium concentrations stimulate the release of PTH, which increases bone resorption, augments renal conservation of calcium, and activates vitamin D, which in turn increases intestinal calcium absorption. Calcitonin is released by the thyroid gland in response to elevated serum calcium concentrations and acts to inhibit bone resorption and increase urinary calcium excretion. In healthy individuals, any excess calcium is excreted in the urine, whereas any decrease in total serum calcium is met by an increase in calcium mobilization from bone to restore the serum calcium concentration to normal.

About 99% of total body calcium is found in teeth and bones, with less than 1% in the serum.69 Serum calcium exists in 3 forms: complexed, protein bound, and ionized. The ionized fraction of calcium, with a normal range of 1.12 to 1.3 mmol/L, is the metabolically active form and is of greatest physiological importance.68 Serum pH, phosphorus, and albumin levels affect the percentage of ionized calcium. A metabolic alkalosis decreases the percentage of ionized calcium, as does an increase in serum phosphorus. Hypoalbuminemia decreases total serum calcium but does not affect ionized calcium levels. For each 1 g/dL decrease in albumin below 4 g/dL, total serum calcium decreases by approximately 0.8 mg/dL.70 Total calcium can be adjusted for hypoalbuminemia, as follows:

Corrected Total Serum Ca^{2+} = Measured Total Serum Ca^{2+} + [0.8 × (4 – Serum Albumin)]

where serum calcium is measured in mg/dL and serum albumin is measured in g/dL.

However, direct measurement of ionized calcium is the most accurate method to assess calcium abnormalities. Direct measurement is especially important in critically ill patients because this equation often overestimates the corrected calcium concentration.71

Hypocalcemia

Hypocalcemia (total serum calcium less than 8.6 mg/dL or ionized calcium less than 1.12 mmol/L) frequently occurs secondary to hypoalbuminemia; however, this hypocalcemia is usually not clinically significant as long as the ionized calcium concentration remains normal.26 Causes of hypocalcemia include decreased vitamin D activity (vitamin D deficiency, hyperphosphatemia, pseudohypoparathyroidism), decreased PTH activity (acute pancreatitis, hypomagnesemia, hypoparathyroidism), citrate anticoagulation during continuous renal replacement therapy, and hungry bone syndrome (which can occur after total parathyroidectomy or thyroidectomy). Hypocalcemia is common in critically ill patients and is also associated with sepsis, rhabdomyolysis, and massive blood transfusions (secondary to citrate preservative in the blood bank binding with serum calcium).71,72 Drugs implicated in the etiology of hypocalcemia include bisphosphonates, calcitonin, furosemide, foscarnet, and long-term therapy with phenobarbital and phenytoin.73 Clinical manifestations may be cardiovascular (ie, hypotension, decreased myocardial contractility, or prolonged QT interval) or neuromuscular (ie, distal extremity paresthesias, Chvostek sign, Trousseau sign, muscle cramps, tetany, or seizures).

Acute symptomatic hypocalcemia (total serum calcium less than 7.5 mg/dL or ionized calcium less than 0.9 mmol/L) requires prompt correction with IV calcium gluconate or calcium chloride.74 Although calcium chloride (10 mL 10% solution = 272 mg [13.6 mEq] elemental calcium) contains 3 times more elemental calcium than an equivalent amount of calcium gluconate (10 mL 10% solution = 92 mg [4.65 mEq] elemental calcium), it may cause tissue necrosis if extravasation occurs.75,76 Initially, 1 g of calcium chloride (13.6 mEq calcium) or 3 g calcium gluconate (14 mEq calcium) may be given over 10 minutes to control hypocalcemia symptoms. Continuous infusions of IV calcium may be required for severe acute hypocalcemia refractory to intermittent bolus doses.74 Guidelines for the acute treatment of hypocalcemia are provided in Table 7-10.77,78 If concomitant hypomagnesemia is present, magnesium supplements should be provided to facilitate the correction of hypocalcemia.79,80 In cases of hypocalcemia related to elevated serum phosphorus levels, treatment with phosphate binders is warranted prior to calcium replacement to reduce the risk of soft tissue calcification. Chronic or asymptomatic hypocalcemia can be treated with oral calcium supplements and vitamin D.32 Common calcium supplements are listed in Table 7-11. Recent evidence suggests that dose-dependent calcium administration with PN for critically ill patients who are not on mechanical ventilation or vasopressor support is associated with an increased mortality, acute respiratory failure, and new-onset shock; therefore, the risk vs benefit should be assessed in these patients prior to IV calcium use.81

