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Fluid and Electrolyte Disorders

PART VI

Chapter 73 Electrolyte and Acid-Base Disorders

73.1 Composition of Body Fluids

Larry A. Greenbaum

TOTAL BODY WATER

Total body water (TBW) as a percentage of body weight varies with age (Fig. 73.1). The fetus has very high TBW, which gradually decreases to approximately 75% of birthweight for a term infant. Premature infants have higher TBW than term infants. During the first year of life, TBW decreases to approximately 60% of body weight and remains at this level until puberty. At puberty, the fat content of females increases more than that in males, who acquire more muscle mass than females. Because fat has very low water content and muscle has high water content, by the end of puberty TBW in males remains at 60%, but TBW in females decreases to approximately 50% of body weight. The high fat content in overweight children causes a decrease in TBW as a percentage of body weight. During dehydration, TBW decreases and thus is a smaller percentage of body weight.

FLUID COMPARTMENTS

TBW is divided between two main compartments: **intracellular fluid (ICF)** and **extracellular fluid (ECF)**. In the fetus and newborn, the ECF volume is larger than the ICF volume (see Fig. 73.1). The normal postnatal diuresis causes an immediate decrease in the ECF volume. This is followed by continued expansion of the ICF volume, which results from cellular growth. By 1 year of age, the ratio of ICF volume to ECF volume approaches adult levels. The ECF volume is approximately 20–25% of body weight, and the ICF volume is approximately 30–40% of body weight, close to twice the ECF volume (Fig. 73.2). With puberty, the increased muscle mass of males causes them to have a higher ICF volume than females. There is no significant difference in the ECF volume between postpubertal females and males.

The ECF is further divided into the plasma water and the interstitial fluid (see Fig. 73.2). The *plasma water* is 5% of body weight. The blood volume, given a hematocrit of 40%, is usually 8% of body weight, although it is higher in newborns and young infants; in premature newborns it is approximately 10% of body weight. The volume of plasma water can be altered by pathologic conditions, including dehydration, anemia, polycythemia, heart failure, abnormal plasma osmolality, and hypoalbuminemia. The *interstitial fluid,* normally 15% of body weight, can increase dramatically in diseases associated with edema, such as heart failure, protein-losing enteropathy, liver failure, nephrotic syndrome, and sepsis. An increase in interstitial fluid also occurs in patients with ascites or pleural effusions.

There is a delicate equilibrium between the intravascular fluid and the interstitial fluid. The balance between hydrostatic and

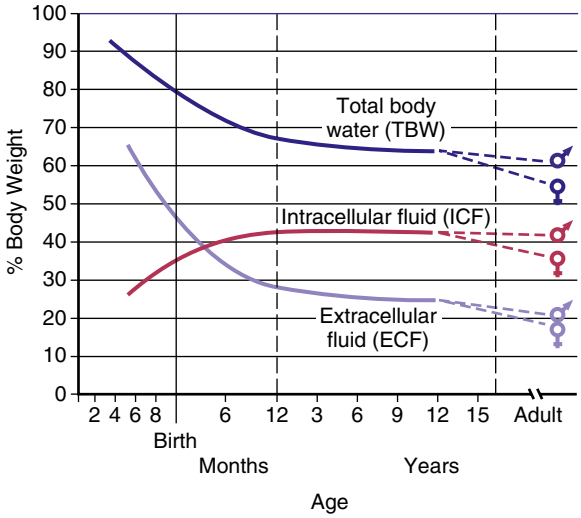

Fig. 73.1 Total body water, intracellular fluid, and extracellular fluid as a percentage of body weight as a function of age. *(From Winters RW. Water and electrolyte regulation. In: Winters RW, ed. The Body Fluids in Pediatrics. Little, Brown; 1973.)*

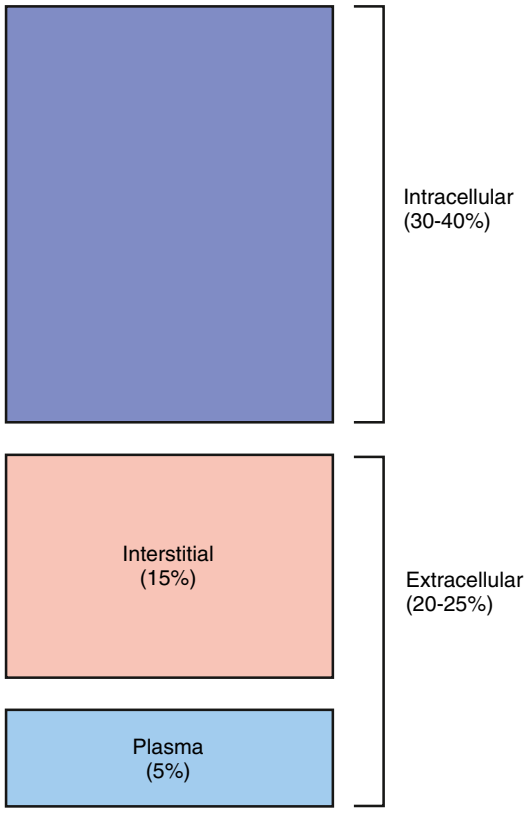

Fig. 73.2 Compartments of total body water, expressed as percentages of body weight, in an older child or adult.

oncotic forces regulates the intravascular volume, which is critical for proper tissue perfusion. The *intravascular fluid* has a higher concentration of albumin than the interstitial fluid, and the consequent oncotic force draws water into the intravascular space. The maintenance of this gradient depends on the limited permeability of albumin across the capillaries. The hydrostatic pressure of the intravascular space, which is caused by the pumping action of the heart, drives fluid out of the intravascular space. These forces favor movement into the interstitial space at the arterial ends of the capillaries. The decreased hydrostatic forces and increased oncotic forces, which result from the dilutional increase in albumin concentration, cause movement of fluid into the venous ends of the capillaries. Overall, there is usually a net movement of fluid out of the intravascular space to the interstitial space, but this fluid is returned to the circulation via the *lymphatics*.

An imbalance in these forces may cause expansion of the interstitial volume at the expense of the intravascular volume. In children with hypoalbuminemia, the decreased oncotic pressure of the intravascular fluid contributes to the development of **edema**. Loss of fluid from the intravascular space may compromise the intravascular volume, placing the child at risk for inadequate blood flow to vital organs. This is especially likely in diseases in which capillary leak occurs because the loss of albumin from the intravascular space is associated with an increase in the albumin concentration in the interstitial space, further compromising the oncotic forces that normally maintain intravascular volume. In contrast, with **heart failure**, there is an increase in venous hydrostatic pressure from expansion of the intravascular volume, which is caused by impaired pumping by the heart, and the increase in venous pressure causes fluid to move from the intravascular space to the interstitial space. Expansion of the intravascular volume and increased intravascular pressure also cause the edema that occurs with acute glomerulonephritis.

ELECTROLYTE COMPOSITION

The composition of the solutes in the ICF and ECF are very different (Fig. 73.3). **Sodium** (Na^+) and **chloride** (Cl^-) are the dominant cation and anion, respectively, in ECF. The sodium and chloride concentrations ([Na^+], [Cl^-]) in the ICF are much lower. **Potassium** (K^+) is the most abundant cation in the ICF, and its concentration ([K^+]) within the cells is approximately 30 times higher than in the ECF. Proteins, organic anions, and phosphate are the most plentiful anions in the ICF. The dissimilarity between the anions in the ICF and the ECF is largely determined by the presence of intracellular molecules that do not cross the cell membrane, the barrier separating the ECF and the ICF. In contrast, the difference in the distribution of cations (Na^+ and K^+) relies on activity of the Na^+,K^+-adenosine triphosphatase (ATPase) pump and membrane ion channels.

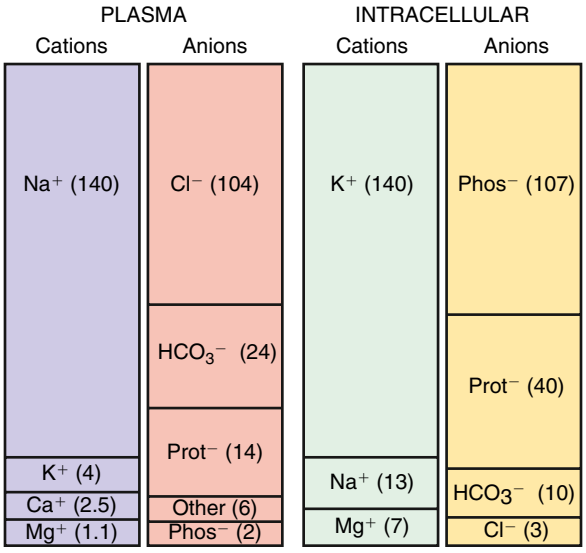

Fig. 73.3 Concentrations of the major cations and anions in the intracellular space and the plasma, expressed in mEq/L.

The difference in the electrolyte compositions of the ECF and the ICF has important ramifications in the evaluation and treatment of electrolyte disorders. Serum concentrations of electrolytes ([Na^+], [K^+], and [Cl^-]) do not always reflect total body content. Intracellular [K^+] is much higher than the serum concentration. A shift of K^+ from the **intracellular space (ICS)** can maintain a normal or even an elevated serum [K^+] despite massive losses of K^+ from the ICS. This effect is seen in diabetic ketoacidosis, in which significant K^+ depletion is masked by transmembrane shift of K^+ from the ICF to the ECF. Therefore, for K^+ and phosphorus, electrolytes with a high intracellular concentration, serum level may not reflect total body content. Similarly, the serum **calcium** concentration ([Ca^{2+}]) does not reflect total body content of Ca^{2+}, which is largely contained in bone (see Chapter 69).

OSMOLALITY

The ICF and the ECF are in **osmotic equilibrium** because the cell membrane is permeable to water. If the osmolality in one compartment changes, then water movement leads to a rapid equalization of osmolality, with a shift of water between the ICS and **extracellular space (ECS)**. Clinically, the primary process is usually a change in the osmolality of the ECF, with resultant shift of water into the ICF if ECF osmolality decreases, or vice versa if ECF osmolality increases. The *ECF osmolality* can be determined and *usually equals ICF osmolality*. **Plasma osmolality**, normally 285-295 mOsm/kg, is measured by the degree of freezing-point depression. The plasma osmolality can also be *estimated* by a calculation based on the following formula:

$$\text{Osmolality} = 2 \times [\text{Na}] + [\text{glucose}]/18 + [\text{BUN}]/2.8$$

Glucose and blood urea nitrogen (BUN) are reported in mg/dL. Division of these values by 18 and 2.8, respectively, converts the units into mmol/L. Multiplication of the [Na^+] value by 2 accounts for its accompanying anions, principally Cl^- and bicarbonate. The calculated osmolality is usually slightly lower than measured osmolality.

Urea is not confined to the ECS because it readily crosses the cell membrane, and its intracellular concentration approximately equals its extracellular concentration. Whereas an elevated [Na^+] causes a shift of water from the ICS, with **uremia** there is no osmolar gradient between the two compartments and consequently no movement of water. The only exception is during **hemodialysis**, when the decrease in extracellular urea is so rapid that intracellular urea does not have time to equilibrate. **Disequilibrium syndrome** during hemodialysis may result in a shift of water into brain cells and lead to severe symptoms. Ethanol, because it freely crosses cell membranes, is another ineffective osmole. Hence, the effective osmolality can be calculated as follows:

$$\text{Effective osmolality} = 2 \times [\text{Na}] + [\text{glucose}]/18$$

The *effective osmolality* determines the osmotic force that is mediating the shift of water between the ECF and the ICF.

Hyperglycemia causes an increase in the plasma osmolality because it is not in equilibrium with the ICS. During hyperglycemia, there is shift of water from the ICS to the ECS. This shift causes dilution of the Na^+ in the ECS, causing hyponatremia despite elevated plasma osmolality. The magnitude of this effect can be calculated as follows:

$$[Na]_{corrected} = [Na]_{measured} + 1.6 \times ([glucose] - 100 \text{ mg/dL})/100$$

where $[Na]_{measured}$ = Na^+ concentration measured by the clinical laboratory and $[Na]_{corrected}$ = corrected Na^+ concentration (the Na^+ concentration if the glucose concentration were normal and its accompanying water moved back into the cells). The $[Na]_{corrected}$ is the more reliable indicator of the ratio of total body Na^+ to TBW, the usual determinant of the $[Na^+]$.

Normally, measured osmolality and calculated osmolality are within 10 mOsm/kg. However, there are some clinical situations in which this difference does not occur. The presence of **unmeasured osmoles** causes measured osmolality to be significantly elevated in comparison with the calculated osmolality. An **osmolal gap** is present when the difference between measured osmolality exceeds calculated osmolality by >10 mOsm/kg. Examples of unmeasured osmoles include ethanol, ethylene glycol, methanol, sucrose, sorbitol, and mannitol. These substances increase measured osmolality but are not part of the equation for calculating osmolality. The presence of an osmolal gap is a clinical clue to the presence of unmeasured osmoles and may be diagnostically useful when there is clinical suspicion of poisoning with methanol or ethylene glycol.

Pseudohyponatremia is a second situation in which there is discordance between measured osmolality and calculated osmolality. Lipids and proteins are the solids of the serum. In patients with elevated serum lipids or proteins, the water content of the serum decreases because water is displaced by the larger amounts of solids. Some instruments measure $[Na^+]$ by determining the amount of Na^+ per liter of serum, including the solid component. When the solid component increases, there is a decrease in $[Na^+]$ per liter of serum, despite a normal concentration when based on the amount of Na^+ per liter of serum water. *It is the concentration of Na^+ in serum water that is physiologically relevant.* A similar problem occurs when using instruments that require dilution of the sample before measurement of Na^+ (indirect potentiometry). In both situations, the plasma osmolality is normal despite the presence of pseudohyponatremia, because the method for measuring osmolality is not appreciably influenced by the percentage of serum that is composed of lipids and proteins. Pseudohyponatremia is diagnosed by the finding of a normal measured plasma osmolality despite hyponatremia. This laboratory artifact does not occur if the $[Na^+]$ in water is measured directly with an ion-specific electrode, as with arterial blood gas (ABG) analyzers. **Pseudohypernatremia** may occur in patients with very low levels of serum proteins by a similar mechanism.

When there are no unmeasured osmoles and pseudohyponatremia is not a concern, the calculated osmolality provides an accurate estimate of the plasma osmolality. Measurement of plasma osmolality is useful for detecting or monitoring unmeasured osmoles and confirming the presence of true hyponatremia. Whereas many children with high plasma osmolality are dehydrated—as seen with hypernatremic dehydration or diabetic ketoacidosis—high osmolality does not always equate with dehydration. A child with salt poisoning or uremia has an elevated plasma osmolality but may be volume overloaded.

POINT-OF-CARE TESTING

Point-of-care (POC) testing offers a number of advantages, including rapid turnaround and usually smaller blood sample volume required. POC devices may provide more accurate results in certain situations, such as pseudohyponatremia (see earlier) and pseudohyperkalemia (see Chapter 73.4). However, the agreement between POC and the laboratory is variable, and thus caution is needed when interpreting results. Because of bias, POC and laboratory results should not be used on an alternating basis when following critical trends (e.g., during correction of hypernatremia or hyponatremia; see Chapter 73.3).

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73.2 Regulation of Osmolality and Volume

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The regulation of plasma **osmolality** and the intravascular **volume** is controlled by independent systems for water balance, which determines osmolality, and sodium balance, which determines volume status. Maintenance of normal osmolality depends on control of water balance. Control of volume status depends on regulation of sodium balance. When present, volume depletion takes precedence over regulation of osmolality, and retention of water contributes to the maintenance of intravascular volume.

REGULATION OF OSMOLALITY

The plasma osmolality is tightly regulated and maintained at 285-295 mOsm/kg. Modification of water intake and excretion maintains normal plasma osmolality. In the steady state, the combination of water intake and water produced by the body from oxidation balances water losses from the skin, lungs, urine, and gastrointestinal (GI) tract. Only water intake and urinary losses can be regulated.

Osmoreceptors in the hypothalamus sense plasma osmolality (see Chapter 594). An elevated effective osmolality leads to secretion of **antidiuretic hormone (ADH)** by neurons in the supraoptic and paraventricular nuclei in the hypothalamus. The axons of these neurons terminate in the posterior pituitary. Circulating ADH binds to its V_2 receptors in the collecting duct cells of the kidney and causes insertion of water channels (aquaporin-2) into the renal collecting duct cells. This produces increased permeability to water, permitting resorption of water into the hypertonic renal medulla. Urine concentration increases and water excretion decreases. Urinary water losses cannot be eliminated because there is obligatory excretion of urinary solutes, such as urea and sodium. The regulation of ADH secretion is tightly linked to plasma osmolality, responses being detectable with a 1% change in osmolality. ADH secretion virtually disappears when plasma osmolality is low, allowing excretion of maximally dilute urine. The resulting loss of free water (i.e., water without Na^+) corrects plasma osmolality. ADH secretion is not an all-or-nothing response; there is a graded adjustment as the osmolality changes.

Water intake is regulated by hypothalamic osmoreceptors, which stimulate thirst when the serum osmolality increases. Thirst occurs with a small increase in the serum osmolality. *Control of osmolality is subordinate to maintenance of an adequate intravascular volume.* When volume depletion is present, both ADH secretion and thirst are stimulated, regardless of the plasma osmolality. The sensation of thirst requires moderate volume depletion but only a 1–2% change in the plasma osmolality.

A number of conditions can limit the kidney's ability to excrete adequate water to correct low plasma osmolality. In the **syndrome of inappropriate antidiuretic hormone (SIADH)**, ADH continues to be produced despite a low plasma osmolality (see Chapters 73.3 and 597).

The glomerular filtration rate (GFR) affects the kidney's ability to eliminate water. With a decrease in the GFR, less water is delivered to

the collecting duct, limiting the amount of water that can be excreted. The impairment in the GFR must be quite significant to limit the kidney's ability to respond to an excess of water.

The **minimum urine osmolality** is approximately 30-50 mOsm/kg. This places an upper limit on the kidney's ability to excrete water; sufficient solute must be present to permit water loss. Massive water intoxication may exceed this limit, whereas a lesser amount of water is necessary in the child with a diet that has very little solute. This can produce severe hyponatremia in children who receive little salt and have minimal urea production as a result of inadequate protein intake. Volume depletion is an extremely important cause of decreased water loss by the kidney despite a low plasma osmolality. This "appropriate" secretion of ADH occurs because volume depletion takes precedence over the osmolality in the regulation of ADH.

The **maximum urine osmolality** is approximately 1,200 mOsm/kg. The obligatory solute losses dictate the minimum volume of urine that must be produced, even when maximally concentrated. Obligatory water losses increase in patients with high salt intake or high urea losses, as may occur after relief of a urinary obstruction or during recovery from acute kidney injury. An increase in urinary solute and thus water losses occurs with an **osmotic diuresis**, which results classically from glycosuria in diabetes mellitus as well as iatrogenically after mannitol administration. There are developmental changes in the kidney's ability to concentrate the urine. The maximum urine osmolality in a newborn, especially a premature newborn, is less than that in an older infant or child. This limits the ability to conserve water and makes such a patient more vulnerable to hypernatremic dehydration. Very high fluid intake, as seen with **psychogenic polydipsia**, can dilute the high osmolality in the renal medulla, which is necessary for maximal urinary concentration. If fluid intake is restricted in patients with this condition, the kidney's ability to concentrate the urine may be somewhat impaired, although this defect corrects after a few days without polydipsia. This may also occur during the initial treatment of central diabetes insipidus with desmopressin acetate; the renal medulla takes time to achieve its normal maximum osmolality.

REGULATION OF VOLUME

An appropriate intravascular volume is critical for survival; both volume depletion and volume overload may cause significant morbidity and mortality. Because sodium is the principal extracellular cation and is restricted to the ECF, adequate body sodium is necessary for maintenance of intravascular volume. The principal extracellular anion, Cl^-, is also necessary, but for simplicity, Na^+ balance is considered the main regulator of volume status because body content of sodium and that of chloride usually change proportionally, given the need for equal numbers of cations and anions. In some situations, Cl^- depletion is considered the dominant derangement causing volume depletion (metabolic alkalosis with volume depletion).

The kidney determines sodium balance because there is little homeostatic control of sodium intake, even though **salt craving** does occasionally occur, typically in children with chronic renal salt loss. The kidney regulates Na^+ balance by altering the percentage of filtered Na^+ that is resorbed along the nephron. Normally, the kidney excretes <1% of the Na^+ filtered at the glomerulus. In the absence of disease, extrarenal losses and urinary output match intake, with the kidney having the capacity to adapt to large variations in sodium intake. When necessary, urinary sodium excretion can be reduced to virtually undetectable levels or increased dramatically.

The most important determinant of renal Na^+ excretion is the volume status of the child; it is the effective intravascular volume that influences urinary Na^+ excretion. The *effective intravascular volume* is the volume status that is sensed by the body's regulatory mechanisms. Heart failure is a state of volume overload, but the effective intravascular volume is low because poor cardiac function prevents adequate perfusion of the kidneys and other organs. This explains the avid renal Na^+ retention often present in patients with heart failure.

The **renin-angiotensin system** is an important regulator of renal Na^+ excretion. The juxtaglomerular apparatus produces renin in response to decreased effective intravascular volume. Specific stimuli for renin release are decreased perfusion pressure in the afferent arteriole of the glomerulus, decreased delivery of sodium to the distal nephron, and β_1-adrenergic agonists, which increase in response to intravascular volume depletion. Renin, a proteolytic enzyme, cleaves angiotensinogen, producing angiotensin I. Angiotensin-converting enzyme (ACE) converts angiotensin I into angiotensin II. The actions of angiotensin II include direct stimulation of the proximal tubule to increase sodium resorption *and* stimulation of the adrenal gland to increase aldosterone secretion. Through its actions in the distal nephron—specifically, the late distal convoluted tubule and the collecting duct—aldosterone increases sodium resorption. Aldosterone also stimulates potassium excretion, increasing urinary losses. Along with decreasing urinary loss of sodium, angiotensin II acts as a vasoconstrictor, which helps maintain adequate blood pressure in the presence of volume depletion.

Volume expansion stimulates the synthesis of **atrial natriuretic peptide (ANP)**, which is produced by the atria in response to atrial wall distention. Along with increasing the GFR, ANP inhibits Na^+ resorption in the medullary portion of the collecting duct, facilitating an increase in urinary Na^+ excretion.

Volume overload occurs when Na^+ intake exceeds output. Children with kidney failure have impaired ability to excrete Na^+. The GFR is low at birth, limiting a newborn's ability to excrete a Na^+ load. In other situations, there is a loss of the appropriate regulation of renal Na^+ excretion. This loss of regulation occurs in patients with excessive aldosterone, as seen in primary hyperaldosteronism or renal artery stenosis, where excess renin production leads to high aldosterone levels. In acute glomerulonephritis, even without significantly reduced GFR, the normal intrarenal mechanisms that regulate Na^+ excretion malfunction, causing excessive renal retention of Na^+ and volume overload.

Renal retention of Na^+ occurs during volume depletion, but this appropriate response causes the severe excess in total body Na^+ that is present in heart failure, liver failure, nephrotic syndrome, and other causes of hypoalbuminemia. In these diseases, the effective intravascular volume is decreased, causing the kidney and the various regulatory systems to respond, leading to renal Na^+ retention and edema formation.

Volume depletion usually occurs when Na^+ losses exceed intake. The most common etiology in children is gastroenteritis. Excessive losses of sodium may also occur from the skin in children with burns, in sweat from patients with cystic fibrosis, or after vigorous exercise. Inadequate intake of Na^+ is uncommon except in neglect, in famine, or with an inappropriate choice of liquid diet in a child who cannot take solids. Urinary Na^+ wasting may occur in a range of renal diseases, from renal dysplasia to tubular disorders, such as Bartter syndrome. The neonate, especially if premature, has a mild impairment in the ability to conserve Na^+. Iatrogenic renal Na^+ wasting takes place during diuretic therapy. Renal Na^+ loss occurs as a result of derangement in the normal regulatory systems. An absence of aldosterone, seen most frequently in children with **congenital adrenal hyperplasia** caused by 21-hydroxylase deficiency, causes sodium wasting (see Chapter 616).

Isolated disorders of water balance can affect volume status and Na^+ balance. Because the cell membrane is permeable to water, changes in TBW influence both the extracellular volume and the intracellular volume. In isolated water loss, as occurs in diabetes insipidus, the impact is greater on the ICS because it has a greater volume than the ECS. Thus, compared with other types of dehydration, hypernatremic dehydration has less impact on plasma volume; most of the fluid loss comes from the ICS. Yet, significant water loss eventually affects intravascular volume and will stimulate renal Na^+ retention, even if total body Na^+ content is normal. Similarly, with acute water intoxication or SIADH, there is an excess of TBW, but most is in the ICS. However, there is some effect on the intravascular volume, which causes renal excretion

of Na^+. Children with SIADH or water intoxication have high urine Na^+ concentration despite hyponatremia. This finding reinforces the concept of independent control systems for water and Na^+, but the 2 systems interact when pathophysiologic processes dictate, and control of effective intravascular volume always takes precedence over control of osmolality.

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73.3 Sodium

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SODIUM METABOLISM

Body Content and Physiologic Function

Sodium is the dominant cation of the ECF (see Fig. 73.3), and it is the principal determinant of extracellular osmolality. Na^+ is therefore necessary for the maintenance of intravascular volume. Less than 3% of Na^+ is intracellular. More than 40% of total body Na^+ is in bone; the remainder is in the interstitial and intravascular spaces. The low intracellular [Na^+], approximately 10 mEq/L, is maintained by Na^+,K^+-ATPase, which exchanges intracellular Na^+ for extracellular K^+.

Sodium Intake

A child's diet determines the amount of Na^+ ingested—a predominantly cultural determination in older children. An occasional child has salt craving because of an underlying salt-wasting renal disease or adrenal insufficiency. Children in the United States tend to have very high salt intakes because their diets include a large amount of "junk" food or fast food. Infants receive sodium from breast milk (approximately 7 mEq/L) and formula (7-13 mEq/L, for 20 calorie/oz formula).

Sodium is readily absorbed throughout the GI tract. Mineralocorticoids increase sodium transport into the body, although this effect has limited clinical significance. The presence of glucose enhances sodium absorption because of the presence of a co-transport system. This is the rationale for including sodium and glucose in oral rehydration solutions (see Chapter 387).

Sodium Excretion

Sodium excretion occurs in stool and sweat, but the kidney regulates Na^+ balance and is the principal site of Na^+ excretion. There is some Na^+ loss in stool, but it is minimal unless diarrhea is present. Normally, sweat has 5-40 mEq/L of sodium. Sweat [Na^+] is increased in children with cystic fibrosis, aldosterone deficiency, or pseudohypoaldosteronism. The higher sweat losses in these conditions may cause or contribute to Na^+ depletion.

Sodium is unique among electrolytes because water balance, not Na^+ balance, usually determines its concentration. When the [Na^+] increases, the resultant higher plasma osmolality causes increased thirst and increased secretion of ADH, which leads to renal conservation of water. Both these mechanisms increase the water content of the body, and the [Na^+] returns to normal. During hyponatremia, the decrease in plasma osmolality stops ADH secretion, and consequent renal water excretion leads to an increase in the [Na^+]. Even though water balance is usually regulated by osmolality, volume depletion does stimulate thirst, ADH secretion, and renal conservation of water. Volume depletion takes precedence over osmolality; volume depletion stimulates ADH secretion, even if a patient has hyponatremia.

The excretion of Na^+ by the kidney is not regulated by the plasma osmolality. The patient's effective plasma volume determines the amount of sodium in the urine. This is mediated by a variety of regulatory systems, including the renin-angiotensin-aldosterone system and intrarenal mechanisms. In hyponatremia or hypernatremia, the underlying pathophysiology determines the amount of urinary Na^+, not the serum [Na^+].

Table 73.1 Causes of Hypernatremia

EXCESSIVE SODIUM
Improperly mixed formula
Excess sodium bicarbonate
Ingestion of seawater or sodium chloride
Intentional salt poisoning (child abuse or fictitious disorder inflicted on another)
Intravenous hypertonic saline
Sodium phosphate enemas
Hyperaldosteronism
WATER DEFICIT
Nephrogenic Diabetes Insipidus
Acquired
X-linked (OMIM 304800)
Autosomal recessive (OMIM 125800)
Autosomal dominant (OMIM 125800)
Central Diabetes Insipidus
Acquired*
Autosomal recessive (OMIM 125700/600955)
Autosomal dominant (OMIM 125700)
Wolfram syndrome (OMIM 222300/604928/598500)
Hypothalamic neurogenic (essential) adipsic hypernatremia
Increased Insensible Losses
Premature infants
Radiant warmers
Phototherapy
Inadequate Intake
Ineffective breastfeeding
Child neglect or abuse
Adipsia (lack of thirst)
WATER AND SODIUM DEFICITS
Gastrointestinal Losses
Diarrhea
Emesis/nasogastric suction
Osmotic cathartics (lactulose)
Cutaneous Losses
Burns
Excessive sweating
Renal Losses
Osmotic diuretics (mannitol)
Diabetes mellitus
Chronic kidney disease (dysplasia and obstructive uropathy)
Polyuric phase of acute tubular necrosis
Postobstructive diuresis

*Acquired: central diabetes insipidus from CNS malformations, trauma, meningitis, tumor, infiltration, unknown.

OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

HYPERNATREMIA

Hypernatremia is a [Na^+] >145 mEq/L, although it is sometimes defined as >150 mEq/L. Mild hypernatremia is common in children, especially among infants with gastroenteritis. Hypernatremia in hospitalized patients may be iatrogenic, which is caused by inadequate water administration or, less often, by excessive Na^+ administration. Moderate or severe hypernatremia has significant morbidity because of the underlying disease, the effects of hypernatremia on the brain, and the risks of overly rapid correction.

Etiology and Pathophysiology

There are three basic mechanisms of hypernatremia (Table 73.1). *Sodium intoxication* may be iatrogenic in a hospital setting because of correction of metabolic acidosis with sodium bicarbonate. Baking soda, a putative home remedy for upset stomach, is another source of sodium bicarbonate; the hypernatremia is accompanied by a profound metabolic alkalosis. Hypernatremia may develop following sodium phosphate emesis. In hyperaldosteronism, there is renal retention of sodium and resultant hypertension; hypernatremia may not be present or is usually mild.

The classic causes of hypernatremia from a *water deficit* are **nephrogenic** and **central diabetes insipidus** (see Chapters 570 and 596). Hypernatremia develops in diabetes insipidus only if the patient does not have access to water or cannot drink adequately because of immaturity, neurologic impairment, emesis, or anorexia. Infants are at high risk because of their inability to control their own water intake. Central diabetes insipidus and the genetic forms of nephrogenic diabetes insipidus typically cause massive urinary water losses and very dilute urine. The water losses are less dramatic, and the urine often has the same osmolality as plasma when nephrogenic diabetes insipidus is secondary to intrinsic renal disease (obstructive uropathy, renal dysplasia, sickle cell disease).

The other causes of a water deficit are also secondary to an imbalance between losses and intake. Newborns, especially if premature, have high insensible water losses. Losses are further increased if the infant is placed under a radiant warmer or with the use of phototherapy for hyperbilirubinemia. The renal concentrating mechanisms are not optimal at birth, providing an additional source of water loss. Ineffective breastfeeding, often in a primiparous mother, can cause severe hypernatremic dehydration. **Adipsia**, the absence of thirst, is usually secondary to damage to the hypothalamus, such as from trauma, tumor, hydrocephalus, or histiocytosis. Primary adipsia (**essential hypernatremia**) is rare but is seen in children with central nervous system (CNS) malformations (septo-optic dysphasia, holoprosencephaly, optic nerve hypoplasia).

When hypernatremia occurs in conditions with *deficits of sodium and water,* the water deficit exceeds the sodium deficit. This occurs only if the patient is unable to ingest adequate water. Diarrhea results in depletion of both Na^+ and water. Because diarrhea is hypotonic—typical Na^+ concentration of 35-65 mEq/L—water losses exceed Na^+ losses, potentially leading to hypernatremia. Most children with gastroenteritis do not have hypernatremia because they drink enough hypotonic fluid to compensate for stool water losses (see Chapter 387). Fluids such as water, juice, and formula are more hypotonic than the stool losses, allowing correction of the water deficit and potentially even causing hyponatremia. Hypernatremia is most likely to occur in the child with diarrhea who has inadequate intake because of emesis, lack of access to water, or anorexia.

Osmotic agents, including mannitol, and glucose in diabetes mellitus, cause excessive renal losses of water and Na^+. Because the urine is hypotonic ($[Na^+]$ of approximately 50 mEq/L) during an osmotic diuresis, water loss exceeds Na^+ loss, and hypernatremia may occur if water intake is inadequate. Certain chronic kidney diseases, such as renal dysplasia and obstructive uropathy, are associated with tubular dysfunction, leading to excessive losses of water and Na^+. Many children with such diseases have disproportionate water loss and are at risk for hypernatremic dehydration, especially if gastroenteritis supervenes. Similar mechanisms occur during the polyuric phase of acute kidney injury and after relief of urinary obstruction (postobstructive diuresis). Patients with either condition may have an osmotic diuresis from urinary losses of urea and an inability to conserve water because of tubular dysfunction.

Clinical Manifestations

Most children with hypernatremia are dehydrated and show the typical clinical signs and symptoms (see Chapter 75). Children with hypernatremic dehydration tend to have better preservation of intravascular volume because of the shift of water from the ICS to the ECS. This shift maintains blood pressure and urine output and allows hypernatremic infants to be less symptomatic initially and potentially to become more dehydrated before medical attention is sought. Breastfed infants with hypernatremia are often profoundly dehydrated, with failure to thrive (malnutrition). Probably because of intracellular water loss, the pinched abdominal skin of a dehydrated, hypernatremic infant has a "doughy" feel.

Hypernatremia, even without dehydration, causes central nervous system (CNS) symptoms that tend to parallel the degree of $[Na^+]$ elevation and the acuity of the increase. Patients are irritable, restless, weak, and lethargic. Some infants have a high-pitched cry and hyperpnea. Alert patients are very thirsty, even though nausea may be present. Hypernatremia may cause fever, although many patients have an underlying process that contributes to the fever. Hypernatremia is associated with hyperglycemia and mild hypocalcemia; the mechanisms are unknown. Beyond the sequelae of dehydration, there is no clear direct effect of hypernatremia on other organs or tissues, except the brain.

Brain hemorrhage is the most devastating consequence of *untreated* hypernatremia. As the extracellular osmolality increases, water moves out of brain cells, leading to a decrease in brain volume. This decrease can result in tearing of intracerebral veins and bridging blood vessels as the brain moves away from the skull and the meninges. Patients may have subarachnoid, subdural, and parenchymal hemorrhages. Seizures and coma are possible sequelae of the hemorrhage, although seizures are more common during correction of hypernatremia. The cerebrospinal fluid protein is often elevated in infants with significant hypernatremia, probably because of leakage from damaged blood vessels. Neonates, especially if premature, seem especially vulnerable to hypernatremia and excessive sodium intake. There is an association between rapid or hyperosmolar sodium bicarbonate administration and the development of intraventricular hemorrhages in neonates. Even though **osmotic demyelination syndrome (ODS)**, which includes central pontine myelinolysis and extrapontine myelinolysis, is classically associated with overly rapid correction of hyponatremia, it can occur in children with hypernatremia (see "Treatment"). Thrombotic complications occur in severe hypernatremic dehydration, including stroke, dural sinus thrombosis, peripheral thrombosis, and renal vein thrombosis. This is secondary to dehydration and possibly hypercoagulability associated with hypernatremia.

Diagnosis

The etiology of hypernatremia is usually apparent from the history. Hypernatremia resulting from water loss occurs only if the patient does not have access to water or is unable to drink. In the absence of dehydration, it is important to ask about sodium intake. Children with excess salt intake do not have signs of dehydration, unless another process is present. Severe Na^+ intoxication causes signs of volume overload, such as pulmonary edema and weight gain. **Salt poisoning** is associated with an elevated fractional excretion of Na^+, whereas hypernatremic dehydration causes a low fractional excretion of Na^+. Gastric sodium concentrations are often elevated in salt poisoning. In hyperaldosteronism, hypernatremia is usually mild or absent and is associated with edema, hypertension, hypokalemia, and metabolic alkalosis.

When there is isolated water loss, the signs of volume depletion are usually less severe initially because much of the loss is from the ICS. When pure water loss causes signs of dehydration, the hypernatremia and water deficit are usually severe. In the child with renal water loss, either central or nephrogenic diabetes insipidus, the urine is inappropriately dilute and urine volume is not low. The urine is maximally concentrated and urine volume is low if the losses are extrarenal or caused by inadequate intake. With extrarenal causes of loss of water, the urine osmolality should be >1,000 mOsm/kg. When diabetes insipidus is suspected, the evaluation may include measurement of ADH and a water-deprivation test, including a trial of desmopressin acetate (synthetic ADH analog) to differentiate between nephrogenic diabetes insipidus and central

diabetes insipidus (see Chapters 570 and 596). A water-deprivation test is unnecessary if the patient has simultaneous documentation of hypernatremia and poorly concentrated urine (osmolality lower than that of plasma). In children with central diabetes insipidus, administration of desmopressin acetate increases the urine osmolality above the plasma osmolality, although maximum osmolality does not occur immediately because of the decreased osmolality of the renal medulla as a result of the chronic lack of ADH. In children with nephrogenic diabetes insipidus, there is no response to desmopressin acetate. *Hypercalcemia or hypokalemia may produce a nephrogenic diabetes insipidus–like syndrome.*

With combined Na^+ and water deficits, analysis of the urine differentiates between renal and nonrenal etiologies. When the losses are extrarenal, the kidney responds to volume depletion with low urine volume, concentrated urine, and Na^+ retention (urine $[Na^+]$ <20 mEq/L, fractional excretion of Na^+ <1%). With renal causes, the urine volume is not appropriately low, the urine is not maximally concentrated, and the urine $[Na^+]$ may be inappropriately elevated.

Treatment

As hypernatremia develops, the brain generates **idiogenic osmoles** to increase the intracellular osmolality and prevent the loss of brain water. This mechanism is not instantaneous and is most prominent when hypernatremia has developed gradually. If the serum $[Na^+]$ is lowered rapidly, there is movement of water from the serum into the brain cells to equalize the osmolality in the two compartments. The resultant brain swelling may manifest as seizures or coma.

Because of the associated dangers, *chronic hypernatremia should not be corrected rapidly.* The goal is to decrease the serum $[Na^+]$, but avoid a decrease of more than 10 mEq/L every 24 hours. The most important component of correcting moderate or severe hypernatremia is frequent monitoring of the serum $[Na^+]$ value so that fluid therapy can be adjusted to provide adequate correction, neither too slow nor too fast. If a child has seizures because of brain edema secondary to rapid correction, administration of hypotonic fluid should be stopped. An infusion of 3% saline can acutely increase the serum $[Na^+]$, reversing the cerebral edema.

Chapter 75 outlines a detailed approach to the child with hypernatremic dehydration. Acute, severe hypernatremia, usually secondary to sodium administration, can be corrected more rapidly with 5% dextrose in water (D5W) because idiogenic osmoles have not had time to accumulate. This fact balances the high morbidity and mortality rates associated with hypernatremia with the dangers of overly rapid correction. When hypernatremia is severe and is caused by sodium intoxication, it may be impossible to administer enough water to correct the hypernatremia rapidly without worsening the volume overload. In this situation, dialysis allows for removal of the excess Na^+, with the precise strategy dependent on the mode of dialysis. In less severe cases, the addition of a loop diuretic increases the removal of excess Na^+ and water, decreasing the risk of volume overload. With Na^+ overload, hypernatremia is corrected with Na^+-free intravenous (IV) fluid (D5W).

Hyperglycemia from hypernatremia is not usually a problem and is not treated with insulin because the acute decrease in glucose may precipitate cerebral edema by lowering plasma osmolality. Rarely, the glucose concentration of IV fluids must be reduced (from 5% to 2.5% dextrose in water). The secondary hypocalcemia is treated as needed.

It is important to address the underlying cause of the hypernatremia, if possible. The child with central diabetes insipidus should receive desmopressin acetate. Because this treatment reduces renal excretion of water, excessive intake of water must be avoided to prevent both overly rapid correction of the hypernatremia and the development of hyponatremia. Over the long-term, reduced sodium intake and the use of medications can somewhat ameliorate the water losses in nephrogenic diabetes insipidus (see Chapter 570). The daily water intake of a child receiving tube feeding may need to be increased to compensate for high losses. The patient with significant ongoing losses, such as through diarrhea, may need supplemental water and electrolytes (see Chapter 74). Sodium intake is reduced if it contributed to the hypernatremia.

HYPONATREMIA

Hyponatremia, a very common electrolyte abnormality in hospitalized patients, is a serum sodium level <135 mEq/L. Both total body sodium and TBW determine the serum sodium concentration. Hyponatremia exists when the ratio of water to Na^+ is increased. This condition can occur with low, normal, or high levels of body Na^+. Similarly, body water can be low, normal, or high.

Etiology and Pathophysiology

Table 73.2 lists the causes of hyponatremia. **Pseudohyponatremia** is a laboratory artifact present when the plasma contains very high concentrations of protein (multiple myeloma, intravenous immune globulin [IVIG] infusion) or lipid (hypertriglyceridemia, hypercholesterolemia). It does not occur when a direct ion-selective electrode determines the $[Na^+]$ in undiluted plasma, a technique that is used by ABG analyzers or POC instruments (see Chapter 73.1). In true hyponatremia, the measured osmolality is low, whereas it is normal in pseudohyponatremia. **Hyperosmolality,** as may occur with hyperglycemia, causes a low $[Na^+]$ because water moves down its osmotic gradient from the ICS into the ECS, diluting the $[Na^+]$. However, because the manifestations of hyponatremia are a result of the low plasma osmolality, patients with hyponatremia resulting from hyperosmolality do not have symptoms of hyponatremia. When the etiology of the hyperosmolality resolves, such as hyperglycemia in diabetes mellitus, water moves back into the cells, and the $[Na^+]$ rises to its "true" value. Mannitol or sucrose, a component of IVIG preparations, may cause hyponatremia because of hyperosmolality.

Classification of hyponatremia is based on the patient's volume status. In **hypovolemic hyponatremia,** the child has lost Na^+ from the body. The water balance may be positive or negative, but Na^+ loss has been higher than water loss. The pathogenesis of the hyponatremia is usually a combination of Na^+ loss and water retention to compensate for the volume depletion. The patient has a pathologic increase in fluid loss, and this fluid contains Na^+. Most fluid that is lost has a lower $[Na^+]$ than that of plasma. Viral diarrhea fluid has an average $[Na^+]$ of 50 mEq/L. Replacing diarrhea fluid, which has $[Na^+]$ of 50 mEq/L, with formula, which has only approximately 7-10 mEq/L of Na^+, reduces the serum $[Na^+]$. Intravascular volume depletion interferes with renal water excretion, the body's usual mechanism for preventing hyponatremia. The volume depletion stimulates ADH synthesis, resulting in renal water retention. Volume depletion also decreases the GFR and enhances water resorption in the proximal tubule, thereby reducing water delivery to the collecting duct.

Diarrhea as a result of gastroenteritis is the most common cause of hypovolemic hyponatremia in children. Emesis causes hyponatremia if the patient takes in hypotonic fluid, either IV or enterally, despite the emesis. Most patients with emesis have either a normal $[Na^+]$ or hypernatremia. Burns may cause massive losses of isotonic fluid and resultant volume depletion. Hyponatremia develops if the patient receives hypotonic fluid. Losses of sodium from sweat are especially high in children with cystic fibrosis, aldosterone deficiency, or pseudohypoaldosteronism, although high losses can also occur in a hot climate. Third space losses are isotonic and can cause significant volume depletion, leading to ADH production and water retention, which can cause hyponatremia if the patient receives hypotonic fluid. In diseases that cause volume depletion through extrarenal Na^+ loss, the urine Na^+ level should be low (<10 mEq/L) as part of the renal response to maintain the intravascular volume. The only exceptions are diseases that cause both extrarenal and renal Na^+ losses: adrenal insufficiency and pseudohypoaldosteronism.

Table 73.2 Causes of Hyponatremia

PSEUDOHYPONATREMIA
Hyperlipidemia
Hyperproteinemia
HYPEROSMOLALITY
Hyperglycemia
Iatrogenic (mannitol, sucrose, glycine)
HYPOVOLEMIC HYPONATREMIA
Extrarenal Losses
Gastrointestinal (emesis, diarrhea)
Skin (sweating or burns)
Third space losses (bowel obstruction, peritonitis, sepsis)
Renal Losses
Thiazide or loop diuretics
Osmotic diuresis
Postobstructive diuresis
Polyuric phase of acute tubular necrosis
Juvenile nephronophthisis (OMIM 256100/606966/602088/604387/611498)
Autosomal recessive polycystic kidney disease (OMIM 263200)
Tubulointerstitial nephritis
Obstructive uropathy
Cerebral salt wasting
Proximal (type II) renal tubular acidosis (OMIM 604278)*
Lack of aldosterone effect (high serum potassium):
Absence of aldosterone (e.g., 21-hydroxylase deficiency [OMIM 201910])
Pseudohypoaldosteronism type I (OMIM 264350/177735)
Urinary tract obstruction and/or infection
Addison disease
EUVOLEMIC HYPONATREMIA
Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Nephrogenic syndrome of inappropriate antidiuresis (OMIM 304800)
Desmopressin acetate
Glucocorticoid deficiency
Hypothyroidism
Antidepressant medications
Water intoxication
Iatrogenic (excess hypotonic intravenous fluids)
Feeding infants excessive water products
Swimming lessons
Tap water enema
Child abuse
Psychogenic polydipsia
Diluted formula
Beer potomania
Exercise-induced hyponatremia
HYPERVOLEMIC HYPONATREMIA
Heart failure
Cirrhosis
Nephrotic syndrome
Acute, chronic kidney injury
Capillary leak caused by sepsis
Hypoalbuminemia caused by gastrointestinal disease (protein-losing enteropathy)

*Most cases of proximal renal tubular acidosis are not caused by this primary genetic disorder. Proximal renal tubular acidosis is usually part of Fanconi syndrome, which has multiple etiologies.

OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

Table 73.3 Diagnostic Criteria for Syndrome of Inappropriate Antidiuretic Hormone Secretion

- Absence of:
  Renal, adrenal, or thyroid insufficiency
  Heart failure, nephrotic syndrome, or cirrhosis
  Diuretic ingestion
  Dehydration
- Urine osmolality >100 mOsm/kg (usually > plasma)
- Serum osmolality <280 mOsm/kg and serum sodium <135 mEq/L
- Urine sodium >30 mEq/L
- Reversal of "sodium wasting" and correction of hyponatremia with water restriction

Renal Na^+ loss may occur in a variety of situations. In some situations the urine $[Na^+]$ is >140 mEq/L; thus hyponatremia may occur without any fluid intake. In many cases, the urine Na^+ level is less than the serum $[Na^+]$; hence, the intake of hypotonic fluid is necessary for hyponatremia to develop. In diseases associated with urinary Na^+ loss, the urine Na^+ level is >20 mEq/L despite volume depletion. This may not be true if the urinary Na^+ loss is no longer occurring, as is frequently the case if diuretics are discontinued. Because loop diuretics prevent generation of a maximally hypertonic renal medulla, the patient can neither maximally dilute nor concentrate the urine. The inability to maximally retain water provides some protection against severe hyponatremia. The patient receiving thiazide diuretics can concentrate the urine and is at higher risk for severe hyponatremia. Osmotic agents, such as glucose during diabetic ketoacidosis, cause loss of both water and Na^+. Urea accumulates during kidney failure and then acts as an osmotic diuretic after relief of urinary tract obstruction and during the polyuric phase of acute tubular necrosis. Transient tubular damage in these conditions further impairs Na^+ conservation. The serum $[Na^+]$ in these conditions depends on $[Na^+]$ of the fluid used to replace the losses. Hyponatremia develops when the fluid is hypotonic relative to the urinary losses.