TABLE 7-10 Empirical Treatment of Acute Hypocalcemia

Serum Ionized Calcium Concentration, mmol/L	Intravenous Calcium Dose
1–1.12	1–2 g (4.65–9.3 mEq) calcium gluconate over 1–2 hours
<1	2–4 g (9.3–18.6 mEq) calcium gluconate over 2–4 hours

TABLE 7-11 Common Calcium Supplements

Calcium Salt	Available Dosage Forms	Elemental Calcium, %
Calcium acetate	Tablet	25
Calcium carbonate	Powder for solution Suspension Chewable tablet Soft chew tablet Tablet	40
Calcium citrate	Granules for solution Capsule Tablet	21
Calcium glubionate	Powder for solution Capsule Tablet	9
Calcium lactate	Tablet	13

Hypercalcemia

Hypercalcemia (total serum calcium greater than 10.2 mg/dL or ionized calcium greater than 1.3 mmol/L) most often occurs in hyperparathyroidism and cancer with bone metastases (primarily breast cancer, lung cancer, and multiple myeloma). It can also occur with toxic levels of vitamin A or vitamin D,

chronic ingestion of milk and/or calcium carbonate–containing antacids in the setting of renal insufficiency (milk-alkali syndrome), adrenal insufficiency, immobilization, tuberculosis, and use of various medications (eg, thiazide diuretics and lithium).68 Early clinical manifestations are nonspecific and include fatigue, nausea, vomiting, constipation, anorexia, and confusion. In more severe causes, cardiac arrhythmias (bradycardia) may be present.

Mild hypercalcemia (total serum calcium 10.3 to 11.9 mg/dL) usually responds well to hydration and ambulation. Severe hypercalcemia (total serum calcium equal to or greater than 14 mg/dL) requires immediate treatment because it can lead to acute renal failure, obtundation, ventricular arrhythmias, coma, and death.69,82,83 IV hydration using 0.9% NaCl should be started promptly at 200 to 300 mL/h to reverse the volume depletion caused by hypercalcemia. After adequate hydration is achieved, 40 to 80 mg IV furosemide may be used to enhance renal calcium excretion if the patient is vigilantly monitored to avoid further volume depletion, although diuretic use remains controversial in the treatment of hypercalcemia. Saline hydration can reduce serum calcium levels by 2 to 3 mg/dL within the first 48 hours of treatment. Calcitonin can also be used to treat acute hypercalcemia, but tachyphylaxis often limits its usefulness after 48 hours. Hemodialysis may be necessary in life-threatening hypercalcemia or in patients with CKD. Although bisphosphonates have a primary role in the treatment of hypercalcemia of malignancy, their delayed onset of action of 4 to 10 days renders these agents useful only as maintenance therapy.

Phosphorus

The normal serum phosphorus concentration of 2.7 to 4.5 mg/dL reflects less than 1% of total body phosphorus, with most phosphorus found in bones and soft tissues.68 Phosphorus is the main intracellular anion (which exists primarily as phosphate in the serum) and has many important functions, including bone and cell membrane composition and maintenance of normal pH. It provides energy-rich bonds in the form of adenosine triphosphate and is required in all cellular functions that require energy.84–86 Adequate total body phosphorus is necessary for carbohydrate use, glycolysis, maintenance of normal pH, 2,3-diphosphoglycerate synthesis and function (which are necessary for oxygen release from hemoglobin and, ultimately, tissue oxygenation), neurologic function, and muscular function (especially the myocardium and diaphragm).84–90

Serum phosphorus concentrations are determined by intake, intestinal absorption, renal excretion, hormonal regulation of bone resorption and deposition, and distribution between intracellular and extracellular compartments. Carbohydrate and insulin administration, catecholamines, and alkalosis are causes of intracellular shifts of phosphorus. Alternatively, cellular destruction and acidosis result in the release of phosphorus from the cell to the ECF.68

Hypophosphatemia

Hypophosphatemia (serum phosphorus concentration less than 2.7 mg/dL) can cause a variety of adverse effects. Manifestations may be neurologic (ataxia, confusion, paresthesias), neuromuscular (weakness, myalgia, rhabdomyolysis), cardiopulmonary (cardiac and ventilatory failure), or hematologic (reduced 2,3-diphosphoglycerate concentration, hemolysis).2 Hypophosphatemia is common in chronic

alcoholism, critical illness, respiratory and metabolic alkalosis, following the treatment of diabetic ketoacidosis, and in patients receiving phosphate-binding medications.84–86 The administration of carbohydrate loads or PN is likely to cause hypophosphatemia if an inadequate amount of phosphate is provided, especially in malnourished patients at risk for developing severe hypophosphatemia and refeeding syndrome.87,88,91,92 See Practice Scenario 7-2 for a discussion of prevention of refeeding syndrome.92

Practice Scenario 7-2

Question: How can complications be prevented when providing nutrition support therapy to a malnourished esophageal cancer patient?