Renal salt wasting occurs in hereditary kidney diseases, such as juvenile nephronophthisis and autosomal recessive polycystic kidney disease. Obstructive uropathy, most often a result of posterior urethral valves, produces salt wasting, but patients with the disease may also have hypernatremia as a result of impaired ability to concentrate urine and high-water loss. Acquired tubulointerstitial nephritis, usually secondary to either medications or infections, may cause salt wasting, along with other evidence of tubular dysfunction. CNS injury may produce cerebral salt wasting, which is theoretically caused by the production of a natriuretic peptide that causes renal salt wasting. In type II **renal tubular acidosis (RTA)**, usually associated with Fanconi syndrome (see Chapter 569.1), there is increased excretion of Na^+ and bicarbonate in the urine. Patients with Fanconi syndrome also have glycosuria, aminoaciduria, and hypophosphatemia because of renal phosphate wasting.

Aldosterone is necessary for renal Na^+ retention and for the excretion of K^+ and acid. In congenital adrenal hyperplasia caused by 21-hydroxylase deficiency, the block of aldosterone production results in hyponatremia, hyperkalemia, and metabolic acidosis. Decreased aldosterone secretion may be seen in Addison disease (adrenal insufficiency). In pseudohypoaldosteronism, aldosterone levels are elevated, but there is no response because of either a defective Na^+ channel or a deficiency of aldosterone receptors. A lack of tubular response to aldosterone may occur in children with urinary tract obstruction, especially during an acute urinary tract infection.

In **hypervolemic hyponatremia,** there is an excess of TBW and Na^+, although the increase in water is greater than the increase in Na^+. In most conditions that cause hypervolemic hyponatremia, there is a decrease in the *effective blood volume*, resulting from third space fluid loss, vasodilation, or poor cardiac output. The regulatory systems sense a decrease in effective blood volume and attempt to retain water and Na^+ to correct the problem. ADH causes renal water retention, and the kidney, under the influence of aldosterone and other intrarenal mechanisms, retains sodium. The patient's

sodium concentration decreases because water intake exceeds sodium intake and ADH prevents the normal loss of excess water.

In these disorders, there is low urine [Na^+] (<10 mEq/L) and an excess of both TBW and Na^+. The only exception is in patients with kidney failure and hyponatremia. These patients have an expanded intravascular volume, and hyponatremia can therefore appropriately suppress ADH production. Water cannot be excreted because very little urine is being made. Serum Na^+ is diluted through ingestion of water. Because of renal dysfunction, the urine [Na^+] may be elevated, but urine volume is so low that urine Na^+ excretion has not kept up with Na^+ intake, leading to sodium overload. The urine [Na^+] in kidney failure varies. In patients with acute glomerulonephritis, because it does not affect the tubules, the urine Na^+ level is usually low, whereas in patients with acute tubular necrosis, it is elevated because of tubular dysfunction.

Patients with hyponatremia and no evidence of volume overload or volume depletion have **euvolemic hyponatremia.** These patients typically have an excess of TBW and a slight decrease in total body Na^+. Some of these patients have an increase in weight, implying that they are volume overloaded. Nevertheless, from a clinical standpoint, they usually appear normal or have subtle signs of fluid overload. In SIADH the secretion of ADH is not inhibited by either low serum osmolality or expanded intravascular volume (see Chapter 597). The result is that the child with SIADH is unable to excrete water. This results in dilution of the serum Na^+ and hyponatremia. The expansion of the extracellular volume because of the retained water causes a mild increase in intravascular volume. The kidney increases Na^+ excretion to decrease intravascular volume to normal; thus the patient has a mild decrease in body Na^+. SIADH typically occurs with disorders of the CNS (infection, hemorrhage, trauma, tumor, thrombosis, Guillain-Barré syndrome), but lung disease (infection, asthma, positive pressure ventilation) and malignant tumors (producing ADH) are other potential causes. A variety of medications may cause SIADH, including recreational use of 3,4 -methylenedioxymethylamphetamine (MDMA, or "Ecstasy"), opiates, antiepileptic drugs (carbamazepine, oxcarbazepine, valproate), tricyclic antidepressants, vincristine, cyclophosphamide, and selective serotonin reuptake inhibitors (SSRIs). The diagnosis of SIADH is one of exclusion, because other causes of hyponatremia must be eliminated (Table 73.3). Because SIADH is a state of intravascular volume expansion, low serum uric acid and BUN levels are supportive of the diagnosis. A rare gain-of-function pathogenic variant in the renal ADH receptor causes **nephrogenic syndrome of inappropriate antidiuresis**. Patients with this X-linked disorder appear to have SIADH but have undetectable levels of ADH.

Hyponatremia in hospitalized patients is frequently caused by inappropriate production of ADH and administration of hypotonic IV fluids (see Chapter 74). Causes of inappropriate ADH production include stress, medications such as narcotics or anesthetics, nausea, and respiratory illness. The synthetic analog of ADH, desmopressin acetate, causes water retention and may cause hyponatremia if fluid intake is not appropriately limited. The main uses of desmopressin acetate in children are for the management of central diabetes insipidus and nocturnal enuresis.

Excess water ingestion can produce hyponatremia. In these cases, [Na^+] decreases as a result of dilution. This decrease suppresses ADH secretion, and there is a marked water diuresis by the kidney. Hyponatremia develops only because the intake of water exceeds the kidney's ability to eliminate water. This condition is more likely to occur in infants because their lower GFR limits their ability to excrete water.

Hyponatremia may develop in infants <6 months of age when caregivers offer water to their infant as a supplement, during hot weather, or when they run out of formula. Hyponatremia may result in transient seizures, hypothermia, and poor tone. With cessation of water intake, the hyponatremia rapidly corrects. *Infants <6 months of age should not be given water to drink; infants 6-12 months of age should not receive >1-2 ounces. If the infant appears thirsty, the parent should offer formula or breastfeed the child.*

In some situations the water intoxication causes acute hyponatremia and is caused by a massive **acute water load**. Causes include infant swimming lessons, inappropriate use of hypotonic IV fluids, water enemas, and forced water intake as a form of child abuse. Chronic hyponatremia occurs in children who receive water but limited sodium and protein. The minimum urine osmolality is approximately 50 mOsm/kg; the kidney can excrete 1 L of water only if there is enough solute ingested to produce 50 mOsm for urinary excretion. Because Na^+ and urea (a breakdown product of protein) are the principal urinary solutes, a lack of intake of Na^+ and protein prevents adequate water excretion. This occurs with the use of diluted formula or other inappropriate diets. Subsistence on beer, a poor source of Na^+ and protein, causes hyponatremia because of the inability to excrete the high water load ("beer potomania"). **Exercise-induced hyponatremia**, reported frequently during marathons, is caused by excessive water intake, salt losses from sweat, and secretion of ADH.

The pathogenesis of the hyponatremia in glucocorticoid deficiency (adrenal insufficiency) is multifactorial and includes increased ADH secretion. In hypothyroidism there is an inappropriate retention of water by the kidney, but the precise mechanisms are not clearly elucidated.

Cerebral salt wasting, an uncommon disorder in children, may be confused with SIADH and is often associated with CNS injury or lesions. Cerebral salt wasting produces renal salt losses and hypovolemia (orthostatic hypotension and elevated hematocrit, BUN, or creatinine). Hypovolemia is not seen in SIADH.

Clinical Manifestations

Hyponatremia causes a decrease in the osmolality of the ECS. Because the ICS then has a higher osmolality, water moves from the ECS to the ICS to maintain osmotic equilibrium. The increase in intracellular water causes cells to swell. Although cell swelling is not problematic in most tissues, it is dangerous for the brain, which is confined by the skull. As brain cells swell, there is an increase in intracranial pressure (ICP), which impairs cerebral blood flow. Acute, severe hyponatremia can cause brainstem herniation and apnea; respiratory support is often necessary. Brain cell swelling is responsible for most of the symptoms of hyponatremia. Neurologic symptoms of hyponatremia include anorexia, nausea, emesis, malaise, lethargy, confusion, agitation, headache, seizures, coma, and decreased reflexes. Patients may have hypothermia and Cheyne-Stokes respirations. Hyponatremia can cause muscle cramps and weakness; rhabdomyolysis can occur with water intoxication.

The symptoms of hyponatremia are mostly a result of the decrease in extracellular osmolality and the resulting movement of water down its osmotic gradient into the ICS. Brain swelling can be significantly obviated if the hyponatremia develops gradually, because brain cells adapt to the decreased extracellular osmolality by reducing intracellular osmolality. This reduction is achieved by extrusion of the main intracellular ions (K^+, Cl^-) and a variety of small organic molecules. This process explains why the range of symptoms in hyponatremia is related to both the serum [Na^+] and its rate of decrease. A patient with chronic hyponatremia may have only subtle neurologic abnormalities with a serum [Na^+] of 110 mEq/L, but another patient may have seizures because of an acute decline in serum [Na^+] from 140 to 125 mEq/L.

Diagnosis

The history usually points to a likely etiology of the hyponatremia. Most patients with hyponatremia have a history of volume depletion. Diarrhea and diuretic use are common causes of hyponatremia in children. A history of polyuria, perhaps with enuresis, and/or salt craving is present in children with primary kidney diseases or absence of aldosterone effect. Children may have signs or symptoms suggesting a diagnosis of hypothyroidism or adrenal insufficiency (see Chapters 603 and 615). Brain injury raises the possibility of SIADH or cerebral salt wasting, with the caveat that SIADH is much more likely. Liver disease, nephrotic syndrome, kidney failure, or congestive heart failure may be

acute or chronic. The history should include a review of the patient's intake, both IV and enteral, with careful attention to the amounts of water, Na^+, and protein.

The traditional first step in the diagnostic process is determination of the plasma osmolality. This is done because some patients with a low serum [Na^+] do not have low osmolality. The clinical effects of hyponatremia are secondary to the associated low osmolality. Without a low osmolality, there is no movement of water into the ICS.

A patient with hyponatremia can have a low, normal, or high osmolality. A normal osmolality in combination with hyponatremia occurs in pseudohyponatremia. Children with elevation of serum glucose concentration or of another effective osmole (mannitol) have a high plasma osmolality and hyponatremia. The presence of a low osmolality indicates "true" hyponatremia. Patients with low osmolality are at risk for neurologic symptoms and require further evaluation to determine the etiology of the hyponatremia.

In some situations, true hyponatremia is present despite a normal or elevated plasma osmolality. The presence of an ineffective osmole, usually urea, increases the plasma osmolality, but because urea has the same concentration in the ICS, it does not cause fluid to move into the ECS. There is no dilution of the serum Na^+ by water, and the [Na^+] remains unchanged if the ineffective osmole is eliminated. Most importantly, the ineffective osmole does not protect the brain from edema caused by hyponatremia. Therefore a patient may have symptoms of hyponatremia despite having a normal or increased osmolality because of uremia.

In patients with true hyponatremia, the next step in the diagnostic process is to clinically evaluate the volume status. Patients with hyponatremia can be hypovolemic, hypervolemic, or euvolemic. The diagnosis of volume depletion relies on the usual findings with dehydration (see Chapter 75), although subtle volume depletion may not be clinically apparent. Children with hypervolemia are edematous on physical examination. They may have ascites, pulmonary edema, pleural effusion, or hypertension.

Hypovolemic hyponatremia can have renal or nonrenal causes. The urine [Na^+] is very useful in differentiating between renal and nonrenal causes. When the losses are nonrenal and the kidney is working properly, there is renal retention of Na^+, a normal homeostatic response to volume depletion. Thus the urinary [Na^+] is low, typically <10 mEq/L, although Na^+ conservation in neonates is less avid. When the kidney is the cause of the Na^+ loss, the urine [Na^+] is >20 mEq/L, reflecting the defect in renal Na^+ retention. The interpretation of the urine Na^+ level is challenging with diuretic therapy because it is high when diuretics are being used but low after the diuretic effect is gone. This becomes an issue only when diuretic use is surreptitious. The urine [Na^+] is not useful if a metabolic alkalosis is present; the urine [Cl^-] must be used instead (see Chapter 73.7).

Differentiating among the nonrenal causes of hypovolemic hyponatremia is usually facilitated by the history. Although the renal causes are more challenging to distinguish, a high serum [K^+] is associated with disorders in which the Na^+ wasting is caused by absence of or ineffectiveness of aldosterone.

In the patient with hypervolemic hyponatremia, the urine [Na^+] is a helpful parameter. It is usually <10 mEq/L, except in the patient with kidney failure.

Treatment

The management of hyponatremia is based on the pathophysiology of the specific etiology. The management of all causes requires judicious monitoring and avoidance of an overly quick normalization of the serum [Na^+]. A patient with severe symptoms (seizures), no matter the etiology, should be given a bolus of hypertonic saline to produce a small, rapid increase in serum sodium. *Hypoxia worsens cerebral edema,* and *hyponatremia may exacerbate hypoxic cell swelling.* Therefore pulse oximetry should be monitored and hypoxia aggressively corrected.

With all causes of hyponatremia, it is important to avoid overly rapid correction, which may cause *osmotic demyelination syndrome (ODS)*, which includes central pontine myelinolysis and extrapontine myelinolysis. This syndrome, which occurs within several days of rapid correction of hyponatremia, produces neurologic symptoms, including confusion, agitation, flaccid or spastic quadriparesis, and death. There are usually characteristic pathologic and radiologic changes in the brain. Despite severe symptoms, full recovery does occur in some patients.

ODS is more common in patients who are treated for *chronic* hyponatremia than for acute hyponatremia. Presumably, this difference is based on the adaptation of brain cells to the hyponatremia. The reduced intracellular osmolality, an adaptive mechanism for chronic hyponatremia, makes brain cells susceptible to dehydration during rapid correction of the hyponatremia, which may be the mechanism of ODS. Even though ODS is rare in pediatric patients, it is advisable to avoid correcting the serum [Na^+] by >10 mEq/L/24 hr or >18 mEq/L/48 hr. Desmopressin is a potential option if the serum [Na^+] is increasing too rapidly. This guideline *does not* apply to acute hyponatremia, as may occur with water intoxication, because the hyponatremia is more often symptomatic, and the adaptive decrease in brain osmolality has not had time to occur. The consequences of brain edema in acute hyponatremia exceed the small risk of ODS.

Patients with hyponatremia can have severe neurologic symptoms, such as seizures and coma. The seizures associated with hyponatremia generally are poorly responsive to anticonvulsants. The child with hyponatremia and severe symptoms needs treatment that will quickly reduce cerebral edema. This goal is best accomplished by increasing the extracellular osmolality so that water moves down its osmolar gradient from the ICS to the ECS.

Intravenous hypertonic saline rapidly increases serum [Na^+], and the effect on serum osmolality leads to a decrease in brain edema. Each mL/kg of 3% NaCl increases the serum [Na^+] by approximately 1 mEq/L. A child with active symptoms often improves after receiving 4-6 mL/kg of 3% NaCl.

The child with **hypovolemic hyponatremia** has a deficiency in Na^+ and may have a deficiency in water. The cornerstone of therapy is to replace the Na^+ deficit and any water deficit present. The first step in treating any dehydrated patient is to restore the intravascular volume with isotonic saline. Ultimately, complete restoration of intravascular volume suppresses ADH production, thereby permitting excretion of the excess water. Chapter 75 discusses the management of hyponatremic dehydration.

The management of **hypervolemic hyponatremia** is difficult; patients have an excess of both water and Na^+. Administration of Na^+ leads to worsening volume overload and edema. In addition, patients are retaining water and Na^+ because of their ineffective intravascular volume or renal insufficiency. The cornerstone of therapy is water and Na^+ restriction, because patients have volume overload. Diuretics may help by causing excretion of both Na^+ and water. Vasopressin receptor antagonists (**vaptans**), by blocking the action of ADH and causing a water diuresis, are effective in correcting the hypervolemic hyponatremia caused by heart failure. Vaptans are contraindicated if there are moderate to severe CNS symptoms.

Hyponatremic patients with low albumin from nephrotic syndrome have a better response to diuretics after an infusion of 25% albumin; the [Na^+] often normalizes as a result of expansion of the intravascular volume. A child with heart failure may have an increase in renal water and Na^+ excretion if there is an improvement in cardiac output. This improvement will "turn off" the regulatory hormones causing renal water (ADH) and Na^+ (aldosterone) retention. The patient with kidney failure cannot respond to any of these therapies except fluid restriction. Insensible fluid losses eventually result in an increase in the [Na^+] as long as insensible and urinary losses are greater than intake. A more definitive approach in children with kidney failure is to perform dialysis, which removes water and Na^+.

In **isovolumic hyponatremia** there is usually an excess of water and a mild Na^+ deficit. Therapy is directed at eliminating the excess water. The child with acute excessive water intake loses water in the urine

because ADH production is turned off as a result of the low plasma osmolality. Children may correct their hyponatremia spontaneously over 3-6 hours. For acute, symptomatic hyponatremia as a result of water intoxication, hypertonic saline may be needed to reverse cerebral edema. For chronic hyponatremia from poor solute intake, the child needs an appropriate formula, and excess water intake should be eliminated.

Children with **iatrogenic hyponatremia** caused by the administration of hypotonic IV fluids should receive 3% saline if symptomatic. Subsequent management is dictated by the patient's volume status. The hypovolemic child should receive isotonic IV fluids. The child with nonphysiologic stimuli for ADH production should undergo fluid restriction. Prevention of this iatrogenic complication requires judicious use of IV fluids (see Chapter 74).

Specific hormone replacement is the cornerstone of therapy for the hyponatremia of hypothyroidism or cortisol deficiency. Correction of the underlying defect permits appropriate elimination of the excess water.

SIADH is a condition of excess water, with limited ability of the kidney to excrete water. The mainstay of its therapy is fluid restriction with normal sodium intake. Furosemide and NaCl supplementation are effective in the patient with SIADH and *severe* hyponatremia. Even in a patient with SIADH, furosemide causes an increase in water and Na^+ excretion. The loss of Na^+ is somewhat counterproductive, but this Na^+ can be replaced with hypertonic saline. Because the patient has a net loss of water and the urinary losses of Na^+ have been replaced, there is an increase in the $[Na^+]$, but no significant increase in blood pressure. Vaptans, which block the action of ADH and cause a water diuresis, are effective at correcting **euvolemic hyponatremia**, but overly rapid correction is a potential complication. Vaptans are not appropriate for treating symptomatic hyponatremia because it can take a few hours before the water diuresis occurs.

Treatment of chronic SIADH is challenging. Fluid restriction in children is difficult for nutritional and behavioral reasons. Other options are long-term furosemide therapy with Na^+ supplementation, an oral vaptan (tolvaptan), or oral urea.

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73.4 Potassium

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POTASSIUM METABOLISM

Body Content and Physiologic Function

The intracellular $[K^+]$, approximately 150 mEq/L, is much higher than the plasma $[K^+]$ (see Fig. 73.3). The majority of body K^+ is contained in muscle. As muscle mass increases, there is an increase in body K^+. Thus an increase in body K^+ occurs during puberty, and it is more significant in males. The majority of extracellular K^+ is in bone; <1% of total body K^+ is in plasma.

Because most K^+ is intracellular, the plasma concentration does not always reflect the total body K^+ content. A variety of conditions alter the distribution of K^+ between the intracellular and extracellular compartments. Na^+,K^+-ATPase maintains the high intracellular $[K^+]$ by pumping Na^+ out of the cell and K^+ into the cell. This activity balances the normal leak of K^+ out of cells via potassium channels that is driven by the favorable chemical gradient. Insulin increases K^+ movement into cells by activating Na^+,K^+-ATPase. Hyperkalemia stimulates insulin secretion, which helps mitigate the hyperkalemia. Acid-base status affects K^+ distribution, probably via K^+ channels and the Na^+,K^+-ATPase. A decrease in pH drives potassium extracellularly; an increase in pH has the opposite effect. β-Adrenergic agonists stimulate the Na^+,K^+-ATPase, increasing cellular uptake of K^+. This increase is protective, in that hyperkalemia stimulates adrenal release of catecholamines. α-Adrenergic agonists and exercise cause a net movement of K^+ out of the ICS. An increase in plasma osmolality, as with mannitol infusion, leads to water movement out of the cells, and K^+ follows as a result of solvent drag. The serum $[K^+]$ increases by approximately 0.6 mEq/L with each 10 mOsm rise in plasma osmolality.

The high intracellular concentration of K^+, the principal intracellular cation, is maintained through Na^+,K^+-ATPase. The resulting chemical gradient is used to produce the resting membrane potential of cells. K^+ is necessary for the electrical responsiveness of nerve and muscle cells and for the contractility of cardiac, skeletal, and smooth muscle. The changes in membrane polarization that occur during muscle contraction or nerve conduction make these cells susceptible to changes in serum $[K^+]$. The ratio of intracellular to extracellular K^+ determines the threshold for a cell to generate an action potential and the rate of cellular repolarization. The intracellular $[K^+]$ affects cellular enzymes. K^+ is necessary for maintaining cell volume because of its important contribution to intracellular osmolality.

Potassium Intake

Potassium is plentiful in food. Dietary consumption varies considerably, even though 1-2 mEq/kg is the recommended intake. The intestines normally absorb approximately 90% of ingested K^+. Most absorption occurs in the small intestine, whereas the colon exchanges body K^+ for luminal Na^+. Regulation of intestinal losses normally has a minimal role in maintaining potassium homeostasis, although kidney failure, aldosterone, and glucocorticoids increase colonic secretion of K^+. The increase in intestinal losses in the setting of kidney failure and hyperkalemia, which stimulates aldosterone production, is clinically significant, helping to protect against hyperkalemia.

Potassium Excretion

Some loss of K^+ occurs in sweat but is normally minimal. The colon has the ability to eliminate some K^+. In addition, after an acute K^+ load, much of the K^+ (>40%) moves intracellularly, through the actions of epinephrine and insulin, which are produced in response to hyperkalemia. This process provides transient protection from hyperkalemia, but most ingested K^+ is eventually excreted in the urine. The kidneys principally regulate long-term K^+ balance, and they alter excretion in response to a variety of signals. K^+ is freely filtered at the glomerulus, but 90% is resorbed before reaching the distal tubule and collecting duct, the principal sites of K^+ regulation that have the ability to absorb and secrete K^+. The amount of tubular secretion regulates the amount of K^+ that appears in the urine. The plasma $[K^+]$ directly influences secretion in the distal nephron. As the $[K^+]$ increases, secretion increases.

The principal hormone regulating potassium secretion is **aldosterone**, which is released by the adrenal cortex in response to increased plasma K^+. Its main site of action is the cortical collecting duct, where aldosterone stimulates Na^+ movement from the tubule into the cells. This movement creates a negative charge in the tubular lumen, facilitating K^+ excretion. In addition, the increased intracellular Na^+ stimulates the basolateral Na^+,K^+-ATPase, causing more K^+ to move into the cells lining the cortical collecting duct. Glucocorticoids, ADH, a high urinary flow rate, and high Na^+ delivery to the distal nephron also increase urinary K^+ excretion. Insulin, catecholamines, and urinary ammonia decrease K^+ excretion. Whereas ADH increases K^+ secretion, it also causes water resorption, decreasing urinary flow. The net effect is that ADH has little overall impact on K^+ balance. Alkalosis causes potassium to move into cells, including the cells lining the collecting duct. This movement increases K^+ secretion, and because acidosis has the opposite effect; acidosis decreases K^+ secretion.

The kidney can dramatically vary K^+ excretion in response to changes in intake. Normally, approximately 10–15% of the filtered load is excreted. In an adult, excretion of K^+ can vary from 5-1,000 mEq/day.

HYPERKALEMIA

Hyperkalemia—because of the potential for lethal arrhythmias—is one of the most alarming electrolyte abnormalities.