Scenario: JR is a 37-year-old man (weight, 68 kg; height, 6 feet; usual body weight, 78 kg) with esophageal cancer status post esophagectomy and chemoradiation. He is admitted to the hospital for progressive weight loss (10-kg weight loss in the previous 2 months) and failure to thrive. On hospital Day 2, a percutaneous jejunostomy tube is placed and a 1.5 kcal/mL high-protein enteral formula is started and advanced to 70 mL/h within 24 hours. On hospital Day 4, JR falls while attempting to get out of bed and attributes this event to new-onset muscle weakness and pain. His laboratory test values are as follows:

Day	Na^+, mEq/L	K^+, mEq/L	Cl^-, mEq/L	HCO_3^-, mEq/L	BUN, mg/dL	Creatinine, mg/dL	Glucose, mg/dL	Mg, mg/dL	Phos, mg/dL
1	133	3.6	99	27	3	0.3	89	1.8	2.8
2	132	3.6	98	28	4	0.3	97	1.7	2.6
4	138	2.6	102	21	8	0.4	105	1.2	1.4

Intervention: The rate of enteral feeds is reduced to 20 mL/h. Intravenous electrolyte replacement is ordered to correct electrolyte abnormalities, and serum chemistry monitoring is ordered every 12 hours. The nutrition support team initiates daily administration of thiamin 100 mg via the feeding tube.

Answer: Nutrition support therapy should be advanced cautiously for patients at risk for refeeding. In this case, JR received 2520 kcal/d (35 kcal/kg/d) with no enteral feeding titration. This aggressive feeding rate and energy provision resulted in a massive intracellular shift of potassium, magnesium, and phosphorus that caused symptomatic hypokalemia, hypomagnesemia, and hypophosphatemia. Electrolyte abnormalities should be corrected as soon as they are identified, and nutrition support therapy should be decreased to a safe rate of 500 kcal/d before the rate is further advanced. Thiamin supplementation is also indicated to facilitate efficient carbohydrate metabolism, correct existing thiamin deficiency, and prevent potential lactic acidosis and Wernicke encephalopathy. The energy prescription should be advanced to meet estimated nutrition needs as permitted by the resolution of symptoms and normalization of serum electrolyte values (eg, 480 kcal/d for 2 days, then 960 kcal/d for 1 day, then 1440 kcal/d for 1 day, then 100% of energy goal).92

Rationale: JR was at significant risk for refeeding complications secondary to significant weight loss prior to the initiation of enteral feeds. Severely malnourished patients such as those undergoing anticancer

treatment, especially radiation to the gastrointestinal tract, are at an increased risk for electrolyte abnormalities and fluid shifts upon the initiation of nutrition support. Electrolyte abnormalities should be corrected prior to nutrition support therapy, and electrolyte concentrations should be closely monitored as the amount of energy administered is carefully increased to meet estimated needs.

Treatment of hypophosphatemia varies according to the degree of severity and the presence of symptoms. Asymptomatic mild hypophosphatemia may be treated with oral phosphate supplements if the GI tract is functional. Table 7-12 lists the most commonly used oral and enteral phosphate supplements.93 Limitations of oral phosphate supplementation include diarrhea and unreliable absorption. Patients with symptomatic, moderate, or severe hypophosphatemia as well as patients who cannot tolerate oral phosphate formulations should receive IV potassium or sodium phosphate to correct serum phosphorus levels.31 Phosphate boluses should always be ordered as millimoles of phosphate. Phosphate is present in 2 different valence states at physiological pH. Phosphorus supplements combine both monobasic and dibasic salts, with the ratio of the 2 being dependent on pH. Thus, milliequivalents of phosphate are not exactly known. IV potassium phosphate is preferred unless the potassium concentration is greater than 4 mEq/L (3 mmol potassium phosphate = 4.4 mEq potassium) or renal insufficiency exists. Dosing recommendations (Table 7-13) are largely empirical because serum phosphorus concentrations may not accurately reflect total body stores.94–96 Reduced phosphate dosages (approximately 50%) are recommended for patients with renal impairment to prevent the development of hyperphosphatemia. Infusion rates should not exceed 7 mmol/h because faster infusion rates can often cause thrombophlebitis and soft tissue calcium-phosphate deposition.97,98 If potassium phosphate is being used to replete phosphate, the rate of infusion of potassium may also be rate-limited.

TABLE 7-12 Common Oral Phosphate Replacement Products

Dosage Form	Brand Names	Strength	Clinical Considerations
Enteral or oral administration			
Potassium phosphate:			
• Tablet for solution	K-Phos	500 mg (3.7 mEq potassium, 3.7 mmol phosphate per tablet)	Dissolve in 90 mL water
• Powder for solution	Phos-NaK	250 mg/packet (7.1 mEq potassium, 8 mmol phosphate per packet)	Dilute in 75 mL of water; fruit flavor
Sodium phosphate	OsmoPrep	1.5 g sodium phosphate per tablet (10.8 mmol phosphate, 13.6 mEq sodium per tablet)	Dilute in 240 mL water Saline laxative; concern for renal failure when used for bowel cleansing in high-risk patients (age >55 years, dehydration, baseline kidney disease, bowel obstruction, active colitis, medications that affect renal perfusion)

TABLE 7-13 Empirical Treatment of Hypophosphatemia

Severity	Serum Phosphorus Concentration, mg/dL	Intravenous Phosphate Dose, mmol/kg[a]
Mild	2.3–2.7	0.08–0.16
Moderate	1.5–2.2	0.16–0.32
Severe	<1.5	0.32–1

[a]These guidelines are recommended for patients with normal renal function. Patients with renal impairment should receive 50% of the initial empirical dose. Maximum infusion rate is 7 mmol phosphate per hour. Potassium phosphate is preferred over sodium phosphate when the serum potassium concentration is <4 mEq/L.

Hyperphosphatemia

Hyperphosphatemia (serum phosphorus greater than 4.5 mg/dL) most often occurs in the setting of CKD. Hyperphosphatemia can also be caused by the endogenous release of phosphorus into the ECF from cellular destruction, such as with massive trauma, cytotoxic agents (especially in the treatment of lymphomas and leukemias with large tumor burden), hypercatabolism, hemolysis, rhabdomyolysis, and malignant hyperthermia. Transcellular shifts of phosphorus from the ICF to the ECF caused by a respiratory or metabolic acidosis may also result in hyperphosphatemia. The administration of large quantities of phosphate-containing laxatives or enemas, especially in the elderly, has been reported to contribute to severe hyperphosphatemia and end-organ damage (renal failure).99

The most serious complication of hyperphosphatemia is soft tissue and vascular calcification.39 Calcification occurs when the calcium-phosphorus product (ie, total serum calcium × serum phosphorus) exceeds 55 mg2/dL2.2,100,101 Additional consequences of hyperphosphatemia include secondary hyperparathyroidism and renal osteodystrophy. Other signs and symptoms are secondary to the development of hypocalcemia and manifest as anorexia, nausea, vomiting, dehydration, and neuromuscular irritability.

Exogenous sources of phosphorus (eg, dietary sources, PN, and phosphate-containing enemas or laxatives) should be decreased or eliminated in the setting of hyperphosphatemia. Conventional aluminum- and calcium-based phosphate binders can be used to reduce intestinal absorption of phosphorus. However, calcium-free binders (ie, lanthanum carbonate, sevelamer hydrochloride or carbonate) are at least as effective and without the untoward risks of anemia and osteomalacia seen with use of aluminum-based agents.102 Dialysis may be required to treat severe hyperphosphatemia associated with CKD. In patients with normal renal function, volume repletion is usually sufficient.

Acid-Base Disorders

Nearly all biochemical reactions are influenced by the pH of their fluid environment. Accordingly, the acid-base balance of body fluids is critical and tightly regulated. Alterations in acid-base balance can have adverse consequences and, when severe, can be life-threatening.

Terminology

An understanding of acid-base terminology is critical to accurately diagnose and manage acid-base disorders. An acid is a substance that can donate hydrogen ions (H+). A base is a substance that can accept or combine with hydrogen ions.1 The free H+ concentration determines the acidity of body fluids and is represented by the pH. Because the pH varies inversely with the H+ concentration, an increase in the H+ concentration reduces the pH and a decrease in the H+ concentration elevates the pH. The pH of arterial blood is normally maintained within the narrow range of 7.35 to 7.45. A pH below 7.35 is called acidemia; a pH greater than 7.45 is called alkalemia.1 Processes that tend to raise or lower the H+ concentration are called acidosis and alkalosis, respectively. Recognizing the distinction between these terms is necessary to evaluate acid-base disorders in patients in whom both acidotic and alkalotic processes may coexist (mixed acid-base disorders).