Etiology and Pathophysiology

Three basic mechanisms cause hyperkalemia including increased intake, cellular shifts, and decreased excretion; spurious lab values are also commonly seen (Table 73.4). In the individual patient, the etiology is sometimes multifactorial.

Spurious hyperkalemia or **pseudohyperkalemia** is very common in children because of the difficulties in obtaining blood specimens. This laboratory result is usually caused by hemolysis during a heelstick or phlebotomy, but it can be the result of prolonged tourniquet application or fist clenching, either of which causes local potassium release from muscle.

The serum $[K^+]$ is normally 0.4 mEq/L higher than the plasma value, secondary to K^+ release from cells during clot formation. This phenomenon is exaggerated with thrombocytosis because of K^+ release from platelets. For every 100,000/m^3 increase in the platelet count, the serum $[K^+]$ rises by approximately 0.15 mEq/L. This phenomenon also occurs with the marked white blood cell (WBC) count elevations sometimes seen with leukemia. Elevated WBC counts, typically >200,000/m^3, can cause a dramatic elevation in the measured serum $[K^+]$. Analysis of a plasma sample usually provides an accurate result. It is important to analyze the sample promptly to avoid K^+ release from cells, which occurs if the sample is stored in the cold, or cellular uptake of K^+ and spurious hypokalemia, which occurs with storage at room temperature. Pneumatic tube transport can cause pseudohyperkalemia if cell membranes are fragile (leukemia). Occasionally, heparin causes lysis of leukemic cells and a false elevation of the plasma sample; a blood gas syringe has less heparin and may provide a more accurate reading than a standard tube. There are rare genetic disorders causing in vitro leakage of K^+ from red blood cells (RBCs) that may causes familial **pseudohyperkalemia** (autosomal dominant; *ABCB6* gene).

Because of the kidney's ability to excrete K^+, it is unusual for excessive intake, by itself, to cause hyperkalemia. This condition can occur in a patient who is receiving large quantities of IV or oral K^+ for excessive losses that are no longer present. Frequent or rapid blood transfusions can acutely increase the $[K^+]$ because of the K^+ content of blood, which is variably elevated. Increased intake may precipitate hyperkalemia if there is an underlying defect in K^+ excretion.

The ICS has a very high $[K^+]$, so a shift of K^+ from the ICS to the ECS can have a significant effect on the plasma $[K^+]$. This shift occurs with metabolic acidosis, but the effect is minimal with an organic acid (lactic acidosis, ketoacidosis). A respiratory acidosis has less impact than a metabolic acidosis. Cell destruction, as seen with rhabdomyolysis, tumor lysis syndrome, tissue necrosis, or hemolysis, releases K^+ into the extracellular milieu. The K^+ released from RBCs in internal bleeding, such as hematomas, is resorbed and enters the ECS.

Normal doses of succinylcholine or β blockers and fluoride or digitalis intoxication all cause a shift of K^+ out of the intracellular compartment. *Succinylcholine should not be used during anesthesia in patients at risk for hyperkalemia.* β Blockers prevent the normal cellular uptake of K^+ mediated by binding of β-agonists to the β_2-adrenergic receptors. K^+ release from muscle cells occurs during exercise, and levels can increase by 1-2 mEq/L with high activity. With an increased plasma osmolality, water moves from the ICS, and K^+ follows. This process occurs with hyperglycemia, although in nondiabetic patients the resultant increase in insulin causes K^+ to move intracellularly. In diabetic ketoacidosis (DKA), the absence of insulin causes potassium to leave the ICS, and the problem is compounded by the hyperosmolality. The effect of hyperosmolality causes a transcellular shift of K^+ into the ECS after mannitol or hypertonic saline infusions. **Malignant hyperthermia**, which is triggered by some inhaled anesthetics, causes muscle release of potassium (see Chapter 651.2). **Hyperkalemic periodic paralysis** is an autosomal dominant disorder caused by pathogenic variants in *SCN4A*, the gene for a Na^+ channel. It results in episodic cellular release of K^+ and attacks of paralysis (see Chapter 651.1).

Table 73.4 Causes of Hyperkalemia

SPURIOUS LABORATORY VALUE
Hemolysis
Tissue ischemia during blood drawing
Thrombocytosis
Leukocytosis
Familial pseudohyperkalemia (OMIM 609153)
INCREASED INTAKE
Intravenous or oral
Blood transfusions
TRANSCELLULAR SHIFTS
Acidosis
Rhabdomyolysis
Tumor lysis syndrome
Tissue necrosis
Hemolysis/hematomas/gastrointestinal bleeding
Succinylcholine
Digitalis intoxication
Fluoride intoxication
β-Adrenergic blockers
Exercise
Hyperosmolality
Insulin deficiency
Malignant hyperthermia (OMIM 145600/601887/601888)
Hyperkalemic periodic paralysis (OMIM 170500)
DECREASED EXCRETION
Kidney failure
Primary adrenal disease
Acquired Addison disease
21-Hydroxylase deficiency (OMIM 201910)
3β-Hydroxysteroid dehydrogenase deficiency (OMIM 201810)
Lipoid congenital adrenal hyperplasia (OMIM 201710)
Adrenal hypoplasia congenita (OMIM 300200)
Aldosterone synthase deficiency (OMIM 203400/610600)
Adrenoleukodystrophy (OMIM 300100)
Hyporeninemic hypoaldosteronism
Urinary tract obstruction
Sickle cell disease (OMIM 603903)
Kidney transplant
Lupus nephritis
Renal tubular disease
Pseudohypoaldosteronism type I (OMIM 264350/177735)
Pseudohypoaldosteronism type II (OMIM 614491/614492/614495)
Bartter syndrome, type 2 (OMIM 241200)
Urinary tract obstruction
Kidney transplant
Medications
Renin inhibitors
Angiotensin-converting enzyme inhibitors
Angiotensin II blockers
Potassium-sparing diuretics
Calcineurin inhibitors
Nonsteroidal antiinflammatory drugs
Trimethoprim
Heparin
Drospirenone (in some oral contraceptives)

OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

The kidneys excrete most of the daily K^+ intake, so a decrease in kidney function can cause hyperkalemia. Newborn infants in general, and especially premature infants, have decreased kidney function at birth; thus they are at increased risk for hyperkalemia despite an absence of intrinsic renal disease. Neonates also have decreased expression of K^+ channels, further limiting K^+ excretion.

A wide range of primary **adrenal disorders**, both hereditary and acquired, can cause decreased production of aldosterone, with secondary hyperkalemia (see Chapters 615 and 616). Patients with these disorders typically have metabolic acidosis and salt wasting with hyponatremia. Children with subtle adrenal insufficiency may have electrolyte problems only during acute illnesses. The most common form of **congenital adrenal hyperplasia**, 21-hydroxylase deficiency, typically manifests in male infants as hyperkalemia, metabolic acidosis, hyponatremia, and volume depletion. Females with this disorder usually are diagnosed as newborns because of their ambiguous genitals; treatment prevents the development of electrolyte problems.

Renin, via angiotensin II, stimulates aldosterone production. A deficiency in renin, a result of kidney damage, can lead to decreased aldosterone production. **Hyporeninemia** occurs in many kidney diseases, with some of the more common pediatric causes listed in Table 73.4. These patients typically have hyperkalemia and a metabolic acidosis, without hyponatremia. Some of these patients have impaired renal function, partially accounting for the hyperkalemia, but the impairment in K^+ excretion is more extreme than expected for the degree of renal insufficiency.

A variety of **renal tubular disorders** impair renal excretion of K^+. Children with **pseudohypoaldosteronism type 1** have hyperkalemia, metabolic acidosis, and salt wasting (kidney, colon, sweat) leading to hyponatremia and volume depletion; aldosterone values are elevated. In the autosomal recessive variant, there is a defect in the renal Na^+ channel that is normally activated by aldosterone. Patients with this variant have severe symptoms (failure to thrive, diarrhea, recurrent respiratory infections, miliaria-rubra like rash), beginning in infancy. Patients with the autosomal dominant form have a defect in the aldosterone receptor, and the disease is milder, often remitting in adulthood. **Pseudohypoaldosteronism type 2 (familial hyperkalemic hypertension),** also called **Gordon syndrome,** is an autosomal dominant disorder characterized by hypertension caused by salt retention and impaired excretion of K^+ and acid, leading to hyperkalemia and hyperchloremic metabolic acidosis. Pathogenic variants in at least four genes (*WNK4*, *WNK1*, *KLHL3*, *CUL3)* may cause Gordon syndrome. Patients may respond well to thiazide diuretics. In **Bartter syndrome**, caused by pathogenic variants in the potassium channel *ROMK* (type 2 Bartter syndrome), there can be transient hyperkalemia in neonates, but hypokalemia subsequently develops (see Chapter 571.1).

Acquired renal tubular dysfunction, with an impaired ability to excrete K^+, occurs in a number of conditions. These disorders, all characterized by **tubulointerstitial disease,** are often associated with impaired acid secretion and a secondary metabolic acidosis. In some affected children, the metabolic acidosis is the dominant feature, although a high K^+ intake may unmask the defect in K^+ handling. The tubular dysfunction can cause renal salt wasting, potentially leading to hyponatremia. Because of the tubulointerstitial damage, these conditions may also cause hyperkalemia as a result of hyporeninemic hypoaldosteronism.

The risk of hyperkalemia resulting from medications is greatest in patients with underlying renal insufficiency. The predominant mechanism of medication-induced hyperkalemia is impaired renal excretion, although ACE inhibitors may worsen hyperkalemia in anuric patients, probably by inhibiting GI potassium loss, which is normally upregulated in renal insufficiency. The hyperkalemia caused by trimethoprim is especially problematic at higher doses. Potassium-sparing diuretics may easily cause hyperkalemia because they are often used in patients receiving oral K^+ supplements. Oral contraceptives containing drospirenone, which blocks the action of aldosterone, may cause hyperkalemia and should not be used in patients with decreased renal function.

Clinical Manifestations

The most important effects of hyperkalemia result from the role of K^+ in membrane polarization. The cardiac conduction system is usually the dominant concern. Changes in the electrocardiogram (ECG) begin with peaking of the T waves. This is followed, as K^+ level increases, by ST-segment depression, an increased PR interval, flattening of the P wave, and widening of the QRS complex (Fig. 73.4). However, the correlation between K^+ level and ECG changes is poor. This process can eventually progress to ventricular fibrillation. Asystole may also occur. Some patients have paresthesias, fasciculations, weakness, and even an ascending paralysis, but cardiac toxicity usually precedes these clinical symptoms, emphasizing the danger of assuming that an absence of symptoms implies an absence of danger. Chronic hyperkalemia is generally better tolerated than acute hyperkalemia.

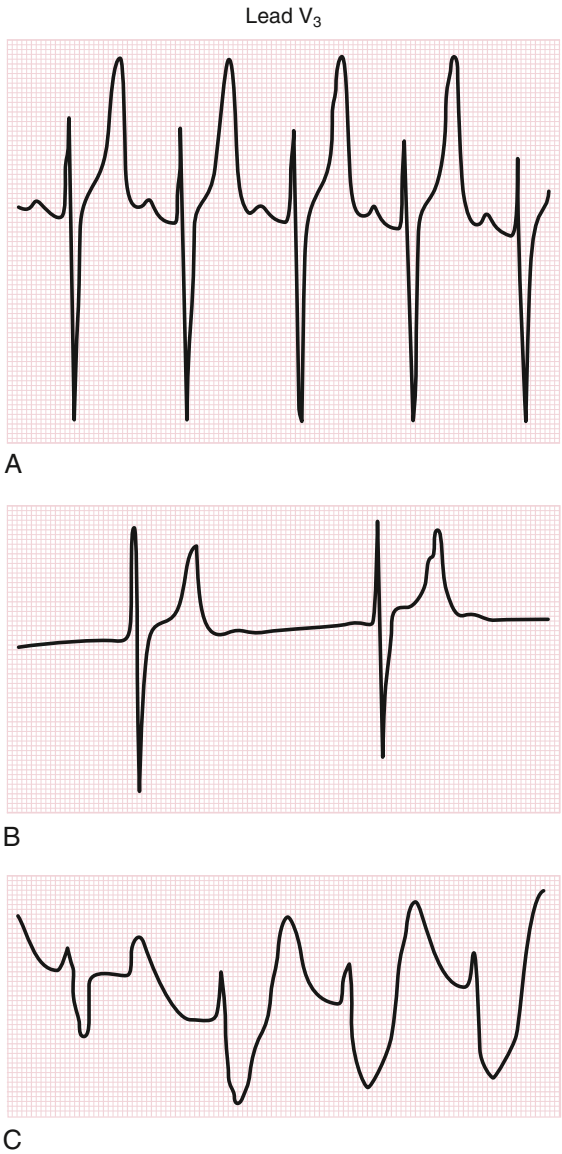

Fig. 73.4 The effects of progressive hyperkalemia on the electrocardiogram. All of the ECGs are from lead V_3. **A,** Serum potassium concentration ($[K^+]$) = 6.8 mEq/L; note the peaked T waves together with normal sinus rhythm. **B,** Serum $[K^+]$ = 8.9 mEq/L; note the peaked T waves and absent P waves. **C,** Serum $[K^+]$ >8.9 mEq/L; note the classic sine wave with absent P waves, marked prolongation of the QRS complex, and peaked T waves. *(From Goldman L, Schafer AI, eds. Goldman-Cecil Medicine. 26th ed. Elsevier; 2020. Fig. 109.2, p. 727.)*

Diagnosis

The etiology of hyperkalemia is often readily apparent. Spurious hyperkalemia is very common in children, so obtaining a second potassium measurement is often appropriate. If there is a significant elevation of WBC or platelet count, the second measurement should be performed on a plasma sample that is evaluated promptly. The history should initially focus on potassium intake, risk factors for transcellular shifts of K^+, medications that cause hyperkalemia, and signs of renal insufficiency, such as oliguria and edema. Initial laboratory evaluation should include creatinine, BUN, and assessment of the acid-base status. Many etiologies of hyperkalemia cause **metabolic acidosis**, which worsens hyperkalemia through the transcellular shift of K^+ out of cells. Decreased kidney function is a common cause of the combination of metabolic acidosis and hyperkalemia, also seen in diseases associated with aldosterone insufficiency or aldosterone resistance. Children with absent or ineffective aldosterone often have hyponatremia and volume depletion because of salt wasting. Genetic diseases, such as congenital adrenal hyperplasia and pseudohypoaldosteronism, usually manifest in infancy and should be strongly considered in the infant with hyperkalemia and metabolic acidosis, especially if hyponatremia is present.

It is important to consider the various etiologies of a transcellular K^+ shift. In some of these disorders, the K^+ level continues to increase, despite the elimination of all K^+ intake, especially with concurrent renal insufficiency. This increase is potentially seen in tumor lysis syndrome, hemolysis, rhabdomyolysis, and other causes of cell death. All these entities can cause concomitant hyperphosphatemia and hyperuricemia. **Rhabdomyolysis** produces an elevated creatinine phosphokinase (CPK) value and hypocalcemia, whereas children with hemolysis have hemoglobinuria and a decreasing hematocrit. For the child with diabetes, elevated blood glucose and acidosis suggest a transcellular shift of K^+.

Treatment

The plasma K^+ level, the ECG, and the risk of the problem worsening determine the aggressiveness of the therapeutic approach. High serum $[K^+]$ and the presence of ECG changes require vigorous treatment. An additional source of concern is the patient in whom plasma K^+ levels are rising despite minimal intake. This situation can happen if there is cellular release of K^+ (tumor lysis syndrome), especially in the setting of diminished excretion (kidney failure).

The first action in a child with a concerning elevation of plasma $[K^+]$ is to stop all sources of additional K^+ (oral, IV). Washed RBCs can be used for patients who require blood transfusions. If the $[K^+]$ is >6.5 mEq/L, an ECG should be obtained to help assess the urgency of the situation. Peaked T waves are the first sign of hyperkalemia, followed by a prolonged PR interval, and when most severe, prolonged QRS complex. Life-threatening ventricular arrhythmias may also develop. The treatment of hyperkalemia has two basic goals: (1) to stabilize the heart to prevent life-threatening arrhythmias and (2) to remove K^+ from the body. The treatments that acutely prevent arrhythmias all have the advantage of working quickly (within minutes) but do not remove K^+ from the body. **Calcium** stabilizes the cell membrane of heart cells, preventing arrhythmias; it is given IV over a few minutes, and its action is almost immediate. Calcium should be given over 30 minutes in a patient receiving digitalis because the calcium may cause arrhythmias. **Bicarbonate** causes potassium to move intracellularly, lowering the plasma $[K^+]$; it is most efficacious in a patient with a metabolic acidosis. **Insulin** causes K^+ to move intracellularly but must be given with **glucose** to avoid hypoglycemia. The combination of insulin and glucose works within 30 minutes. Nebulized **albuterol**, by stimulation of β_1-adrenergic receptors, leads to rapid intracellular movement of K^+. This has the advantage of not requiring an IV route of administration, allowing it to be given concurrently with the other measures.

It is critical to begin measures that remove K^+ from the body. In patients who are not anuric, a **loop diuretic** increases renal excretion of K^+. A high dose may be required in a patient with significant renal insufficiency. **Sodium polystyrene sulfonate** (**SPS**; Kayexalate) is an exchange resin that is given either rectally or orally. **Patiromer** and **sodium zirconium cyclosilicate** are oral exchange resins for treating hyperkalemia. Some patients require **dialysis** for acute K^+ removal. Dialysis is often necessary if the patient has either severe kidney failure or an especially high rate of endogenous K^+ release, as is sometimes present with tumor lysis syndrome or rhabdomyolysis. Hemodialysis rapidly lowers plasma $[K^+]$. Peritoneal dialysis is not nearly as quick or reliable, but it is usually adequate as long as the acute problem can be managed with medications and the endogenous release of K^+ is not high.

Long-term management of hyperkalemia includes reducing intake through dietary changes and eliminating or reducing medications that cause hyperkalemia (see Chapter 572). Some patients require medications to increase potassium excretion, such as SPS, patiromer, sodium zirconium cyclosilicate, and loop or thiazide diuretics. Some infants with chronic kidney disease may need to start dialysis to allow adequate caloric intake without hyperkalemia. It is unusual for an older child to require dialysis principally to control chronic hyperkalemia. The disorders caused by aldosterone deficiency respond to replacement therapy with fludrocortisone.

HYPOKALEMIA

Hypokalemia is common in children, with most cases related to gastroenteritis.

Etiology and Pathophysiology

There are four basic mechanisms of hypokalemia (Table 73.5). **Spurious hypokalemia** occurs in patients with leukemia and very elevated WBC counts if plasma for analysis is left at room temperature, permitting the WBCs to take up K^+ from the plasma. With a transcellular shift, there is no change in total body K^+, although there may be concomitant potassium depletion resulting from other factors. Decreased intake, extrarenal losses, and renal losses are all associated with total body K^+ depletion. In addition, seasonal pseudo-hypokalemia is seen during warm summer months as a laboratory phenomenon when blood samples are exposed to a warm environment. On immediate retesting, the potassium level is normal. This should not be confused with a pseudo-Bartter syndrome (hypokalemic, hypochloremic, alkalosis) seen in children with cystic fibrosis in a very warm environment due to excessive sweating.

Because the intracellular $[K^+]$ is much higher than the plasma level, a significant amount of K^+ can move into cells without greatly changing the intracellular $[K^+]$. **Alkalemia** is one of the more common causes of a transcellular shift. The effect is much greater with a *metabolic* alkalosis than with a respiratory alkalosis. The impact of exogenous insulin on K^+ movement into the cells is substantial in patients with DKA. Endogenous insulin may be the cause when a patient is given a bolus of glucose. Both endogenous (epinephrine in stress) and exogenous (albuterol) β-adrenergic agonists stimulate cellular uptake of K^+. Theophylline overdose, barium intoxication, administration of cesium chloride (a homeopathic cancer remedy), and toluene intoxication from paint or glue sniffing can cause a transcellular shift hypokalemia, often with severe clinical manifestations. Children with **hypokalemic periodic paralysis,** a rare autosomal dominant disorder, have acute cellular uptake of K^+ (see Chapter 651). **Thyrotoxic periodic paralysis,** which is more common in Asians, is an unusual initial manifestation of hyperthyroidism. Affected patients have dramatic hypokalemia as a result of a transcellular shift of potassium. Hypokalemia can occur during refeeding syndrome (see Chapters 63 and 385.7).

Inadequate K^+ intake occurs in **anorexia nervosa**; accompanying bulimia and laxative or diuretic abuse exacerbates the K^+ deficiency.

Table 73.5 Causes of Hypokalemia

SPURIOUS LABORATORY VALUE
High white blood cell count

TRANSCELLULAR SHIFTS
Alkalemia
Insulin
α-Adrenergic agonists
Drugs/toxins (theophylline, barium, toluene, cesium chloride, hydroxychloroquine)
Hypokalemic periodic paralysis (OMIM 170400)
Thyrotoxic period paralysis
Refeeding syndrome

DECREASED INTAKE
Anorexia nervosa

EXTRARENAL LOSSES
Diarrhea
Laxative abuse
Sweating
Sodium polystyrene sulfonate (Kayexalate) or clay ingestion

RENAL LOSSES
With Metabolic Acidosis
Distal renal tubular acidosis (OMIM 179800/602722/267300/611590)
Proximal renal tubular acidosis (OMIM 604278)*
Ureterosigmoidostomy
Diabetic ketoacidosis

Without Specific Acid-Base Disturbance
Tubular toxins: amphotericin, cisplatin, aminoglycosides
Interstitial nephritis
Diuretic phase of acute tubular necrosis
Postobstructive diuresis
Hypomagnesemia
High urine anions (e.g., penicillin or penicillin derivatives)

With Metabolic Alkalosis
Low urine chloride
- Emesis or nasogastric suction
- Chloride-losing diarrhea (OMIM 214700)
- Cystic fibrosis (OMIM 219700)
- Low-chloride formula
- Posthypercapnia
- Previous loop or thiazide diuretic use

High urine chloride and normal blood pressure
- Gitelman syndrome (OMIM 263800)
- Bartter syndrome (OMIM 241200/607364/602522/601678/300971/601198/613090)
- Autosomal dominant hypoparathyroidism (OMIM 146200)
- EAST syndrome (OMIM 612780)
- Autosomal dominant kidney hypomagnesemia due to *RRAGD* variant (OMIM not assigned)
- Loop and thiazide diuretics (current)

High urine chloride and high blood pressure
- Adrenal adenoma or hyperplasia
- Glucocorticoid-remediable aldosteronism (OMIM 103900)
- Hyperaldosteronism type II (OMIM 605635)
- Familial hyperaldosteronism type III (OMIM 613677)
- Familial hyperaldosteronism type IV (OMIM 617027)
- Renovascular disease
- Renin-secreting tumor
- 17β-Hydroxylase deficiency (OMIM 202110)
- 11β-Hydroxylase deficiency (OMIM 202010)
- Cushing syndrome
- 11β-Hydroxysteroid dehydrogenase deficiency (OMIM 218030)
- Licorice ingestion
- Liddle syndrome (OMIM 177200)
- Early-onset autosomal dominant hypertension with exacerbation in pregnancy (OMIM 605115)

*Most cases of proximal renal tubular acidosis are not caused by this primary genetic disorder. Proximal renal tubular acidosis is usually part of Fanconi syndrome, which has multiple etiologies.
EAST, Epilepsy, ataxia, sensorineural hearing loss, and tubulopathy; OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

Sweat losses of K^+ can be significant during vigorous exercise in a hot climate. Associated volume depletion and hyperaldosteronism increase renal losses of K^+ (discussed later). Diarrheal fluid has a high concentration of K^+, and hypokalemia because of diarrhea is usually associated with metabolic acidosis resulting from stool losses of bicarbonate. In contrast, normal acid-base balance or mild metabolic alkalosis is seen with laxative abuse. Intake of potassium-binding resins (SPS) or ingestion of clay because of pica increases stool losses of potassium.