Acid-Base Physiology

Although small amounts of acidic substances enter the body via ingested foods, most hydrogen ions originate as byproducts or end products of cellular metabolism. Metabolism of carbohydrates and fats alone results in the daily production of approximately 15,000 mmol carbon dioxide (CO_2), which combines with water to form carbonic acid (H_2CO_3). Protein metabolism accounts for another 50 to 100 mEq of daily acid (noncarbonic acid) production.103 A progressive accumulation of acid would occur if these substances were not excreted from the body.

The concentration of H+ in body fluids must be tightly regulated to maintain a pH compatible with life (6.80 to 7.80).1 The process of H+ regulation involves 3 sequential steps: (1) chemical buffering by extracellular and intracellular mechanisms; (2) control of the partial pressure of CO_2 in the blood by alterations in the rate of alveolar ventilation; and (3) control of the plasma bicarbonate concentration by changes in renal H+ excretion.

Buffering prevents large changes in the H+ concentration in the body. This process is the body's first line of defense and occurs immediately to resist changes in pH. Buffer systems are primarily weak acids and base pairs that can take up or release H+ so that changes in the free H+ concentration are minimized. The principal buffer system is the carbonic acid/bicarbonate (H_2CO_3/HCO_3^-) system. Other buffer systems, including proteins, phosphate, and hemoglobin, also contribute to the maintenance of normal pH.

The principal role of the lungs in maintaining acid-base balance is to regulate the pressure exerted by dissolved CO_2 gas in the blood (PCO_2). Of all the chemicals influencing respiration, CO_2 is the most powerful respiratory stimulant. Both the rate and depth of ventilation can be altered to allow for the

excretion of CO2 generated by diet and cellular metabolism. Adjustments in the rate and depth of ventilation begin to compensate for acid-base disturbances within minutes. Conditions that impair respiratory system functioning (eg, opiate overdose) have the potential to cause acid-base imbalances.

The final and slowest mechanism by which the body maintains acid-base balance is via alterations in renal H+ excretion. Two processes achieve this: (1) reabsorption of filtered HCO3– and (2) excretion of the H+ produced daily as a result of protein metabolism. Of all the regulatory mechanisms involved in acid-base homeostasis, only the kidneys have the ability to regulate levels of alkaline substances in the blood and eliminate metabolic acids (organic acids other than carbonic acid) from the body.

Assessment

Blood gases are used to assess a patient's oxygenation and acid-base status. Arterial blood gases (ABGs) reflect the ability of the lungs to oxygenate blood, whereas venous blood gases (VBGs) reflect tissue oxygenation. Blood gas measurements consist of the pH, PCO2, partial pressure of oxygen in the blood (PO2), oxygen saturation (SaO2), calculated HCO3–, and the base excess. Table 7-14 lists normal values for ABGs and VBGs.

TABLE 7-14 Normal Blood Gas Values

pH	7.40 (7.35–7.45)	7.36 (7.33–7.43)
	Arterial Blood Gas	**Mixed Venous Blood Gas**
PCO_2, mm Hg	35–45	41–51
PO_2, mm Hg	80–100	35–40
O_2 saturation, %	95	70–75
HCO_3–, mEq/L	22–26	24–28
Base excess	–2 to +2	0 to +4

HCO3–, bicarbonate; O2, oxygen; PCO2, partial pressure of carbon dioxide in the blood; PO2, partial pressure of oxygen in the blood.

As previously described, the pH reflects the degree of blood acidity. The PCO2 provides information on the lung's ability to excrete CO2, and changes in PCO2 are associated with respiratory processes that can lead to acid-base disorders. Serum CO2 (HCO3–) is the acid component of the carbonic acid/bicarbonate buffer system. Increases in PCO2 represent an acidosis, and decreases in PCO2 represent an alkalosis. PO2 reflects the ability of hemoglobin to carry oxygen. The higher the PO2 value, the more saturated hemoglobin is with oxygen. The PO2 value is directly related to the SaO2 (eg, when PO2 is high, the SaO2 of the blood is high).

Either the calculated HCO3– reported in a blood gas or the measured serum HCO3– can be used to evaluate acid-base status. Changes in HCO3– are associated with metabolic processes that can lead to acid-base disorders. HCO3– is the base component of the carbonic acid/bicarbonate buffer system. Increases in serum or calculated HCO3– represent an alkalosis, and decreases represent an acidosis. HCO3– can also be reported by clinical laboratories as total CO2 content, which is the sum of measured serum HCO3– plus dissolved CO2 in blood plus carbonic acid. Thus, the values for total CO2 content are slightly higher than measured serum HCO3– alone.

Base excess is a calculated value that estimates the metabolic component of an acid-base disorder. An elevated base excess indicates metabolic alkalosis, whereas a base deficit occurs in metabolic acidosis.