Urinary potassium wasting may be accompanied by a **metabolic acidosis** (proximal or distal RTA). In DKA, although it is often associated with normal plasma [K^+] from transcellular shifts, there is significant total body K^+ depletion from urinary losses because of the osmotic diuresis, and the K^+ level may decrease dramatically with insulin therapy (see Chapter 629). Both the polyuric phase of acute tubular necrosis and postobstructive diuresis cause transient, highly variable K^+ wasting and may be associated with metabolic acidosis. Tubular damage, which occurs either directly from medications or secondary to interstitial nephritis, is often accompanied by other tubular losses, including magnesium, Na^+, and water. Such tubular damage may cause a secondary RTA with metabolic acidosis. Isolated magnesium deficiency causes renal K^+ wasting. Penicillin is an anion excreted in the urine, resulting in increased K^+ excretion because the penicillin anion must be accompanied by a cation. Hypokalemia from penicillin therapy occurs only with the *sodium* salt of penicillin, not with the potassium salt.

Urinary K^+ wasting is often accompanied by a **metabolic alkalosis**. This condition is usually associated with increased aldosterone, which increases urinary K^+ and acid losses, contributing to the hypokalemia and the metabolic alkalosis. Other mechanisms often contribute to both the K^+ losses and the metabolic alkalosis. With emesis or nasogastric suction, there is gastric loss of K^+, but this is minimal given the low K^+ content of gastric fluid, approximately 10 mEq/L. More important is the gastric loss of hydrochloric acid (HCl), leading to metabolic alkalosis and a state of volume depletion. The kidney compensates for metabolic alkalosis by excreting bicarbonate in the urine, but there is obligate loss of K^+ and Na^+ with the bicarbonate. The volume depletion raises aldosterone levels, further increasing urinary K^+ losses and preventing correction of metabolic alkalosis and hypokalemia until the volume depletion is corrected.

Urinary chloride (Cl^-) is low as a response to the volume depletion. Because the volume depletion is secondary to Cl^- loss, this is a **state of Cl^- deficiency**. There were cases of Cl^- deficiency resulting from infant formula deficient in Cl^-, which caused a metabolic alkalosis with hypokalemia and low urine [Cl^-]. Current infant formula is not deficient in Cl^-. A similar mechanism occurs in cystic fibrosis because of Cl^- loss in sweat. In **congenital chloride-losing diarrhea**, an autosomal recessive

disorder, there is high stool loss of Cl^-, leading to metabolic alkalosis, an unusual sequela of diarrhea. Because of stool K^+ losses, Cl^- deficiency, and metabolic alkalosis, patients with congenital chloride-losing diarrhea have hypokalemia.

During respiratory acidosis, there is renal compensation, with retention of bicarbonate and excretion of Cl^-. After the respiratory acidosis is corrected, the patients have Cl^- deficiency and post–hypercapnic alkalosis with secondary hypokalemia. Patients with Cl^- deficiency, metabolic alkalosis, and hypokalemia have a urinary $[Cl^-]$ of <10 mEq/L. Loop and thiazide diuretics lead to hypokalemia, metabolic alkalosis, and Cl^- deficiency. During treatment, these patients have high urine chloride levels resulting from the effect of the diuretic. However, after the diuretics are discontinued, there is residual Cl^- deficiency, the urinary $[Cl^-]$ is appropriately low, and neither the hypokalemia nor the alkalosis resolves until the Cl^- deficiency is corrected.

The combination of metabolic alkalosis, hypokalemia, high urine $[Cl^-]$, and normal blood pressure is characteristic of Bartter syndrome, Gitelman syndrome, and current diuretic use. Patients with any of these conditions have high urinary losses of Cl^- despite a state of relative volume depletion with secondary hyperaldosteronism with high plasma renin. Bartter and Gitelman syndromes are autosomal recessive disorders caused by defects in tubular transporters (see Chapter 571). **Bartter syndrome** is usually associated with hypercalciuria, and often with nephrocalcinosis, whereas children with **Gitelman syndrome** have low urinary calcium losses but hypomagnesemia because of urinary magnesium losses. Some patients with Bartter syndrome have hypomagnesemia. A transient antenatal form of Bartter syndrome is associated with severe polyhydramnios and pathogenic variants in *MAGED2*.

Some patients with hypoparathyroidism and hypocalcemia caused by activating pathogenic variants of the calcium-sensing receptor (**autosomal dominant hypoparathyroidism**) have hypokalemia, hypomagnesemia, and metabolic alkalosis. The reason is that activation of the calcium-sensing receptor in the loop of Henle impairs tubular resorption of sodium and chloride, causing volume depletion and secondary hyperaldosteronism. **EAST syndrome**, an autosomal recessive disorder caused by pathologic variants in the gene for a potassium channel in the kidney, inner ear, and brain, consists of *e*pilepsy, *a*taxia, *s*ensorineural hearing loss, and *t*ubulopathy (hypokalemia, metabolic alkalosis, hypomagnesemia, and hypocalciuria).

In the presence of *high aldosterone levels*, there is urinary loss of K^+, hypokalemia, metabolic alkalosis, and elevated urinary $[Cl^-]$; renal retention of Na^+ leads to **hypertension**. Primary hyperaldosteronism caused by adenoma or hyperplasia is much less common in children than in adults (see Chapters 619 and 620). **Glucocorticoid-remediable aldosteronism**, an autosomal dominant disorder that leads to high levels of aldosterone (but low renin levels), is often diagnosed in childhood, although hypokalemia is not always present. **Familial hyperaldosteronism type II**, an autosomal dominant disorder, is due to a gain-of-function variant in *CLCN2* that causes increased aldosterone synthesis. **Familial hyperaldosteronism type III**, an autosomal dominant disorder, is due to a gain-of-function variant in *KCNJ5* that causes a dramatic increase in aldosterone synthesis and severe hypertension and hypokalemia. **Familial hyperaldosteronism type IV**, an autosomal dominant disorder, is due to a gain-of-function variant in *CACNA1H* that causes increased aldosterone synthesis.

Increased aldosterone levels may also be *secondary* to increased renin production. Renal artery stenosis leads to hypertension from increased renin and secondary hyperaldosteronism. The increased aldosterone can cause hypokalemia and metabolic alkalosis, although most patients have normal electrolyte levels. Renin-producing tumors, which are extremely rare, can cause hypokalemia.

A variety of disorders cause hypertension and hypokalemia without increased aldosterone levels. Some are a result of increased levels of mineralocorticoids other than aldosterone. Such increases occur in two forms of **congenital adrenal hyperplasia** (see Chapter 616). In **11β-hydroxylase deficiency**, which is associated with virilization, 11-deoxycorticosterone is elevated, causing variable hypertension and hypokalemia. A similar mechanism, increased 11-deoxycorticosterone, occurs in **17α-hydroxylase deficiency**, but patients with this disorder are more uniformly hypertensive and hypokalemic, and they have a defect in sex hormone production. **Cushing syndrome**, frequently associated with hypertension, less frequently causes metabolic alkalosis and hypokalemia, secondary to the mineralocorticoid activity of cortisol. In **11β-hydroxysteroid dehydrogenase deficiency**, an autosomal recessive disorder, the enzymatic defect prevents the conversion of cortisol to cortisone in the kidney. Because cortisol binds to and activates the aldosterone receptor, children with this deficiency have all the features of excessive mineralocorticoids, including hypertension, hypokalemia, and metabolic alkalosis, but low levels of aldosterone and renin. Patients with this disorder, which is also called **apparent mineralocorticoid excess**, respond to spironolactone therapy, which blocks the mineralocorticoid receptor. An acquired form of 11β-hydroxysteroid dehydrogenase deficiency occurs from the ingestion of substances that inhibit this enzyme. A classic example is glycyrrhizic acid, which is found in natural licorice. **Liddle syndrome** is an autosomal dominant disorder that results from activating pathogenic variants of the distal nephron sodium channel that is normally upregulated by aldosterone. Patients have the characteristics of hyperaldosteronism—hypertension, hypokalemia, and alkalosis—but low serum renin and aldosterone levels. These patients respond to the potassium-sparing diuretics (triamterene and amiloride) that inhibit this sodium channel (see Chapter 571.3). A pathogenic variant in the mineralocorticoid receptor causes **early-onset autosomal dominant hypertension with exacerbation in pregnancy**. Hypokalemia is usually mild but worsens during pregnancy; renin and aldosterone levels are low.

Clinical Manifestations

The heart and skeletal muscle are especially vulnerable to hypokalemia. ECG changes include a flattened T wave, a depressed ST segment, and the appearance of a U wave, which is located between the T wave (if still visible) and the P wave (Fig. 73.5). Ventricular fibrillation and torsades de pointes may occur, although usually only in the context of underlying heart disease. Hypokalemia makes the heart especially susceptible to digitalis-induced arrhythmias, such as supraventricular tachycardia, ventricular tachycardia, and heart block (see Chapter 484).

The clinical consequences of hypokalemia in skeletal muscle include muscle weakness and cramps. Paralysis is a possible complication, generally only at $[K^+]$ <2.5 mEq/L. It usually starts in the legs and moves to the arms. Respiratory paralysis may require mechanical ventilation. Some patients have rhabdomyolysis; the risk increases with exercise. Hypokalemia slows GI motility. This effect manifests as constipation; with K^+ levels <2.5 mEq/L, an ileus may occur. Hypokalemia impairs bladder function, potentially leading to urinary retention.

Hypokalemia causes **polyuria** and **polydipsia** by impairing urinary concentrating ability, which produces nephrogenic diabetes insipidus. Hypokalemia stimulates renal ammonia production, an effect that is clinically significant if hepatic failure is present, because the liver cannot metabolize the ammonia. Consequently, hypokalemia may worsen hepatic encephalopathy. Chronic hypokalemia may cause kidney damage, including interstitial nephritis and renal cysts.

Diagnosis

Most causes of hypokalemia are readily apparent from the history. It is important to review the child's diet, GI losses, and medications. Both emesis and diuretic use can be surreptitious. The presence of **hypertension** suggests excess mineralocorticoid effects or levels. Concomitant electrolyte abnormalities are useful clues. The combination of hypokalemia and metabolic acidosis is characteristic of diarrhea and distal and proximal RTA. A concurrent metabolic alkalosis is characteristic of emesis or nasogastric losses, aldosterone excess, use of diuretics, and

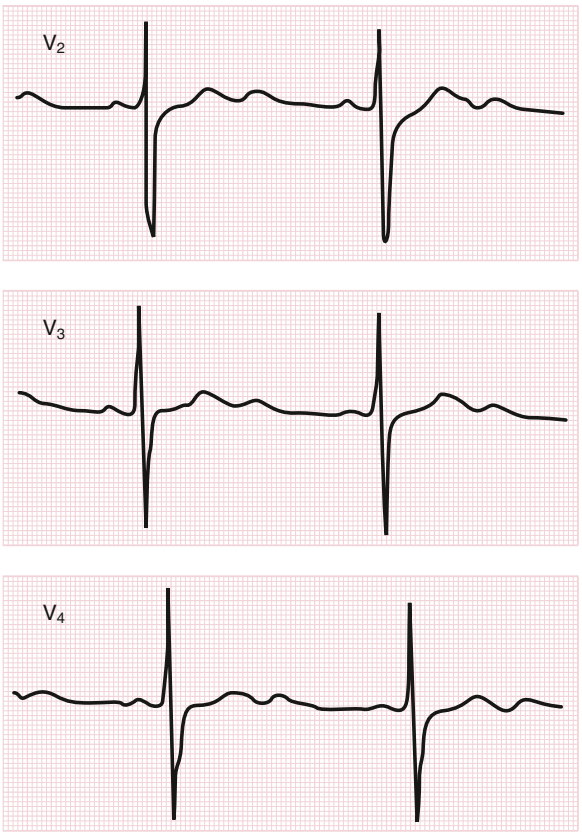

Fig. 73.5 The ECG manifestations of hypokalemia. The serum potassium concentration was 2.2 mEq/L. The ST segment is prolonged, primarily because of a U wave following the T wave, and the T wave is flattened. *(From Goldman L, Schafer AI, eds. Goldman-Cecil Medicine. 26th ed. Elsevier; 2020. Fig. 109.1, p 727.)*

Bartter and Gitelman syndromes. Figure 73.6 shows an approach to persistent hypokalemia.

If a clear etiology is not apparent, the measurement of urinary K^+ distinguishes between renal and extrarenal losses. The kidneys should conserve K^+ in the presence of extrarenal losses. Urinary K^+ losses can be assessed with a 24-hour urine collection, spot K^+:creatinine ratio, fractional excretion of K^+, or calculation of the *transtubular K^+ gradient* (TTKG), which is the most widely used approach in children:

$$\text{TTKG} = [K]_{\text{urine}} / [K]_{\text{plasma}} \times (\text{plasma osmolality} / \text{urine osmolality})$$

where $[K]_{\text{urine}}$ = urine potassium concentration and $[K]_{\text{plasma}}$ = plasma potassium concentration.

The urine osmolality must be greater than the serum osmolality for the result of this calculation to be valid. A TTKG >4 in the presence of hypokalemia suggests excessive urinary losses of K^+. The urinary K^+ excretion value can be misleading if the stimulus for renal loss, such as a diuretic, is no longer present.

Treatment

Factors that influence the treatment of hypokalemia include the K^+ level, clinical symptoms, kidney function, the presence of transcellular shifts of K^+, ongoing losses, and the patient's ability to tolerate oral K^+. Severe, symptomatic hypokalemia requires aggressive treatment. Supplementation is more cautious if renal function is decreased because of the kidney's limited ability to excrete excessive K^+. The plasma potassium level does not always provide an accurate estimation of the total body K^+ deficit because there may be shifts of K^+ from the ICS to the plasma. Clinically, such shifts occur most often with metabolic acidosis and the insulin deficiency of DKA; the plasma $[K^+]$ measurement underestimates the degree of total body K^+ depletion. When these problems are corrected, K^+ moves into the ICS, so more K^+ supplementation is required to correct the hypokalemia. Likewise, the presence of a transcellular shift of K^+ into the cells indicates that the total body K^+ depletion is less severe. In an isolated transcellular shift, as in hypokalemic periodic paralysis, K^+ supplementation should be used cautiously, given the risk of hyperkalemia when the transcellular shift resolves. This caution is especially required in thyrotoxic periodic paralysis, which responds dramatically to propranolol, with correction of weakness and hypokalemia. Patients who have ongoing losses of K^+ need correction of the deficit and replacement of the ongoing losses.

Because of the risk of hyperkalemia, IV K^+ should be used very cautiously. Oral K^+ is safer, but not as rapid in urgent situations. Liquid preparations are bitter tasting; microencapsulated or wax matrix formulations are less irritating than tablets to the gastric mucosa. Oral dosing is variable depending on the clinical situation. A typical starting dose is 1-2 mEq/kg/day, with a maximum of 60 mEq/day in divided doses. The dose of IV potassium is 0.5-1.0 mEq/kg, usually given over 1 hour. The adult maximum dose is 40 mEq. Conservative dosing is generally preferred. Potassium chloride is the usual choice for supplementation, although the presence of concurrent electrolyte abnormalities may dictate other options. Patients with acidosis and hypokalemia can receive potassium acetate or potassium citrate. If hypophosphatemia is present, some of the potassium deficit can be replaced with potassium phosphate. It is sometimes possible to decrease ongoing K^+ losses. For patients with excessive urinary losses, potassium-sparing diuretics are effective, but they need to be used cautiously in patients with decreased kidney function. If hypokalemia, metabolic alkalosis, and volume depletion are present (with gastric losses), restoration of intravascular volume with adequate NaCl will decrease urinary K^+ losses. Correction of concurrent hypomagnesemia is important because it may cause hypokalemia. Disease-specific therapy is effective in many of the genetic tubular disorders.

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73.5 Magnesium

Larry A. Greenbaum

MAGNESIUM METABOLISM

Body Content and Physiologic Function

Magnesium is the fourth most common cation in the body and the third most common intracellular cation (see Fig. 73.3). From 50–60% of body magnesium is in bone, where it serves as a reservoir because 30% is exchangeable, allowing movement to the ECS. Most intracellular magnesium is bound to proteins; only approximately 25% is exchangeable. Because cells with higher metabolic rates have higher magnesium concentrations, most intracellular magnesium is present in muscle and liver.

The normal plasma magnesium concentration is 1.5-2.3 mg/dL (1.2-1.9 mEq/L; 0.62-0.94 mmol/L), with some variation among clinical laboratories. Infants have slightly higher plasma magnesium concentrations than older children and adults. Only 1% of body magnesium is extracellular (60% ionized, 15% complexed, 25% protein bound). In the United States, serum magnesium is reported as mg/dL (Table 73.6). Values in the left-column unit are converted into the right-column unit by multiplying the conversion factor (e.g., calcium of 10 mg/dL × 0.25 = 2.5 mmol/L). Dividing the right-column unit by the conversion factor converts to the units of the left-column unit.

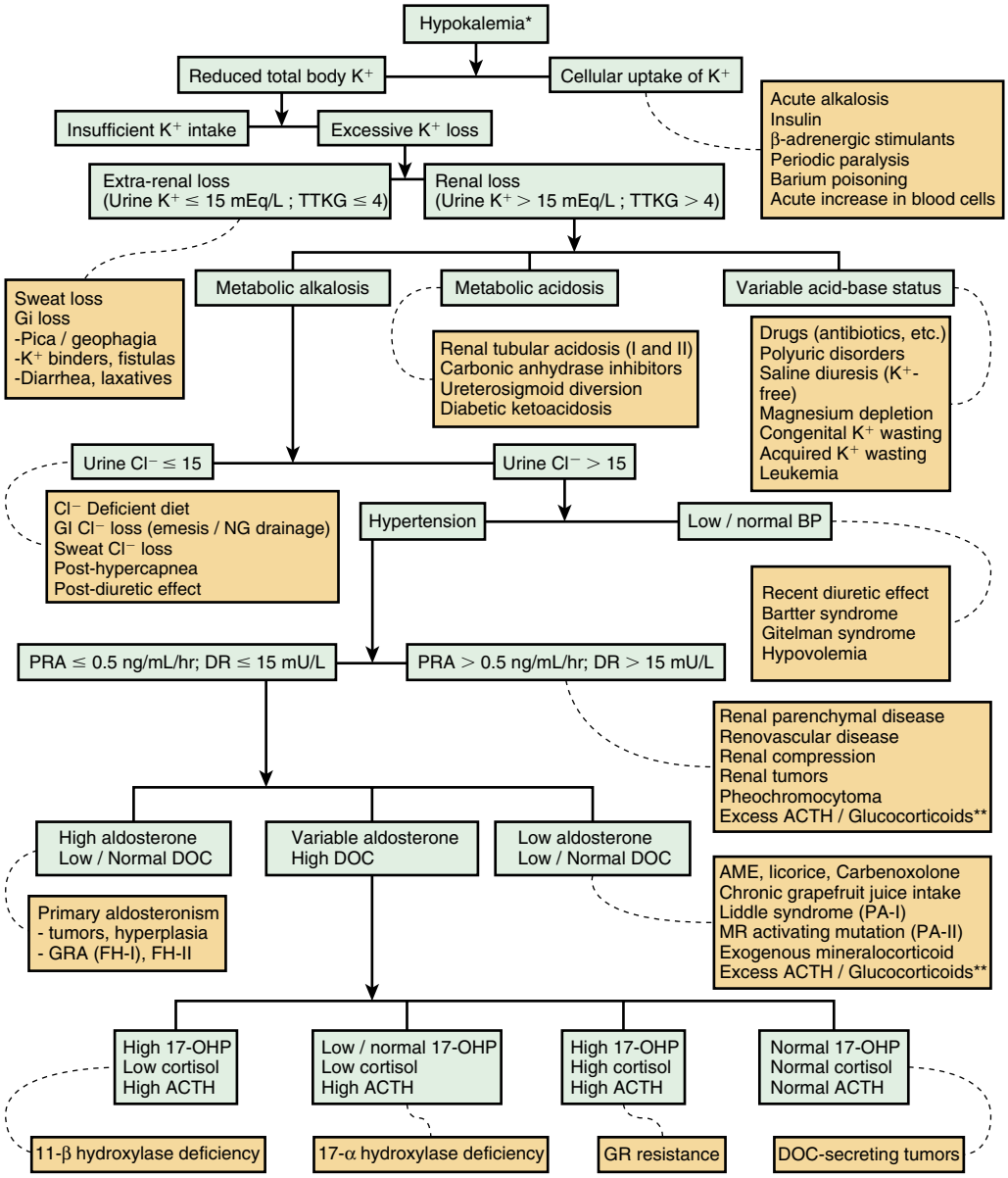

Fig. 73.6 Diagnostic algorithm to evaluate persistent hypokalemia. *Spurious hypokalemia must be excluded. **Hypokalemia is uncommon in uncomplicated edematous disorders and in conditions associated with excessive glucocorticosteroids. Conditions associated with high circulating levels of glucocorticosteroids often have normal renin activity. 17-OHP, 17-Hydroxyprogesterone; ACTH, adrenocorticotropic hormone; AME, apparent mineralocorticoid excess; BP, blood pressure; Cl^-, chloride; DOC, 11-deoxycorticosterone; DR, direct renin assay; GI, gastrointestinal; FH-II, familial hyperaldosteronism type II; GR, glucocorticoid receptor; GRA (FH-I), glucocorticoid remediable aldosteronism (familial hyperaldosteronism type I); K^+, potassium; MR, mineralocorticoid receptor; PA-I, pseudohyperaldosteronism type I; PA-II, pseudohyperaldosteronism type II; PRA, plasma renin activity; TTKG, transtubular potassium gradient. *(From Shoemaker LR, Eaton BV, Buchino JJ. A three-year-old with persistent hypokalemia. J Pediatr. 2007;151[6]:696–699.)*

Magnesium is a necessary cofactor for hundreds of enzymes. It is important for membrane stabilization and nerve conduction. Adenosine triphosphate (ATP) and guanosine triphosphate need associated magnesium when they are used by ATPases, cyclases, and kinases.

Magnesium Intake

Between 30% and 50% of dietary magnesium is absorbed. Good dietary sources include green vegetables, cereals, nuts, meats, and hard water, although many foods contain magnesium. Human milk contains approximately 35 mg/L of magnesium; formula contains 40-70 mg/L. The small intestine is the major site of magnesium absorption, but the regulation of magnesium absorption is poorly understood. There is passive absorption, which permits high absorption in the presence of excessive intake. It probably occurs by a paracellular mechanism. Absorption is diminished in the presence of substances that complex with magnesium (free fatty acids, fiber, phytate, phosphate, oxalate); increased intestinal motility and calcium also decrease magnesium absorption. Vitamin D and parathyroid hormone (PTH) may enhance absorption, although this effect is limited. Intestinal absorption does increase when intake is decreased, possibly by a saturable, active transport system. If there is no oral intake of magnesium, obligatory secretory losses prevent the complete elimination of intestinal losses.

Magnesium Excretion

Renal excretion is the principal regulator of magnesium balance. There is no defined hormonal regulatory system, although PTH may increase

tubular resorption. Approximately 15% of resorption occurs in the proximal tubule and 70% in the thick ascending limb (TAL) of the loop of Henle. Proximal resorption may be higher in neonates. High serum magnesium levels inhibit resorption in the TAL, suggesting that active transport is involved. Approximately 5–10% of filtered magnesium is resorbed in the distal tubule. Hypomagnesemia increases absorption in the TAL and the distal tubule.

HYPOMAGNESEMIA

Hypomagnesemia is relatively common in hospitalized patients, although most cases are asymptomatic. Detection requires a high index of suspicion because magnesium is not measured in most basic metabolic panels.