An analysis of acid-base disorders requires a systematic approach to avoid misdiagnosis and inappropriate treatment. The following stepwise approach is useful in evaluating even the most complex cases:

Step 1: Assess the pH of blood to determine whether the patient is acidemic (pH less than 7.4) or alkalemic (pH greater than 7.4). If the pH is 7.4, an acid-base disorder cannot be ruled out. A mixed acid-base disorder or compensation may be present.

Step 2: Assess the PCO2 to determine whether a respiratory process may be contributing to an acid-base disorder. If the PCO2 is elevated, the patient has a respiratory acidosis. If the PCO2 is low, the patient has a respiratory alkalosis (Table 7-15).

Step 3: Assess the serum HCO3– to determine whether a metabolic process may be contributing to an acid-base disorder. If the HCO3– is elevated, the patient has a metabolic alkalosis (Table 7-16). If the HCO3– is low, the patient has a metabolic acidosis (Table 7-17).

Step 4: Calculate the anion gap (refer to the “Metabolic Acidosis” section later in the chapter for the equation) to determine whether metabolic acidosis is present. This calculation is critical to determine the etiology of the acid-base disorder and select the appropriate treatment.

Step 5: Determine whether the acid-base disorder is acute or chronic, and use the recommended formulas in Table 7-18 to determine whether the acid-base disorders are appropriately compensated. If compensation is not appropriate, the patient has a mixed acid-base disorder.

TABLE 7-15 Causes of Respiratory Acid-Base Disorders

Respiratory acidosis

- Central depression of respiration
- Drugs (opioids, anesthetics, sedatives)
- Stroke
- Head injury
- Sleep apnea
- Perfusion abnormalities
- Massive pulmonary embolism
- Cardiac arrest
- Airway or pulmonary abnormalities:

– Hypoxemia or tissue abnormalities

– Airway obstruction

– Asthma

– Chronic obstructive pulmonary disorder

– Severe pulmonary edema

– Severe pneumonia

– Acute respiratory distress syndrome

– Smoke inhalation

– Pneumothorax

- Neuromuscular abnormalities:

– Brainstem or cervical cord injury

– Guillain-Barré syndrome

– Myasthenia gravis

– Multiple sclerosis

- Obesity hypoventilation (Pickwickian syndrome)
- Mechanical ventilator hypoventilation
- Parenteral or enteral nutrition overfeeding

Respiratory alkalosis

- Central stimulation of respiration
- Anxiety
- Pain
- Fever
- Brain tumors
- Vascular accidents
- Head trauma
- Pregnancy
- Catecholamines
- Salicylates
- Peripheral stimulation
- Pulmonary embolus
- Asthma
- High altitudes
- Pneumonia
- Pulmonary edema

- Severe anemia
- Mechanical ventilator hyperventilation
- Hepatic encephalopathy

TABLE 7-16 Causes of Metabolic Alkalosis

Saline responsive (urine chloride <20 mEq/L)

- Gastrointestinal loss
- Vomiting
- Nasogastric suction
- Renal loss
- Diuretic therapy
- Excessive bicarbonate administration
- Rapid correction of hypocapnia

Saline-resistant (urine chloride >20 mEq/L)

- Excess mineralocorticoids
- Cushing's syndrome
- Hyperaldosteronism
- Profound hypokalemia (serum potassium <2 mEq/L)
- Excessive licorice ingestion (eg, from chewing tobacco)

TABLE 7-17 Causes of Metabolic Acidosis

Normal anion gap

- Gastrointestinal loss of HCO3–:

– Diarrhea

– Pancreatic or small bowel fistula

– Obstructed ileal loop conduit

– Ketoacidosis

– Ureterosigmoidostomy

– Anion-exchange resins

- Renal loss of HCO3–:

– Type 2 renal tubular acidosis

– Carbonic anhydrase inhibitors

– Hyperparathyroidism

– Hypoaldosteronism

- Ingestion of ammonium chloride or parenteral nutrition containing chloride salts

Increased anion gap

- Increased production of endogenous acid:

– Lactic acidosis

– Ketoacidosis (diabetic, starvation, alcoholic)

– Inborn errors of metabolism

- Failure to excrete acids:

– Renal failure

- Ingestion of exogenous acid:

– Salicylates, methanol, ethanol

HCO3–, bicarbonate

TABLE 7-18 Renal and Respiratory Compensation to Primary Acid-Base Disorders

Disorder	Primary Disturbance	Compensatory Response
Metabolic acidosis	HCO_3^-	1.2 mm Hg decrease in PCO_2 for every 1 mEq/L decrease in HCO_3^-
Metabolic alkalosis	HCO_3^-	0.7 mm Hg increase in PCO_2 for every 1 mEq/L increase in HCO_3^-
Acute respiratory acidosis	PCO_2	1 mEq/L increase in HCO_3^- for every 10 mm Hg increase in PCO_2
Chronic respiratory acidosis	PCO_2	3.5 mEq/L increase in HCO_3^- for every 10 mm Hg increase in PCO_2
Acute respiratory alkalosis	PCO_2	2 mEq/L decrease in HCO_3^- for every 10 mm Hg decrease in PCO_2
Chronic respiratory alkalosis	PCO_2	4 mEq/L decrease in HCO_3^- for every 10 mm Hg decrease in PCO_2

HCO3–, bicarbonate; PCO2, partial pressure of carbon dioxide in the blood.

Respiratory Acidosis

Respiratory acidosis is a clinical disorder characterized by a reduced pH, an elevation in the PCO2, and a variable increase in the serum HCO3– concentration (Table 7-19).1 Respiratory acidosis almost always results from decreased effective alveolar ventilation, not an increase in CO2 production. Hypoventilation can occur when any step in the ventilatory process is compromised. Table 7-15 includes common causes of respiratory acidosis.

TABLE 7-19 Characteristics of the Primary Acid-Base Disorders

Disorder	pH	Primary Disturbance	Compensatory Response
Metabolic acidosis	↓	↓ HCO_3^-	↓ PCO_2
Metabolic alkalosis	↑	↑ HCO_3^-	↑ PCO_2
Respiratory acidosis	↓	↑ PCO_2	↑ HCO_3^-
Respiratory alkalosis	↑	↓ PCO_2	↓ HCO_3^-

HCO3–, bicarbonate; PCO2, partial pressure of carbon dioxide in the blood.

Respiratory Alkalosis

Respiratory alkalosis is a clinical disturbance characterized by an elevated pH, a decrease in PCO2, and a variable reduction in serum HCO3– concentration (Table 7-19).1 Respiratory alkalosis occurs when effective alveolar ventilation is increased beyond the level necessary to eliminate metabolically produced CO2. Table 7-15 includes common causes of hyperventilation that can result in respiratory alkalosis.

Metabolic Acidosis

Metabolic acidosis is a clinical disturbance characterized by a reduced pH, reduced serum HCO3– concentration, and compensatory hyperventilation resulting in a decrease in PCO2 (Table 7-19).1 Metabolic acidosis can be induced by 2 fundamental mechanisms: (1) an inability of the kidneys to excrete the dietary H+ load or (2) an increase in the generation of H+ either by the addition of H+ or the loss of HCO3–.

The anion gap represents unmeasured serum anions (proteins, phosphate, sulfate, and organic ions) and unmeasured serum cations (potassium, calcium, magnesium).104 Therefore, calculating the anion gap is often useful in the differential diagnosis of metabolic acidosis. It is equal to the difference between the serum concentrations of the major cations and the major measured anions:1

Anion Gap = [Serum Na+] – ([Serum Cl–] + [Serum HCO3–])

where all values are measured in mEq/L.

Normal anion gap is 9 mEq/L (range 3 to 11 mEq/L). Albumin accounts for a significant portion of the unmeasured serum anions. For every 1 g/dL decrease in serum albumin, 2.5 mEq/L must be added to the anion gap.

The anion gap is used to differentiate between the 2 main types of metabolic acidosis: normal anion gap acidosis (hyperchloremic acidosis) and elevated anion gap acidosis. In the setting of normal anion gap acidosis, there is a milliequivalent-for-milliequivalent replacement of extracellular HCO3– by Cl–; thus, the anion gap does not change because the sum of the major measured anions remains constant. Increased GI or renal bicarbonate losses cause this disorder, also known as hyperchloremic metabolic acidosis. Elevated anion gap acidosis is associated with an accumulation of unmeasured anions, which leads to an elevation in the anion gap. Metabolic acidosis with an elevated anion gap commonly results

from increased endogenous organic acid production. Table 7-17 lists common causes of metabolic acidosis with an increased or normal anion gap. Practice Scenario 7-3 discusses the management of metabolic acidosis.

Practice Scenario 7-3

Question: How would you alter the electrolyte composition of a parenteral nutrition (PN) formulation for a patient with an elevated end ileostomy output?

Scenario: BB was a 54-year-old woman with a 30-year history of Crohn's disease. Her disease course had included small bowel strictures resulting in multiple small bowel resections, ultimately requiring the creation of an end ileostomy. She was admitted to the hospital for progressive weight loss and fatigue, elevated ileostomy output (3 to 4.5 L/d), and acute renal failure secondary to volume depletion. Albumin and prealbumin on admission were 2.1 g/dL and 18.6 mg/dL, respectively. Intravenous fluids with 0.9% sodium chloride (NaCl) were started at 125 mL/h in addition to a regular diet. By Day 3, BB developed a severe metabolic acidosis and continued to experience ileostomy output greater than 3 L/d. The dietitian reported BB primarily consumed high-fat, fried foods and milkshakes. The patient's laboratory test results for the first 3 days included the following results:

Day	Na^+, mEq/L	K^+, mEq/L	Cl^-, mEq/L	HCO_3^-, mEq/L	BUN, mg/dL	Creatinine, mg/dL
1	131	3.3	97	18	69	1.4
2	137	4.1	112	14	30	1.2
3	137	4.1	114	12	23	1.1

Intervention: PN formulated to correct the metabolic acidosis was started on Day 3. The patient was counseled to restrict her diet to small, frequent meals.

Answer: The PN formulation for a high-output ileostomy patient should contain maximum amounts of acetate salts to prevent and/or correct a hyperchloremic metabolic acidosis. In this patient, PN was started at 50% of estimated energy needs to reduce the risk for refeeding syndrome and acetate salts were maximized. Common acetate additives for PN include sodium acetate and potassium acetate. Based on patient laboratory parameters, the amounts of sodium and potassium acetate should be tailored for individual needs/tolerance. In addition, the sodium concentration in the PN should be equal to that of 0.9% NaCl (normal saline) to approximate the sodium concentration of ileostomy fluid.

Rationale: Patients with high-output ileostomies are at risk for acid-base disturbances secondary to anatomical changes. The management of high-output ileostomies (greater than 1 L/d) should include fluid replacement that approximates the electrolyte composition of ileal fluid (Table 7-1).

Metabolic Alkalosis

Metabolic alkalosis is characterized by an elevation in the pH, an increase in the serum HCO_3^- concentration, and compensatory hypoventilation, resulting in a rise in the PCO_2 (Table 7-19).1 Loss of gastric acid (HCl) as a result of vomiting or nasogastric suction and loss of intravascular volume and chloride as a result of diuretic use are common causes of metabolic alkalosis. This disorder is observed in approximately 33% to 55% of hospitalized patients with acid-base disturbances.105 Metabolic alkalosis in this setting is often caused by the overzealous treatment of metabolic acidosis with bicarbonate or an excess of acetate in PN solutions, which is metabolized to bicarbonate with a normally functioning liver. In addition, the transcellular shift of H^+ that typically occurs with severe hypokalemia may contribute to the development of a metabolic alkalosis.

Under normal circumstances, the kidneys are able to correct a metabolic alkalosis by excreting the excess HCO_3^- in the urine. Therefore, some degree of impairment in renal HCO_3^- excretion must be present for maintenance of metabolic alkalosis.1 In general, the mechanisms that sustain metabolic alkalosis can be classified into volume-mediated processes (saline responsive) and volume-independent processes (saline unresponsive). The urine chloride concentration is useful in the differential diagnosis of metabolic alkalosis and predicts those patients likely to respond to volume replacement.

Saline-responsive metabolic alkalosis (urine chloride less than 20 mEq/L) is by far the more prevalent disorder. Common causes are listed in Table 7-16. In these disorders, the increase in HCO_3^- reabsorption that maintains the alkalosis can be reversed by the administration of half-isotonic or isotonic saline. Although adequate NaCl repletion will usually normalize the plasma HCO_3^- concentration, it will not reverse metabolic alkalosis associated with moderate to severe hypokalemia. Only the administration of potassium chloride will correct this disorder.

Saline-resistant disorders (urine chloride greater than 20 mEq/L) are commonly associated with hyperaldosteronism and are characterized by a high urinary chloride concentration. Management of these disorders typically consists of the treatment of the underlying cause of the mineralocorticoid excess. Aggressive potassium repletion should also be employed when hypokalemia is present with metabolic alkalosis in primary hyperaldosteronism.

Mixed Acid-Base Disorders

Patients may simultaneously have more than one acid-base disturbance (ie, a mixed acid-base disorder). The diagnosis of a mixed disorder requires an understanding of the extent of the renal and respiratory compensations for each of the simple acid-base disturbances (Table 7-18). If a given set of blood gases does not fall within the range of expected responses for a simple acid-base disturbance, a mixed disorder should be suspected. Common examples include (1) mixed respiratory acidosis and metabolic acidosis, (2) mixed respiratory alkalosis and metabolic alkalosis, (3) mixed metabolic acidosis and respiratory alkalosis, and (4) mixed metabolic alkalosis and respiratory acidosis.