Table 73.6 Conversion Factors for Calcium, Magnesium, and Phosphorus

	UNIT	CONVERSION FACTOR	UNIT
Calcium	mg/dL	0.25	mmol/L
	mEq/L	0.5	mmol/L
	mg/dL	0.5	mEq/L
Magnesium	mg/dL	0.411	mmol/L
	mEq/L	0.5	mmol/L
	mg/dL	0.822	mEq/L
Phosphorus	mg/dL	0.32	mmol/L

Etiology and Pathophysiology

GI and renal losses are the major causes of hypomagnesemia (Table 73.7). Diarrheal fluid contains up to 200 mg/L of magnesium; gastric contents have only approximately 15 mg/L, but high losses can cause depletion. Steatorrhea causes magnesium loss because of the formation of magnesium-lipid salts; restriction of dietary fat can decrease losses. The potassium-lowering agent patiromer binds magnesium and may cause hypomagnesemia.

Hypomagnesemia with secondary hypocalcemia, a rare autosomal recessive disorder, is caused by decreased intestinal absorption of magnesium and renal magnesium wasting. Patients with this disorder have pathogenic variants in a gene expressed in intestine and kidney; *TRPM6* codes for a transient receptor potential cation channel. The patients have seizures, tetany, tremor, or restlessness at 2-8 weeks of life because of severe hypomagnesemia (0.2-0.8 mg/dL) and secondary hypocalcemia.

Renal losses may occur because of medications that are direct tubular toxins. Amphotericin frequently causes significant magnesium wasting and is typically associated with other tubular defects (especially potassium wasting). Cisplatin produces dramatic renal magnesium losses. Diuretics affect tubular handling of magnesium. Loop diuretics cause a mild increase in magnesium excretion, and thiazide diuretics have even less effect. Chronic use of proton pump inhibitors (PPIs) may cause hypomagnesemia. Potassium-sparing diuretics reduce magnesium losses. Osmotic agents, such as mannitol, glucose in diabetes mellitus, and urea in the recovery phase of acute tubular necrosis, increase urinary magnesium losses. Epidermal growth factor (EGF) receptor inhibitors cause renal magnesium wasting. IV fluid, by expanding the intravascular volume, decreases renal resorption of

Table 73.7 Causes of Hypomagnesemia

GASTROINTESTINAL LOSSES
- Diarrhea
- Nasogastric suction or emesis
- Inflammatory bowel disease
- Celiac disease
- Cystic fibrosis
- Intestinal lymphangiectasia
- Small bowel resection or bypass
- Pancreatitis
- Protein-calorie malnutrition
- Patiromer
- Hypomagnesemia with secondary hypocalcemia (OMIM 602014)*

RENAL DISORDERS
- Medications
  - Amphotericin
  - Cisplatin
  - Cyclosporine, tacrolimus
  - Loop and thiazide diuretics
  - Mannitol
  - Pentamidine
  - Proton pump inhibitors
  - Aminoglycosides
  - Thiazide diuretics
  - Epidermal growth factor receptor inhibitors
- Diabetes
- Acute tubular necrosis (recovery phase)
- Postobstructive nephropathy
- Chronic kidney diseases
  - Interstitial nephritis
  - Glomerulonephritis
  - Post–renal transplantation
- Hypercalcemia
- Intravenous fluids
- Primary aldosteronism
- Genetic diseases
  - Gitelman syndrome (OMIM 263800)
  - Bartter syndrome (OMIM 241200/607364/602522/601678/300971/601198/613090)
  - Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (OMIM 248250)
  - Familial hypomagnesemia with hypercalciuria, nephrocalcinosis, and severe ocular involvement (OMIM 248190)
  - Autosomal recessive renal magnesium wasting with normocalciuria (OMIM 611718)
  - Renal cysts and diabetes syndrome due to *HNF1β* variants (OMIM 137920)
  - Autosomal dominant hypomagnesemia (OMIM 160120/613882/154020)
  - EAST syndrome (OMIM 612780)
  - Autosomal dominant hypoparathyroidism (OMIM 146200)
  - Mitochondrial disorders (OMIM 500005)
- Hyperuricemia, pulmonary hypertension, renal failure in infancy and alkalosis, HUPRA syndrome (OMIM 613845)
- Transient neonatal hyperphenylalaninemia followed by hypomagnesemia and maturity onset diabetes of the young (OMIM 264070)
- Hypomagnesemia, seizures and mental retardation due to *CNNM2* pathogenic variants (OMIM 616418)
- Autosomal dominant kidney hypomagnesemia due to *RRAGD* pathogenic variants (OMIM not assigned)

MISCELLANEOUS CAUSES
- Poor intake
- Hungry bone syndrome
- Insulin administration
- Pancreatitis
- Intrauterine growth restriction
- Infants of diabetic mothers
- Exchange transfusion

*This disorder is also associated with renal magnesium wasting.
EAST, Epilepsy, ataxia, sensorineural hearing loss, and tubulopathy; OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

sodium and water, thereby impairing magnesium resorption. Hypercalcemia inhibits magnesium resorption in the loop of Henle, although this inhibition does not occur in hypercalcemia caused by familial hypercalcemic hypocalciuria or lithium.

A number of rare genetic diseases cause renal magnesium loss. Gitelman and Bartter syndromes, both autosomal recessive disorders, are the most common entities (see Chapter 571). **Gitelman syndrome**, caused by a defect in the thiazide-sensitive Na^+-Cl^- cotransporter in the distal tubule, is usually associated with hypomagnesemia. Hypomagnesemia occurs in a minority of patients with **Bartter syndrome**, which can be caused by pathogenic variants in multiple genes necessary for Na^+ and Cl^- reabsorption in the loop of Henle. In both disorders, there is hypokalemic metabolic alkalosis. Typically, hypomagnesemia is not severe and is asymptomatic, although tetany as a result of hypomagnesemia occasionally occurs.

Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (Michelis-Castrillo syndrome), an autosomal recessive disorder, is caused by pathogenic variants in the gene for claudin 16 (paracellin-1), located in the tight junctions of the TAL of the loop of Henle. Patients with the disease have severe renal wasting of magnesium and calcium with secondary hypomagnesemia and nephrocalcinosis; serum calcium levels are normal. Chronic kidney failure frequently occurs during childhood. Other features include kidney stones, urinary tract infections, hematuria, increased PTH levels, tetany, seizures, incomplete distal RTA, hyperuricemia, polyuria, and polydipsia. Patients with **familial hypomagnesemia with hypercalciuria, nephrocalcinosis, and severe ocular involvement** have pathogenic variants in the gene for claudin 19.

Autosomal recessive renal magnesium wasting with normocalciuria is caused by pathogenic variants in the EGF gene. Clinical manifestations include seizures, mild to moderate psychomotor retardation, and brisk tendon reflexes.

Autosomal dominant renal magnesium wasting is caused by pathogenic variants in a number of different genes. A dominant-negative pathogenic variant in the gene encoding the Na^+,K^+-ATPase γ subunit is associated with hypomagnesemia, increased urinary magnesium losses, hypocalciuria, and normocalcemia. Patients may present with seizures; most are asymptomatic, despite serum magnesium levels of 0.8-1.5 mg/dL. Pathogenic variants in *CNNM2*, which encodes a protein that mediates magnesium-sensitive sodium currents, cause isolated hypomagnesemia. A pathogenic variant in *KCNA1*, a gene that encodes a K^+ channel, also causes an autosomal dominant form of hypomagnesemia; symptoms may be severe.

Renal cysts and diabetes syndrome, which is caused by pathogenic variants in the gene for hepatocyte nuclear factor-1β, is associated with hypomagnesemia, despite the frequent presence of decreased kidney function. The hypomagnesemia is usually mild but may cause symptomatic hypocalcemia. **EAST syndrome** is caused by pathogenic variants in a potassium channel, and patients with this autosomal recessive disorder have hypokalemia, metabolic alkalosis, and hypomagnesemia. Pathogenic variants of *RRAGD* cause **autosomal dominant kidney hypomagnesemia,** and affected patients may have hypokalemia, hypomagnesemia, metabolic alkalosis, hypercalciuria, nephrocalcinosis, and a severe cardiomyopathy. **Autosomal dominant hypoparathyroidism** is caused by an activating pathogenic variant in the calcium-sensing receptor, which also senses magnesium levels in the kidney (see Chapter 611). The abnormal receptor inappropriately perceives that magnesium and calcium levels are elevated, leading to urinary wasting of both cations. Hypomagnesemia, if present, is usually mild. A pathogenic variant in a mitochondrially encoded transfer RNA is associated with hypomagnesemia, hypertension, and hypercholesterolemia. Hypomagnesemia is occasionally present in children with other mitochondrial disorders.

Poor intake is an unusual cause of hypomagnesemia, although it can be seen in children who are hospitalized and receive only IV fluids without magnesium. In **hungry bone syndrome**, which most frequently occurs after parathyroidectomy in patients with hyperparathyroidism, magnesium moves into bone as a result of accelerated bone formation. These patients usually have hypocalcemia and hypophosphatemia through the same mechanism. A similar mechanism can occur during the **refeeding phase of protein-calorie malnutrition** in children, with high magnesium use during cell growth depleting the patient's limited reserves. Insulin therapy stimulates uptake of magnesium by cells, and in DKA, in which total body magnesium is low because of osmotic losses, hypomagnesemia frequently occurs. In **pancreatitis** there is saponification of magnesium and calcium in necrotic fat, causing both hypomagnesemia and hypocalcemia.

Transient hypomagnesemia in newborns, which is sometimes idiopathic, is more common in infants of diabetic mothers, presumably as a result of maternal depletion from osmotic losses. Other maternal diseases that cause magnesium losses predispose infants to hypomagnesemia. Hypomagnesemia is more common in infants with intrauterine growth restriction. Hypomagnesemia may develop in newborn infants who require exchange transfusions because of magnesium removal by the citrate in banked blood.

Clinical Manifestations

Hypomagnesemia causes secondary hypocalcemia by impairing the release of PTH by the parathyroid gland and through blunting of the tissue response to PTH. Thus hypomagnesemia is part of the differential diagnosis of hypocalcemia. It usually occurs only at magnesium levels <0.7 mg/dL. The dominant manifestations of hypomagnesemia are caused by hypocalcemia: tetany, presence of Chvostek and Trousseau signs, and seizures. However, with severe hypomagnesemia, these same signs and symptoms may be present despite normocalcemia. Persistent hypocalcemia caused by hypomagnesemia is a rare cause of rickets.

Many causes of hypomagnesemia also result in hypokalemia. Hypomagnesemia may produce renal potassium wasting and hypokalemia that corrects only with magnesium therapy. ECG changes with hypomagnesemia include flattening of the T wave and lengthening of the ST segment. Arrhythmias may occur, almost always in the setting of underlying heart disease.

Diagnosis

The etiology of hypomagnesemia is often readily apparent from the clinical situation. The child should be assessed for GI disease, adequate intake, and kidney disease, with close attention paid to medications that may cause renal magnesium wasting. When the diagnosis is uncertain, an evaluation of urinary magnesium losses distinguishes between renal and nonrenal causes. The *fractional excretion of magnesium* (FE_{Mg}) is calculated via the following formula:

$$FE_{Mg} = (U_{Mg} \times P_{Cr}) \,/\, ([0.7 \times P_{Mg}] \times U_{Cr}) \times 100$$

where U_{Mg} = urinary magnesium concentration, P_{Cr} = plasma creatinine concentration, P_{Mg} = plasma magnesium concentration, and U_{Cr} = urinary magnesium concentration. The plasma magnesium concentration is multiplied by 0.7 because approximately 30% is bound to albumin and not filtered at the glomerulus.

The FE_{Mg} does not vary with age, but it does change according to the serum magnesium concentration. The FE_{Mg} ranges from 1–8% in children with normal magnesium levels. In the patient with hypomagnesemia as a result of extrarenal causes, FE_{Mg} should be low because of renal conservation, typically <2%. The FE_{Mg} is inappropriately elevated in the setting of renal magnesium wasting; values are usually >4% and frequently >10%. The measurement should not be made during a magnesium infusion, because the acute increase in serum magnesium increases urinary magnesium. Other approaches for evaluating urinary magnesium losses include calculation of 24-hour urinary magnesium losses and the urine magnesium/creatinine ratio, both of which vary with age.

The genetic causes of renal magnesium loss are distinguished based on the measurement of other serum and urinary electrolytes. *Children with Gitelman or Bartter syndrome have hypokalemia and metabolic alkalosis.*

Treatment

Severe hypomagnesemia is treated with parenteral magnesium. Magnesium sulfate is given at a dose of 25-50 mg/kg (0.05-0.1 mL/kg of a 50% solution; 2.5-5.0 mg/kg of elemental magnesium). It is administered as a slow IV infusion, although it may be given intramuscularly in neonates. The rate of IV infusion should be slowed if a patient experiences diaphoresis, flushing, or a warm sensation. The dose is often repeated every 6 hours (every 8-12 hours in neonates), for a total of 2-3 doses, before the plasma magnesium concentration is rechecked. Lower doses are used in children with decreased kidney function.

Long-term therapy is usually given orally. Preparations include magnesium gluconate (5.4 mg elemental magnesium/100 mg), magnesium oxide (60 mg elemental magnesium/100 mg), and magnesium sulfate (10 mg elemental magnesium/100 mg). Sustained-release preparations include Slow-Mag (60 mg elemental magnesium/tablet) and Mag-Tab SR (84 mg elemental magnesium/tablet). Oral magnesium dosing should be divided to decrease cathartic side effects. Alternatives to oral magnesium are intramuscular injections and nighttime nasogastric infusion, both designed to minimize diarrhea. Magnesium supplementation must be used cautiously in the context of renal insufficiency.

HYPERMAGNESEMIA

Clinically significant hypermagnesemia is almost always secondary to excessive intake. It is unusual, except in neonates born to mothers who are receiving IV magnesium for preeclampsia or eclampsia (see Chapter 121.5).

Etiology and Pathophysiology

There is no feedback mechanism to prevent magnesium absorption from the GI tract. Magnesium is present in high amounts in certain laxatives, enemas, cathartics used to treat drug overdoses, and antacids. It is also usually present in total parenteral nutrition (TPN), and neonates may receive high amounts transplacentally if maternal levels are elevated. Usually the kidneys excrete excessive magnesium, but this ability is diminished in patients with chronic kidney disease. In addition, neonates and young infants are vulnerable to excessive magnesium ingestion because of their reduced GFR. Most pediatric cases not related to maternal hypermagnesemia occur in infants because of excessive use of antacids or laxatives. Mild hypermagnesemia may occur in chronic kidney disease, familial hypocalciuric hypercalcemia, DKA, lithium ingestion, milk-alkali syndrome, and tumor lysis syndrome. The hypermagnesemia in DKA occurs despite significant intracellular magnesium depletion because of urinary losses; hypomagnesemia often occurs after insulin treatment.

Clinical Manifestations

Symptoms usually do not appear until the plasma magnesium level is >4.5 mg/dL. Hypermagnesemia inhibits acetylcholine release at the neuromuscular junction, producing hypotonia, hyporeflexia, and weakness; paralysis occurs at high concentrations. The neuromuscular effects may be exacerbated by aminoglycoside antibiotics. Direct CNS depression causes lethargy and sleepiness; infants have a poor suck. Elevated magnesium values are associated with hypotension because of vascular dilation, which also causes flushing. Hypotension can be profound at higher concentrations from a direct effect on cardiac function. ECG changes include prolonged PR interval, QRS complex, and QT interval. Severe hypermagnesemia (>15 mg/dL) causes complete heart block and cardiac arrest. Other manifestations of hypermagnesemia include nausea, vomiting, and hypocalcemia.

Diagnosis

Except for the case of the neonate with transplacental exposure, a high index of suspicion and a good history are necessary to determine the etiology of hypermagnesemia. Prevention is essential; magnesium-containing compounds should be used judiciously in children with decreased kidney function.

Treatment

Most patients with normal kidney function rapidly clear excess magnesium. Intravenous hydration and loop diuretics can accelerate this process. In severe cases, especially in patients with underlying renal insufficiency, dialysis may be necessary. Hemodialysis works faster than peritoneal dialysis. Exchange transfusion is another option in newborn infants. Supportive care includes monitoring of cardiorespiratory status, provision of fluids, monitoring of electrolyte levels, and the use of pressors for hypotension. In acute emergencies, especially in the context of severe neurologic or cardiac manifestations, 100 mg/kg of IV calcium gluconate is transiently effective.

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73.6 Phosphorus

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Approximately 65% of plasma phosphorus is in phospholipids, but these compounds are insoluble in acid and are not measured by clinical laboratories. It is the phosphorus content of *plasma phosphate* that is determined. The result is reported as either phosphate or phosphorus, although even when the term *phosphate* is used, it is actually the *phosphorus* concentration that is measured and reported. The result is that the terms phosphate and phosphorus are often used interchangeably. The term *phosphorus* is preferred when referring to the plasma concentration. Conversion from the units used in the United States (mg/dL) to mmol/L is straightforward (see Table 73.6).

PHOSPHORUS METABOLISM

Body Content and Physiologic Function

Most phosphorus is in bone or is intracellular, with <1% in plasma. At a physiologic pH, there are monovalent and divalent forms of phosphate because the pK_a (ionization constant of acid) of these forms is 6.8. Approximately 80% is divalent, and the remainder is monovalent at a pH of 7.4. A small percentage of plasma phosphate, approximately 15%, is protein bound. The remainder can be filtered by the glomerulus, with most existing as free phosphate and a small percentage complexed with calcium, magnesium, or sodium. Phosphate is the most plentiful intracellular anion, although the majority is part of a larger compound (ATP).

More than that of any other electrolyte, the phosphorus concentration varies with age (Table 73.8). The teleologic explanation for the high concentration during childhood is the need for phosphorus to facilitate growth. There is diurnal variation in the plasma phosphorus concentration, with the peak during sleep.

Table 73.8 Serum Phosphorus Levels During Childhood

AGE	PHOSPHORUS LEVEL (mg/dL)
0-5 day	4.8-8.2
1-3 yr	3.8-6.5
4-11 yr	3.7-5.6
12-15 yr	2.9-5.4
16-19 yr	2.7-4.7

Phosphorus, as a component of adenosine triphosphate (ATP) and other trinucleotides, is critical for cellular energy metabolism. It is necessary for cell signaling and nucleic acid synthesis, and it is a component of cell membranes and other structures. Along with calcium, phosphorus is necessary for skeletal mineralization. A net positive phosphorus balance is required during growth, with the growing skeleton especially vulnerable to deficiency.

Phosphorus Intake

Phosphorus is readily available in food. Milk and milk products are the best sources of phosphorus; high concentrations are present in meat and fish. Vegetables have more phosphorus than fruits and grains. GI absorption of phosphorus is proportional to intake, with approximately 65% of intake being absorbed, including a small amount that is secreted. Absorption, almost exclusively in the small intestine, occurs via a paracellular diffusive process and a vitamin D–regulated transcellular pathway. However, the impact of the change in phosphorus absorption caused by vitamin D is relatively small compared with the effect of variations in phosphorus intake.

Phosphorus Excretion

Despite the wide variation in phosphorus absorption dictated by oral intake, excretion matches intake, except for the needs for growth. The kidney regulates phosphorus balance, which is determined by intrarenal mechanisms and hormonal actions on the nephron.

Approximately 90% of plasma phosphate is filtered at the glomerulus, although there is some variation based on plasma phosphate and calcium concentrations. There is no significant secretion of phosphate along the nephron. Resorption of phosphate occurs mostly in the proximal tubule, although a small amount can be resorbed in the distal tubule. Normally, approximately 85% of the filtered load is resorbed. Sodium-phosphate co-transporters mediate the uptake of phosphate into the cells of the proximal tubule.

Dietary phosphorus determines the amount of phosphate resorbed by the nephron. There are both acute and chronic changes in phosphate resorption that are based on intake. Many of these changes appear to be mediated by intrarenal mechanisms that are independent of regulatory hormones. **Fibroblast growth factor-23** (**FGF-23**) inhibits renal resorption of phosphorus in the proximal tubule, and its level increases in the setting of hyperphosphatemia. FGF-23 also inhibits synthesis of 1,25-vitamin D in the kidney by decreasing 1α-hydroxylase activity.

Secreted in response to a low plasma calcium level, PTH decreases resorption of phosphate, increasing the urinary phosphate level. This process appears to have a minimal effect during normal physiologic variation in PTH levels. However, it does affect urinary phosphate in the setting of pathologic changes in PTH synthesis.

Low plasma phosphorus stimulates the 1α-hydroxylase in the kidney that converts 25-hydroxyvitamin D (25-D) to 1,25-dihydroxyvitamin D (1,25-D; calcitriol). Calcitriol increases intestinal absorption of phosphorus and is necessary for maximal renal resorption of phosphate. The effect of a change in calcitriol on urinary phosphate is significant only when the level of calcitriol was initially low, arguing against a role for calcitriol in nonpathologic conditions.

HYPOPHOSPHATEMIA

Because of the wide variation in normal plasma phosphorus levels, the definition of hypophosphatemia is age dependent (see Table 73.8). The normal range reported by a laboratory may be based on adult normal values and therefore may be misleading in children. A serum phosphorus level of 3 mg/dL, a normal value in an adult, indicates clinically significant hypophosphatemia in an infant.

The plasma phosphorus level does not always reflect the total body stores because only 1% of phosphorus is extracellular. Thus a child may have significant phosphorus deficiency despite a normal plasma phosphorus concentration when there is a shift of phosphorus from the ICS.

Etiology and Pathophysiology

A variety of mechanisms cause hypophosphatemia (Table 73.9). A transcellular shift of phosphorus into cells occurs with processes that stimulate cellular usage of phosphorus (glycolysis). Usually, this shift causes only a minor, transient decrease in plasma phosphorus, but if intracellular phosphorus deficiency is present, the plasma phosphorus level can decrease significantly, producing symptoms of acute hypophosphatemia. Glucose infusion stimulates insulin release, leading to entry of glucose and phosphorus into the cells. Phosphorus is then used during glycolysis and other metabolic processes. A similar phenomenon can occur during the treatment of DKA, and patients with DKA are typically phosphorus depleted because of urinary phosphorus losses.

Table 73.9 Causes of Hypophosphatemia

TRANSCELLULAR SHIFTS
Glucose infusion
Insulin
Refeeding
Total parenteral nutrition
Respiratory alkalosis
Tumor growth
Bone marrow transplantation
Hungry bone syndrome
DECREASED INTAKE
Nutritional
Premature infants
Low phosphorus formula
Antacids and other phosphate binders
RENAL LOSSES
Hyperparathyroidism
Parathyroid hormone–related peptide
X-linked hypophosphatemic rickets (OMIM 307800)
Overproduction of fibroblast growth factor-23
Tumor-induced rickets
McCune-Albright syndrome (OMIM 174800)
Epidermal nevus syndrome
Neurofibromatosis
Autosomal dominant hypophosphatemic rickets (OMIM 193100)
Autosomal recessive hypophosphatemic rickets, types 1, 2, and 3 (OMIM 241520/613312)
Ferric carboxymaltose
Dent disease (OMIM 300009/300555)
Fanconi syndrome (OMIM 134600/613388/615605/616026/618913/612392)*
Hypophosphatemic rickets with hypercalciuria (OMIM 241530)
Hypophosphatemic rickets with nephrolithiasis and osteoporosis types 1 and 2 (OMIM 612286/612287)
Volume expansion and intravenous fluids
Metabolic acidosis
Diuretics
Glycosuria
Glucocorticoids
Chemotherapy (cisplatin, ifosfamide)
Kidney transplantation
MULTIFACTORIAL
Vitamin D deficiency
Vitamin D–dependent rickets type 1 (OMIM 264700)
Vitamin D–dependent rickets type 2 (OMIM 277440)
Alcoholism
Sepsis
Dialysis

*These are primary genetic causes of Fanconi syndrome. Fanconi syndrome may also be secondary to medications, genetic disorders (cystinosis) or systemic disease (Sjögren syndrome).

OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

Refeeding of patients with protein-calorie malnutrition causes anabolism, which leads to significant cellular demand for phosphorus (see Chapter 63). The increased phosphorus uptake for incorporation into newly synthesized compounds containing phosphorus leads to hypophosphatemia, which can be severe and symptomatic. **Refeeding hypophosphatemia** occurs frequently during treatment of severe anorexia nervosa. It can occur during treatment of children with malnutrition from any cause, such as cystic fibrosis, Crohn disease, burns, neglect, chronic infection, or famine. Hypophosphatemia usually occurs within the first 5 days of refeeding and is prevented by a gradual increase in nutrition with appropriate phosphorus supplementation. TPN without adequate phosphorus can cause hypophosphatemia.

Phosphorus moves into the ICS during a respiratory alkalosis and during recovery from a respiratory acidosis. An acute decrease in the carbon dioxide concentration, by raising the intracellular pH, stimulates glycolysis, leading to intracellular use of phosphorus and hypophosphatemia. Because a metabolic alkalosis has less effect on the intracellular pH (CO_2 diffuses across cell membranes much faster than bicarbonate), transcellular phosphorus movement is minimal with a metabolic alkalosis.

Tumors that grow rapidly, such as those associated with leukemia and lymphoma, may use large amounts of phosphorus, leading to hypophosphatemia. A similar phenomenon may occur during the hematopoietic reconstitution that follows bone marrow transplantation. In **hungry bone syndrome**, there is avid bone uptake of phosphorus, along with calcium and magnesium, which can produce plasma deficiency of all three ions. Hungry bone syndrome is most common after parathyroidectomy for hyperparathyroidism because the stimulus for bone dissolution is acutely removed, but bone synthesis continues.

Nutritional phosphorus deficiency is unusual because most foods contain phosphorus. However, infants are especially susceptible because of their high demand for phosphorus to support growth, especially of the skeleton. Very low birthweight infants have particularly rapid skeletal growth, and phosphorus deficiency and rickets may develop if they are fed human milk or formula for term infants. There is also a relative deficiency of calcium. The provision of additional calcium and phosphorus, using breast milk fortifier or special premature infant formula, prevents this complication. Phosphorus deficiency, sometimes with concomitant calcium and vitamin D deficiencies, occurs in infants who are not given enough milk or who receive a milk substitute that is nutritionally inadequate.

Antacids containing aluminum hydroxide (e.g., Maalox, Mylanta) bind dietary phosphorus and secreted phosphorus, preventing absorption. This process can cause phosphorus deficiency and rickets in growing children. A similar mechanism causes hypophosphatemia in patients who are overtreated for hyperphosphatemia with phosphorus binders. In children with kidney failure, the addition of dialysis to phosphorus binders increases the risk of iatrogenic hypophosphatemia in these normally hyperphosphatemic patients. This complication, which is more common in infants, can worsen kidney osteodystrophy.

Excessive renal losses of phosphorus occur in a variety of inherited and acquired disorders. Because PTH inhibits the resorption of phosphorus in the proximal tubule, **hyperparathyroidism** causes hypophosphatemia (see Chapter 613). The dominant clinical manifestation, however, is hypercalcemia, and the hypophosphatemia is usually asymptomatic. The phosphorus level in hyperparathyroidism is not extremely low, and there is no continued loss of phosphorus because a new steady state is achieved at the lower plasma phosphorus level. Renal excretion therefore does not exceed intake over the long term. Occasional malignancies produce PTH-related peptide, which has the same actions as PTH and causes hypophosphatemia and hypercalcemia.

A variety of diseases cause renal phosphate wasting, hypophosphatemia, and rickets resulting from excess FGF-23 (see Chapter 69). These disorders include X-linked hypophosphatemic rickets, tumor-induced osteomalacia, autosomal dominant hypophosphatemic rickets, and autosomal recessive hypophosphatemic rickets types 1-3. Ferric carboxymaltose, an IV iron preparation for correcting iron deficiency, causes hypophosphatemia via increased levels of FGF-23.

Fanconi syndrome is a generalized defect in the proximal tubule leading to urinary wasting of bicarbonate, phosphorus, amino acids, uric acid, and glucose (see Chapter 569.1). The clinical sequelae result from the metabolic acidosis and hypophosphatemia. In children, an underlying genetic disease, usually cystinosis, often causes Fanconi syndrome, but it can be secondary to a variety of toxins and acquired diseases. Some patients have incomplete Fanconi syndrome, and phosphorus wasting may be one of the manifestations.

Dent disease, an X-linked disorder, can cause renal phosphorus wasting and hypophosphatemia, although the latter is not present in most cases. Other possible manifestations of Dent disease include tubular proteinuria, hypercalciuria, nephrolithiasis, rickets, and decreased kidney function. Dent disease may be secondary to pathologic variants in a gene that encodes a chloride channel or the *OCRL1* gene, which may also cause Lowe syndrome (see Chapter 569.1). **Hypophosphatemic rickets with hypercalciuria** is a rare autosomal recessive disorder, principally described in kindreds from the Middle East (see Chapter 69). Pathologic variants in a sodium-phosphate co-transporter cause hypophosphatemia in this disorder, and complications may include nephrolithiasis and osteoporosis. Similar findings are seen in hypophosphatemic rickets with nephrolithiasis and osteoporosis types 1 and 2 (see Chapter 69).

Metabolic acidosis inhibits resorption of phosphorus in the proximal tubule. In addition, metabolic acidosis causes a transcellular shift of phosphorus out of cells because of intracellular catabolism. This released phosphorus is subsequently lost in the urine, leading to significant phosphorus depletion, even though the plasma phosphorus level may be normal. This classically occurs in DKA, in which renal phosphorus loss is further increased by the osmotic diuresis. With correction of the metabolic acidosis and the administration of insulin, both of which cause a transcellular movement of phosphorus into the cells, there is a marked decrease in the plasma phosphorus level.

Volume expansion from any cause, such as hyperaldosteronism or SIADH, inhibits resorption of phosphorus in the proximal tubule. This effect also occurs with high rates of IV fluids. Thiazide and loop diuretics can increase renal phosphorus excretion, but the increase is seldom clinically significant. Glycosuria and glucocorticoids inhibit renal conservation of phosphorus. Hypophosphatemia is common after kidney transplantation because of urinary phosphorus losses. Possible explanations include preexisting secondary hyperparathyroidism from chronic kidney disease, glucocorticoid therapy, and upregulation of FGF-23 before transplantation. The hypophosphatemia usually resolves in a few months.

Both acquired and genetic causes of **vitamin D deficiency** are associated with hypophosphatemia (see Chapter 69). The pathogenesis is multifactorial. By impairing intestinal calcium absorption, vitamin D deficiency causes secondary hyperparathyroidism that leads to increased urinary phosphorus wasting. An absence of vitamin D decreases intestinal absorption of phosphorus and directly decreases renal resorption of phosphorus. The dominant clinical manifestation is rickets, although some patients have muscle weakness that may be related to phosphorus deficiency.

Alcoholism is the most common cause of severe hypophosphatemia in adults. Fortunately, many of the risk factors that predispose alcoholic adults to hypophosphatemia are not usually present in adolescents (malnutrition, antacid abuse, recurrent DKA episodes). Hypophosphatemia often occurs in sepsis, but the mechanism is not clear. Aggressive, protracted hemodialysis, as might be used for

the treatment of methanol or ethylene glycol ingestion, can cause hypophosphatemia.

Clinical Manifestations

There are acute and chronic manifestations of hypophosphatemia. **Rickets** occurs in children with long-term phosphorus deficiency. The clinical features of rickets are described in Chapter 69.

Severe hypophosphatemia, typically at levels <1.0-1.5 mg/dL, may affect every organ in the body because phosphorus has a critical role in maintaining adequate cellular energy. Phosphorus is a component of ATP and is necessary for glycolysis. With inadequate phosphorus, 2,3-diphosphoglycerate levels in RBCs decrease, impairing release of oxygen to the tissues. Severe hypophosphatemia can cause hemolysis and dysfunction of WBCs. Chronic hypophosphatemia causes proximal muscle weakness and atrophy. In the intensive care unit, phosphorus deficiency may slow weaning from mechanical ventilation or cause acute respiratory failure. **Rhabdomyolysis** is the most common complication of acute hypophosphatemia, usually in the setting of an acute transcellular shift of phosphorus into cells in a child with chronic phosphorus depletion (anorexia nervosa). The rhabdomyolysis is actually somewhat protective, in that cellular release of phosphorus occurs. Other manifestations of severe hypophosphatemia include cardiac dysfunction and neurologic symptoms, such as tremor, paresthesia, ataxia, seizures, delirium, and coma.

Diagnosis

The history and basic laboratory evaluation often suggest the etiology of hypophosphatemia. The history should investigate nutrition, medications, and familial disease. Hypophosphatemia and rickets in an otherwise healthy young child suggest a genetic defect in renal phosphorus conservation, Fanconi syndrome, inappropriate use of antacids, poor nutrition, vitamin D deficiency, or a genetic defect in vitamin D metabolism. The patient with Fanconi syndrome usually has metabolic acidosis, glycosuria, aminoaciduria, and a low plasma uric acid level. Measurement of 25-D and 1,25-D, calcium, and PTH differentiates among the various vitamin D deficiency disorders and primary renal phosphate wasting (see Chapter 69). Hyperparathyroidism is easily distinguished by the presence of elevated plasma PTH and calcium values.

Treatment

The plasma phosphorus level, the presence of symptoms, the likelihood of chronic depletion, and the presence of ongoing losses dictate the approach to therapy. Mild hypophosphatemia does not require treatment unless the clinical situation suggests that chronic phosphorus depletion is present or that losses are ongoing. Oral phosphorus can cause diarrhea, so the doses should be divided. IV therapy is effective in patients who have severe deficiency or who cannot tolerate oral medications. IV phosphorus is available as either sodium phosphate or potassium phosphate, with the choice usually based on the patient's plasma potassium level. Starting doses are 0.08-0.16 mmol/kg over 6 hours. The oral preparations of phosphorus are available with various ratios of sodium and potassium. This is an important consideration because some patients may not tolerate the potassium load, whereas supplemental potassium may be helpful in some diseases, such as Fanconi syndrome and malnutrition. Oral maintenance dosages are 2-3 mmol/kg/day in divided doses, although the maintenance dose varies considerably between patients.

Increasing dietary phosphorus is the only intervention needed in infants with inadequate intake. Other patients may also benefit from increased dietary phosphorus, usually from dairy products. Phosphorus-binding antacids should be discontinued in patients with hypophosphatemia. Certain diseases require specific therapy (see Chapter 69). Specifically, X-linked hypophosphatemia responds to burosumab, a monoclonal antibody targeting FGF-23.

Table 73.10 Causes of Hyperphosphatemia

TRANSCELLULAR SHIFTS
Tumor lysis syndrome
Rhabdomyolysis
Acute hemolysis
Diabetic ketoacidosis and lactic acidosis
INCREASED INTAKE
Enemas and laxatives
Cow's milk in infants
Treatment of hypophosphatemia
Vitamin D intoxication
DECREASED EXCRETION
Kidney failure
Hypoparathyroidism or pseudohypoparathyroidism (OMIM 146200/603233/103580/241410/203330)
Acromegaly
Hyperthyroidism
Tumoral calcinosis with hyperphosphatemia: genetic (OMIM 211900/617993/617994) or autoimmune

OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

HYPERPHOSPHATEMIA

Etiology and Pathophysiology

Renal insufficiency is the most common cause of hyperphosphatemia, with the severity proportional to the degree of kidney impairment (see Chapter 572). This occurs because GI absorption of the large dietary intake of phosphorus is unregulated, and the kidneys normally excrete this phosphorus. As kidney function deteriorates, increased excretion of phosphorus is able to compensate. When kidney function is <30% of normal, hyperphosphatemia usually develops, although this varies considerably depending on dietary intake. Many of the other causes of hyperphosphatemia are more likely to develop in the setting of decreased kidney function (Table 73.10).

Cellular content of phosphorus is high relative to plasma phosphorus, and cell lysis can release substantial phosphorus. This is the etiology of hyperphosphatemia in **tumor lysis syndrome**, **rhabdomyolysis**, and **acute hemolysis**. These disorders cause concomitant potassium release and the risk of hyperkalemia. Additional features of tumor lysis and rhabdomyolysis are hyperuricemia and hypocalcemia, whereas indirect hyperbilirubinemia and elevated lactate dehydrogenase (LDH) values are often present with hemolysis. An elevated CPK level is suggestive of rhabdomyolysis. During lactic acidosis or DKA, use of phosphorus by cells decreases, and phosphorus shifts into the ECS. This problem reverses when the underlying problem is corrected, and especially with DKA, patients subsequently become hypophosphatemic because of previous renal phosphorus loss.

Excessive intake of phosphorus is especially dangerous in children with decreased kidney function. Neonates are at risk because kidney function is normally reduced during the first few months of life. In addition, they may erroneously be given doses of phosphorus that are meant for an older child or adult. In infants fed cow's milk, which has higher phosphorus content than breast milk or formula, hyperphosphatemia may develop. **Fleet Enema** has a high amount of phosphorus that can be absorbed, especially in the patient with an ileus; infants and children with Hirschsprung disease are especially vulnerable. There is often associated hypernatremia from sodium absorption and water loss from diarrhea. Sodium phosphorus laxatives may cause hyperphosphatemia if the dose is excessive or if renal insufficiency is present. Hyperphosphatemia occurs in children who receive overaggressive treatment for hypophosphatemia. **Vitamin D intoxication** causes excessive GI absorption of both calcium and phosphorus, and the suppression of PTH by hypercalcemia decreases renal phosphorus excretion.

The absence of PTH in **hypoparathyroidism** or PTH responsiveness in **pseudohypoparathyroidism** causes hyperphosphatemia because of increased resorption of phosphorus in the proximal tubule of the kidney (see Chapters 611 and 612). The associated hypocalcemia is responsible for the clinical symptoms. The hyperphosphatemia in hyperthyroidism or acromegaly is usually mild. It is secondary to increased resorption of phosphorus in the proximal tubule from the actions of thyroxine or growth hormone. Excessive thyroxine can also cause bone resorption, which may contribute to the hyperphosphatemia and cause hypercalcemia. Patients with **familial tumoral calcinosis** (three types), a rare autosomal recessive disorder, have hyperphosphatemia because of decreased renal phosphate excretion and heterotopic calcifications. The disease may be secondary to pathologic variants in the genes for a glycosyltransferase (most common etiology), FGF-23, or klotho, which encodes the co-receptor for FGF-23. Autoimmune hyperphosphatemic tumoral calcinosis occurs with antibodies producing FGF-23 resistance.

Clinical Manifestations

The principal clinical consequences of hyperphosphatemia are hypocalcemia and systemic calcification. The hypocalcemia is probably caused by tissue deposition of calcium-phosphorus salt, inhibition of 1,25-D production, and decreased bone resorption. Symptomatic hypocalcemia is most likely to occur when the phosphorus level increases rapidly or when diseases predisposing to hypocalcemia are present (chronic kidney disease, rhabdomyolysis). Systemic calcification occurs because the solubility of phosphorus and calcium in the plasma is exceeded. Clinically, this condition is often apparent in the conjunctiva, where it manifests as a foreign body feeling, erythema, and injection. More ominous manifestations are hypoxia from pulmonary calcification and kidney failure from nephrocalcinosis.

Diagnosis

Plasma creatinine and BUN levels should be assessed in any patient with hyperphosphatemia. The history should focus on intake of phosphorus and the presence of chronic diseases that may cause hyperphosphatemia. Measurement of K^+, uric acid, calcium, LDH, bilirubin, hemoglobin, and CPK may be indicated if rhabdomyolysis, tumor lysis, or hemolysis is suspected. With mild hyperphosphatemia and significant hypocalcemia, measurement of the serum PTH level distinguishes between hypoparathyroidism and pseudohypoparathyroidism.

Treatment

The treatment of acute hyperphosphatemia depends on its severity and etiology. Mild hyperphosphatemia in a patient with reasonable renal function spontaneously resolves; the resolution can be accelerated by dietary phosphorus restriction. If kidney function is not impaired, IV fluids can enhance renal phosphorus excretion. For more significant hyperphosphatemia or a situation such as tumor lysis or rhabdomyolysis, in which endogenous phosphorus generation is likely to continue, addition of an oral phosphorus binder prevents absorption of dietary phosphorus and can remove phosphorus from the body by binding what is normally secreted and absorbed by the GI tract. Phosphorus binders are most effective when given with food. Binders containing aluminum hydroxide are especially efficient, but calcium carbonate is an effective alternative and may be preferred if there is a need to treat concomitant hypocalcemia. Preservation of renal function, as with high urine flow in rhabdomyolysis or tumor lysis, is an important adjunct because it will permit continued excretion of phosphorus. If the hyperphosphatemia is not responding to conservative management, especially if acute kidney injury is supervening, dialysis may be necessary to increase phosphorus removal.

Dietary phosphorus restriction is necessary for diseases causing chronic hyperphosphatemia. However, such diets are often difficult to follow, given the abundance of phosphorus in a variety of foods. Dietary restriction is often sufficient in conditions such as hypoparathyroidism and mild chronic kidney disease. For more problematic hyperphosphatemia, such as with moderate chronic kidney disease and end-stage kidney disease, phosphorus binders are usually necessary. They include calcium carbonate, calcium acetate, sevelamer, ferric citrate, sucroferric oxyhydroxide, and lanthanum. Aluminum-containing phosphorus binders are no longer used in patients with **chronic kidney disease** because of the risk of aluminum toxicity. Dialysis directly removes phosphorus from the blood in patients with end-stage kidney disease, but it is only an adjunct to dietary restriction and phosphorus binders; removal by dialysis does not keep up with normal dietary intake.

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73.7 Acid-Base Balance

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ACID-BASE PHYSIOLOGY

Terminology

Chronic, mild derangements in acid-base status may interfere with normal growth and development, whereas acute, severe changes in pH can be fatal. Control of acid-base balance depends on the kidneys, the lungs, and intracellular and extracellular buffers.

A normal pH is 7.35-7.45. There is an inverse relationship between the pH and the hydrogen ion concentration([H^+]). At a pH of 7.40, [H^+] is 40 nmol/L. A normal serum sodium concentration, 140 mEq/L, is 1 million times higher. Maintaining a normal pH is necessary because hydrogen ions are highly reactive and are especially likely to combine with proteins, altering their function.

An **acid** is a substance that releases ("donates") a hydrogen ion (H^+). A **base** is a substance that accepts a hydrogen ion. An acid (HA) can dissociate into a hydrogen ion and a conjugate base (A^-), as follows:

$$HA \leftrightarrow H^+ + A^-$$

A strong acid is highly dissociated, so in this reaction, there is little HA. A weak acid is poorly dissociated; not all the hydrogen ions are released from HA. A^- acts as a base when the reaction moves to the left. These reactions are in equilibrium. When HA is added to the system, there is dissociation of some HA until the concentrations of H^+ and A^- increase enough that a new equilibrium is reached. Addition of hydrogen ions causes a decrease in A^- and an increase in HA. Addition of A^- causes a decrease in hydrogen ions and an increase in HA.

Buffers are substances that attenuate the change in pH that occurs when acids or bases are added to the body. Given the extremely low [H^+] in the body at physiologic pH, without buffers a small amount of hydrogen ions could cause a dramatic decline in the pH. Buffers prevent the decrease in pH by binding the added hydrogen ions, as follows:

$$A^- + H^+ \rightarrow HA$$

The increase in [H^+] drives this reaction to the right. Similarly, when base is added to the body, buffers prevent the pH from increasing by releasing hydrogen ions, as follows:

$$HA \rightarrow A^- + H^+$$

The best buffers are weak acids and bases. This is because a buffer works best when it is 50% dissociated (half HA and half A^-). The pH at which a buffer is 50% dissociated is its pK_a (ionization constant

of acid). The best physiologic buffers have a pK_a close to 7.40. The concentration of a buffer and its pK_a determine the buffer's effectiveness (buffering capacity). When the pH is lower than the pK_a of a buffer, there is more HA than A^-. When the pH is higher than the pK_a, there is more A^- than HA.

Physiologic Buffers

The bicarbonate and nonbicarbonate buffers protect the body against major changes in pH. The **bicarbonate buffer system** is routinely monitored clinically and is based on the relationship between carbon dioxide (CO_2) and bicarbonate (HCO_3^-):

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

CO_2 acts as an acid in that, after combining with water, it releases an H^+; bicarbonate acts as its conjugate base in that it accepts an H^+. The pK_a of this reaction is 6.1. The **Henderson-Hasselbalch equation** expresses the relationship among pH, pK_a, and the concentrations of an acid and its conjugate base. This relationship is valid for any buffer. The Henderson-Hasselbalch equation for bicarbonate and CO_2 is as follows:

$$pH = 6.1 + \log [HCO_3^-] \; / \; [CO_2]$$

The **Henderson-Hasselbalch equation** for the bicarbonate buffer system has three variables: pH, bicarbonate concentration ($[HCO_3^-]$), and carbon dioxide concentration ($[CO_2]$). Thus, if any two of these variables are known, it is possible to calculate the third. When one is using the Henderson-Hasselbalch equation, it is important that CO_2 and bicarbonate have the same units. CO_2 is reported clinically as mm Hg and must be multiplied by its solubility constant, 0.03 mmol/L/mm Hg, before the equation can be used. Mathematical manipulation of the Henderson-Hasselbalch equation produces the following relationship:

$$\left[H^+\right] = 24 \times PCO_2 / \left[HCO_3^-\right]$$

At a normal $[H^+]$ of 40 nmol (pH 7.40), the partial pressure of carbon dioxide (P_{CO_2}), which is expressed as mm Hg in this equation, is 40 when the $[HCO_3^-]$ is 24 mEq/L. This equation emphasizes that $[H^+]$, and thus pH, can be determined by the ratio of P_{CO_2} and $[HCO_3^-]$.

The bicarbonate buffer system is very effective because of the high concentration of bicarbonate in the body (24 mEq/L) and because it is an open system. The remaining body buffers are in a closed system. The bicarbonate buffer system is an open system because the lungs increase CO_2 excretion when the blood CO_2 concentration increases. When acid is added to the body, the following reaction occurs:

$$H^+ + HCO_3^- \rightarrow CO_2 + H_2O$$

In a closed system, the CO_2 would increase. The higher CO_2 concentration would lead to an increase in the reverse reaction:

$$CO_2 + H_2O \rightarrow H^+ + HCO_3^-$$

This would increase $[H^+]$, limiting the buffering capacity of bicarbonate. However, because the lungs excrete the excess CO_2, the reverse reaction does not increase; this fact enhances the buffering capacity of bicarbonate. The same principle holds with the addition of base, because the lungs decrease CO_2 excretion and prevent the CO_2 level from falling. The lack of change in $[CO_2]$ dramatically increases the buffering capacity of bicarbonate.

The **nonbicarbonate buffers** include proteins, phosphate, and bone. Protein buffers consist of extracellular proteins, mostly albumin and intracellular proteins, including hemoglobin. Proteins are effective buffers, largely because of the presence of the amino acid *histidine,* which has a side chain that can bind or release H^+. The pK_a of histidine varies slightly, depending on its position in the protein molecule, but its average pK_a is approximately 6.5. This is close enough to a normal pH (7.4) to make histidine an effective buffer. Hemoglobin and albumin have 34 and 16 histidine molecules, respectively.

Phosphate can bind up to three hydrogen molecules, so it can exist as PO_4^{3-}, HPO_4^{2-}, $H_2PO_4^{1-}$, or H_3PO_4. However, at a physiologic pH, most phosphate exists as either HPO_4^{2-} or $H_2PO_4^{1-}$. $H_2PO_4^{1-}$ is an acid, and HPO_4^{2-} is its conjugate base:

$$H_2PO_4^{1-} \leftrightarrow H^+ + HPO_4^{2-}$$

The pK_a of this reaction is 6.8, making phosphate an effective buffer. The concentration of phosphate in the ECS is relatively low, limiting the overall buffering capacity of phosphate; it is less important than albumin. However, phosphate is found at a much higher concentration in the urine, where it is an important buffer. In the ICS, most phosphate is covalently bound to organic molecules (ATP), but it still serves as an effective buffer.

Bone is an important buffer. Bone is *basic*—it is composed of compounds such as sodium bicarbonate and calcium carbonate—and thus dissolution of bone releases base. This release can buffer an acid load, although at the expense of bone density, if it occurs over an extended period. In contrast, bone formation, by consuming base, helps buffer excess base.

Clinically, we measure the extracellular pH, but it is the intracellular pH that affects cell function. Measurement of the intracellular pH is unnecessary because changes in the intracellular pH parallel the changes in the extracellular pH. However, the change in the intracellular pH tends to be less than the change in the extracellular pH because of the greater buffering capacity in the ICS.

NORMAL ACID-BASE BALANCE

The lungs and kidneys maintain a normal acid-base balance. Carbon dioxide generated during normal metabolism is a weak acid. The lungs prevent an increase in the P_{CO_2} in the blood by excreting the CO_2 that the body produces. CO_2 production varies according to the body's metabolic needs, increasing with physical activity. The rapid pulmonary response to changes in the CO_2 concentration occurs via central sensing of the P_{CO_2} and a subsequent increase or decrease in ventilation to maintain a normal P_{CO_2} (35-45 mm Hg). An increase in ventilation decreases the P_{CO_2}, and a decrease in ventilation increases the P_{CO_2}.

The kidneys excrete endogenous acid. An adult normally produces approximately 1-2 mEq/kg/24 hr of H^+. Children normally produce 2-3 mEq/kg/24 hr of H^+. The three principal sources of H^+ are dietary protein metabolism, incomplete metabolism of carbohydrates and fat, and stool losses of bicarbonate. Because metabolism of protein generates H^+, endogenous acid production varies with protein intake. The complete oxidation of carbohydrates or fats to CO_2 and water does not generate H^+; the lungs remove the CO_2. However, incomplete metabolism of carbohydrates or fats produces H^+. Incomplete glucose metabolism can produce lactic acid, and incomplete triglyceride metabolism can produce ketoacids, such as β-hydroxybutyric acid and acetoacetic acid. There is always some baseline incomplete metabolism that contributes to endogenous acid production. This factor increases in pathologic conditions, such as **lactic acidosis** and diabetic ketoacidosis (DKA). Stool loss of bicarbonate is the third major source of endogenous acid production. The stomach secretes H^+, but most of the remainder of the GI tract secretes bicarbonate, and the net effect is a loss of bicarbonate from the body. To secrete bicarbonate, the cells of the intestine produce hydrogen ions that are released into the bloodstream. For each bicarbonate molecule lost in the stool, the body gains one H^+. This source of endogenous acid production is normally minimal but may increase dramatically in a patient with diarrhea.

The hydrogen ions formed from endogenous acid production are neutralized by bicarbonate, potentially causing the bicarbonate concentration to decrease. The kidneys regenerate this bicarbonate by secreting H^+. The lungs cannot regenerate bicarbonate, even though loss of CO_2 lowers the $[H^+]$, as shown in the following reaction:

$$H^+ + HCO_3^- \rightarrow CO_2 + H_2O$$

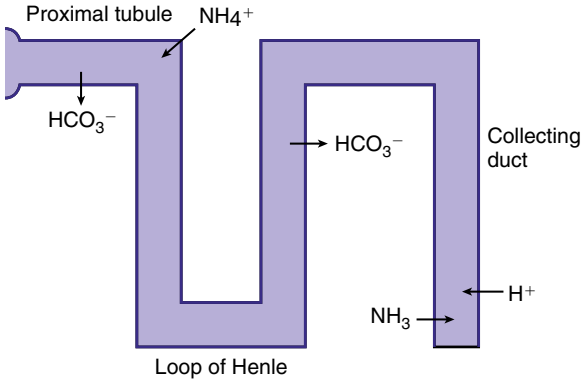

Fig. 73.7 Tubular sites involved in acid-base balance. The proximal tubule is the site where most filtered bicarbonate is reclaimed, even though other sites along the nephron, especially the thick ascending limb of the loop of Henle, resorb some of the filtered bicarbonate. The collecting duct is the principal location for the hydrogen ion secretion that acidifies the urine. The proximal tubule generates the ammonia that serves as a urinary buffer in the collecting duct.

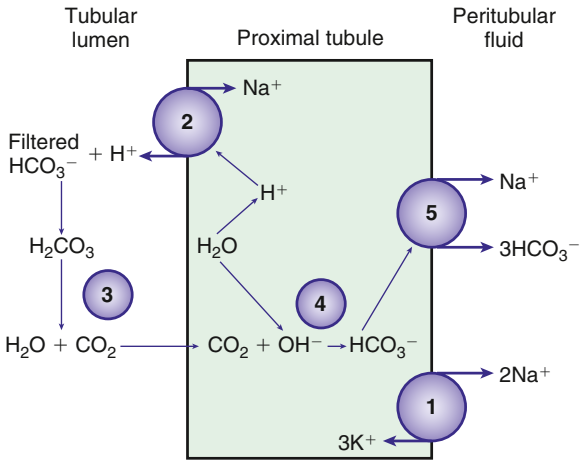

Fig. 73.8 Resorption of filtered bicarbonate in the proximal tubule. The Na^+,K^+-ATPase *(1)* excretes sodium across the basolateral cell membrane, maintaining a low intracellular sodium concentration. The low intracellular sodium concentration provides the energy for the Na^+,H^+ antiporter *(2)*, which exchanges sodium from the tubular lumen for intracellular hydrogen ions. The hydrogen ions that are secreted into the tubular lumen then combine with filtered bicarbonate to generate carbonic acid. CO_2 and water are produced from carbonic acid (H_2CO_3). This reaction is catalyzed by luminal carbonic anhydrase *(3)*. CO_2 diffuses into the cell and combines with OH^- ions to generate bicarbonate. This reaction is catalyzed by an intracellular carbonic anhydrase *(4)*. The dissociation of water generates an OH^- ion and an H^+ ion. The Na^+,H^+ antiporter *(2)* secretes the hydrogen ions. Bicarbonate ions cross the basolateral membrane and enter the blood via the $3HCO_3^-/1Na^+$ co-transporter *(5)*. The energy for the $3HCO_3^-/1Na^+$ co-transporter comes from the negatively charged cell interior, which makes it electrically favorable to transport a net negative charge (i.e., 3 bicarbonates and only 1 sodium) out of the cell.

A decrease in $[CO_2]$ causes the reaction to move to the right, which decreases $[H^+]$, but it also lowers $[HCO_3^-]$. During a metabolic acidosis, hyperventilation can lower $[CO_2]$, decrease $[H^+]$, and thus increase pH. The underlying metabolic acidosis is still present. Similarly, the kidneys cannot correct an abnormally high $[CO_2]$, as shown in the following reaction:

$$H^+ + HCO_3^- \rightarrow CO_2 + H_2O$$

An increase in $[HCO_3^-]$ also causes the reaction to move to the right, which increases $[CO_2]$ while simultaneously decreasing $[H^+]$. During a respiratory acidosis, increased renal generation of bicarbonate can decrease $[H^+]$ and increase pH but cannot repair the respiratory acidosis. Both the lungs and the kidneys can affect $[H^+]$ and thus pH. However, only the lungs can regulate $[CO_2]$, and only the kidneys can regulate $[HCO_3^-]$.

Renal Mechanisms

The kidneys regulate the serum bicarbonate concentration by modifying acid excretion in the urine. This requires a two-step process. First, the renal tubules resorb the bicarbonate that is filtered at the glomerulus. Second, there is tubular secretion of H^+. The urinary excretion of H^+ generates bicarbonate that neutralizes endogenous acid production. The tubular actions necessary for renal acid excretion occur throughout the nephron (Fig. 73.7).

The resorption of filtered bicarbonate is a necessary first step in renal regulation of the acid-base balance. A normal adult has a GFR of approximately 180 L/24 hr. This fluid enters Bowman's space with $[HCO_3^-]$ that is essentially identical to the plasma concentration, normally 24 mEq/L. Multiplying 180 L by 24 mEq/L indicates that >4,000 mEq of bicarbonate enters Bowman's space each day. This bicarbonate, if not reclaimed along the nephron, would be lost in the urine and would cause a profound metabolic acidosis.

The proximal tubule reclaims approximately 85% of the filtered bicarbonate (Fig. 73.8). The final 15% is reclaimed beyond the proximal tubule, mostly in the ascending limb of the loop of Henle. Bicarbonate molecules are not transported from the tubular fluid into the cells of the proximal tubule. Rather, hydrogen ions are secreted into the tubular fluid, leading to conversion of filtered bicarbonate into CO_2 and water. The secretion of H^+ by the cells of the proximal tubule is coupled to generation of intracellular bicarbonate, which is transported across the basolateral membrane of the proximal tubule cell and enters the capillaries. The bicarbonate produced in the cell replaces the bicarbonate filtered at the glomerulus.

Increased bicarbonate resorption by the cells of the proximal tubule—the result of increased H^+ secretion—occurs in a variety of clinical situations. Volume depletion increases bicarbonate resorption. This is partially mediated by activation of the renin-angiotensin system; angiotensin II increases bicarbonate resorption. Increased bicarbonate resorption in the proximal tubule is one of the mechanisms that accounts for the metabolic alkalosis that may occur in some patients with volume depletion. Other stimuli that increase bicarbonate resorption include hypokalemia and an increased P_{CO_2}. This partially explains the observations that hypokalemia causes a metabolic alkalosis, and that a respiratory acidosis leads to a compensatory increase in serum $[HCO_3^-]$.

Stimuli that decrease bicarbonate resorption in the proximal tubule may cause a decrease in the serum $[HCO_3^-]$. A decrease in the P_{CO_2} (respiratory alkalosis) decreases proximal tubule bicarbonate resorption, partially mediating the decrease in serum $[HCO_3^-]$ that compensates for a respiratory alkalosis. PTH decreases proximal tubule bicarbonate resorption; hyperparathyroidism may cause a mild metabolic acidosis. A variety of medications and diseases cause a metabolic acidosis by impairing bicarbonate resorption in the proximal tubule. Examples are the medication acetazolamide, which directly inhibits carbonic anhydrase, and the many disorders that cause proximal RTA (see Chapter 569.1).

After reclaiming filtered bicarbonate, the kidneys perform the second step in renal acid-base handling, the excretion of the acid created by endogenous acid production. Excretion of acid occurs mostly in the collecting duct, with a small role for the distal tubule.

Along with secretion of H^+ by the tubular cells lining the collecting duct, adequate excretion of endogenous acid requires the presence of urinary buffers. The hydrogen pumps in the collecting duct cannot lower the urine pH below 4.5. The $[H^+]$ at pH 4.5 is <0.04 mEq/L; it would require >25 L of water with a pH of 4.5 to excrete one mEq of H^+. A 10-kg child, with an endogenous acid production of 20 mEq H^+ each day, would need to have a daily urinary output of >500 L without the presence of urinary buffers. As in the blood, buffers in the urine attenuate the decrease in pH that occurs with the addition of H^+. The two principal urinary buffers are phosphate and ammonia.

Urinary **phosphate** is proportional to dietary intake. Whereas most of the phosphate filtered at the glomerulus is resorbed in the proximal tubule, the urinary phosphate concentration is usually much greater than the serum phosphate concentration. This arrangement allows phosphate to serve as an effective buffer through the following reaction:

$$H^+ + HPO_4^{2-} \rightarrow H_2PO_4^{1-}$$

The pK_a of this reaction is 6.8, making phosphate an effective buffer as the urinary pH decreases from 7.0 to 5.0 within the collecting duct. Although phosphate is an effective buffer, its buffering capacity is limited by its concentration; there is no mechanism for increasing urinary phosphate excretion in response to changes in acid-base status.

In contrast, **ammonia** production can be modified, allowing for regulation of acid excretion. The buffering capacity of ammonia (NH_3) is based on the reaction of ammonia with hydrogen ions to form ammonium:

$$NH_3 + H^+ \rightarrow NH_4^+$$

The cells of the proximal tubule are the source of the excreted ammonia, mostly through metabolism of glutamine through the following reactions:

$$\text{Glutamine} \rightarrow NH_4^+ + \text{glutamate}^-$$

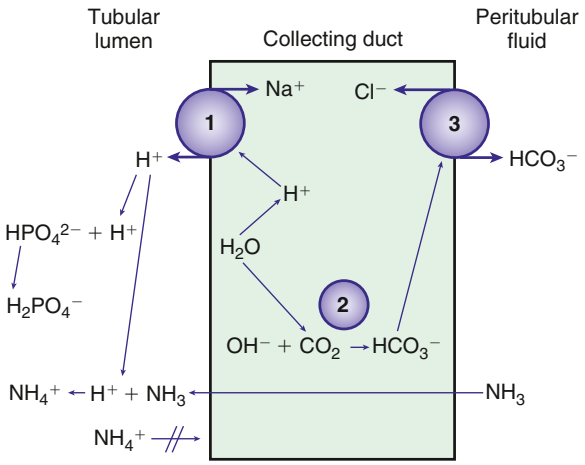

Fig. 73.9 Secretion of hydrogen ions in the collecting duct. The dissociation of water generates an OH^- ion and an H^+ ion. The H^+-ATPase *(1)* secretes hydrogen ions into the tubular lumen. Bicarbonate is formed when an OH^- ion combines with CO_2 in a reaction mediated by carbonic anhydrase *(2)*. Bicarbonate ions cross the basolateral membrane and enter the blood via the HCO_3^-/Cl^- exchanger *(3)*. The hydrogen ions in the tubular lumen are buffered by phosphate and ammonia (NH_3). NH_3 can diffuse from the peritubular fluid into the tubular lumen, but ammonium (NH_4^+) cannot pass through the cells of the collecting duct.

$$\text{Glutamate}^- \rightarrow NH_4^+ + \alpha - \text{ketoglutarate}^{3-}$$

The metabolism of glutamine generates two ammonium ions. In addition, the metabolism of α-ketoglutarate generates two bicarbonate molecules. The ammonium ions are secreted into the lumen of the proximal tubule, whereas the bicarbonate molecules exit the proximal tubule cells via the basolateral $Na^+,3HCO_3^-$ co-transporter (see Fig. 73.8). This arrangement would seem to accomplish the goal of excreting H^+ (as NH_4^+) and regenerating bicarbonate molecules. However, the ammonium ions secreted in the proximal tubule do not remain within the tubular lumen. Cells of the TAL of the loop of Henle resorb the ammonium ions. The result is that there is a high medullary interstitial concentration of ammonia, but the tubular fluid entering the collecting duct does not have significant amounts of ammonium ions. Moreover, the hydrogen ions that were secreted with ammonia (as ammonium ions) in the proximal tubule enter the bloodstream, canceling the effect of the bicarbonate generated in the proximal tubule. The excretion of ammonium ions, and thus of hydrogen ions, depends on the cells of the collecting duct.

The cells of the collecting duct secrete H^+ and regenerate bicarbonate, which is returned to the bloodstream (Fig. 73.9). This bicarbonate neutralizes endogenous acid production. Phosphate and ammonia buffer the H^+ secreted by the collecting duct. Ammonia is an effective buffer because of the high concentrations in the medullary interstitium and because the cells of the collecting duct are permeable to ammonia but not to ammonium. As ammonia diffuses into the lumen of the collecting duct, the low urine pH causes almost all the ammonia to be converted into ammonium. This process maintains a low luminal ammonia concentration. Because the luminal pH is lower than the pH in the medullary interstitium, there is a higher concentration of ammonia within the medullary interstitium than in the tubular lumen, favoring movement of ammonia into the tubular lumen. Even though the concentration of ammonium in the tubular lumen is higher than in the interstitium, the cells of the collecting duct are impermeable to ammonium, preventing back-diffusion of ammonium out of the tubular lumen and permitting ammonia to be an effective buffer.

The kidneys adjust H^+ excretion according to physiologic needs. There is variation in endogenous acid production, largely a result of diet and pathophysiologic stresses, such as diarrheal losses of bicarbonate, which increase the need for acid excretion. H^+ excretion is increased by upregulation of H^+ secretion in the collecting duct, causing the pH of the urine to decrease. This response is prompt, occurring within hours of an acid load, but it is limited by the buffering capacity of the urine; the hydrogen pumps in the collecting duct cannot lower the pH to <4.5. A more significant increase in acid excretion requires upregulation of ammonia production by the proximal tubule so that more ammonia is available to serve as a buffer in the tubular lumen of the collecting duct. This response to a low serum pH reaches its maximum within 5-6 days; ammonia excretion can increase approximately 10-fold over the baseline value.

Acid excretion by the collecting duct increases in a number of different clinical situations. The extracellular pH is the most important regulator of renal acid excretion. A decrease in the extracellular pH from either a respiratory or a metabolic acidosis causes an increase in renal acid excretion. Aldosterone stimulates H^+ excretion in the collecting duct, causing an increase in the serum bicarbonate concentration. This explains the metabolic alkalosis that occurs with primary hyperaldosteronism or secondary hyperaldosteronism caused by volume depletion. Hypokalemia increases acid secretion, by both stimulating ammonia production in the proximal tubule and increasing H^+ secretion in the collecting duct. Hypokalemia therefore tends to produce a metabolic alkalosis. Hyperkalemia has the opposite effects, which may cause a metabolic acidosis.

In patients with an increased pH, the kidney has two principal mechanisms for correcting the problem. First, less bicarbonate is resorbed in the proximal tubule, leading to an increase in urinary bicarbonate losses. Second, in a limited number of specialized cells, the process for

secretion of H^+ by the collecting duct can be reversed (see Fig. 73.9), leading to secretion of bicarbonate into the tubular lumen and secretion of hydrogen ions into the peritubular fluid, where they enter the bloodstream.

CLINICAL ASSESSMENT OF ACID-BASE DISORDERS

The following rearrangement of the Henderson-Hasselbalch equation emphasizes the relationship among P_{CO_2}, bicarbonate concentration, and hydrogen ion concentration:

$$[H^+] = 24 \times PCO_2 [HCO_3^-]$$

An increase in the P_{CO_2} or a decrease in $[HCO_3^-]$ increases $[H^+]$; the pH decreases. A decrease in the P_{CO_2} or an increase in $[HCO_3^-]$ decreases $[H^+]$; the pH increases.

Terminology

Acidemia is a pH below normal (<7.35), and **alkalemia** is a pH above normal (>7.45). An **acidosis** is a pathologic process that causes an increase in $[H^+]$, and an **alkalosis** is a pathologic process that causes a decrease in $[H^+]$. Whereas acidemia is always accompanied by an acidosis, a patient can have an acidosis and a low, normal, or high pH. For example, a patient may have a mild metabolic acidosis but a simultaneous, severe respiratory alkalosis; the net result may be alkalemia. Acidemia and alkalemia indicate the pH abnormality; acidosis and alkalosis indicate the pathologic process that is taking place.

A **simple acid-base disorder** is a single primary disturbance. During a simple metabolic disorder, there is respiratory compensation. With a metabolic acidosis, the decrease in the pH increases the ventilatory drive, causing a decrease in P_{CO_2}. The decrease in the $[CO_2]$ leads to an increase in the pH. This appropriate respiratory compensation is expected with a primary metabolic acidosis. Despite the decrease in $[CO_2]$, appropriate respiratory compensation is not a respiratory alkalosis, even though it is sometimes erroneously called a "compensatory" respiratory alkalosis. A low P_{CO_2} can result either from a primary respiratory alkalosis or from appropriate respiratory compensation for a metabolic acidosis. Appropriate respiratory compensation also occurs with a primary metabolic alkalosis, although in this case $[CO_2]$ increases to attenuate the increase in the pH. The respiratory compensation for a metabolic process happens quickly and is complete within 12-24 hours; it cannot overcompensate for or normalize the pH.

During a primary respiratory process, there is metabolic compensation, mediated by the kidneys. The kidneys respond to a respiratory acidosis by increasing H^+ excretion, thereby increasing bicarbonate generation and raising the serum $[HCO_3^-]$. The kidneys increase bicarbonate excretion to compensate for a respiratory alkalosis; $[HCO_3^-]$ decreases. Unlike respiratory compensation, which occurs rapidly, it takes 3-4 days for the kidneys to complete appropriate metabolic compensation. There is, however, a small and rapid compensatory change in $[HCO_3^-]$ during a primary respiratory process. The expected appropriate metabolic compensation for a respiratory disorder depends on whether the process is acute or chronic.

A **mixed acid-base disorder** is present when there is more than one primary acid-base disturbance. An infant with bronchopulmonary dysplasia may have a respiratory acidosis from chronic lung disease and a metabolic alkalosis from the furosemide used to treat the chronic lung disease. More dramatically, a child with pneumonia and sepsis may have severe acidemia because of a combined metabolic acidosis caused by lactic acid and respiratory acidosis caused by ventilatory failure.

There are formulas for calculating the appropriate metabolic or respiratory compensation for the six primary simple acid-base disorders (Table 73.11). The appropriate compensation is expected in a simple disorder; it is not optional. If a patient does not have the appropriate compensation, a mixed acid-base disorder is present. For example, if a patient has a primary metabolic acidosis with a serum $[HCO_3^-]$ of 10 mEq/L, the expected respiratory compensation is $[CO_2]$ of 23 mm Hg ± 2 ($1.5 \times 10 + 8 \pm 2 = 23 \pm 2$; see Table 73.11). If the patient's $[CO_2]$ is >25 mm Hg, a concurrent respiratory acidosis is present; $[CO_2]$ is higher than expected. A patient may have a respiratory acidosis despite a CO_2 level below the "normal" value of 35-45 mm Hg. In this example, $[CO_2]$ <21 mm Hg indicates a concurrent respiratory alkalosis; $[CO_2]$ is lower than exp ected.

Table 73.11 Appropriate Compensation During Simple Acid-Base Disorders

DISORDER	EXPECTED COMPENSATION
Metabolic acidosis	$P_{CO_2} = 1.5 \times [HCO_3^-] + 8 \pm 2$
Metabolic alkalosis	P_{CO_2} increases by 7 mm Hg for each 10 mEq/L increase in serum $[HCO_3^-]$
Respiratory Acidosis	
Acute	$[HCO_3^-]$ increases by 1 for each 10 mm Hg increase in P_{CO_2}
Chronic	$[HCO_3^-]$ increases by 3.5 for each 10 mm Hg increase in P_{CO_2}
Respiratory Alkalosis	
Acute	$[HCO_3^-]$ falls by 2 for each 10 mm Hg decrease in P_{CO_2}
Chronic	$[HCO_3^-]$ falls by 4 for each 10 mm Hg decrease in P_{CO_2}

Table 73.12 Normal Values of Arterial Blood Gases

pH	7.35-7.45
$[HCO_3^-]$	20-28 mEq/L
P_{CO_2}	35-45 mm Hg

Diagnosis

A systematic evaluation of an arterial blood gas (ABG) sample, combined with the clinical history, can usually explain the patient's acid-base disturbance. Assessment of an ABG sample requires knowledge of normal values (Table 73.12). In most cases, this is accomplished through a three-step process (Fig. 73.10):

1. Determine whether acidemia or alkalemia is present.
2. Determine a cause of the acidemia or alkalemia.
3. Determine whether a mixed disorder is present.

Most patients with an acid-base disturbance have an abnormal pH, although there are two exceptions. One exception is in the patient with a mixed disorder in which the two processes have opposite effects on pH (a metabolic acidosis and a respiratory alkalosis) and cause changes in $[H^+]$ that are comparable in magnitude, although opposite. The other exception is in the patient with a simple chronic respiratory alkalosis; in some cases, the appropriate metabolic compensation is enough to normalize the pH. In both situations, the presence of an acid-base disturbance is deduced because of the abnormal CO_2 and bicarbonate levels. Determining the acid-base disturbance in these patients requires proceeding to the third step of the process.

The second step requires inspection of the serum $[HCO_3^-]$ and P_{CO_2} to determine a cause of the abnormal pH (see Fig. 73.10). In most cases, there is only one obvious explanation for the abnormal pH. In some mixed disorders, however, there may be two possibilities (e.g., a high P_{CO_2} and a low $[HCO_3^-]$ in a patient with acidemia). In such cases, the patient has two causes for abnormal pH—a metabolic acidosis and a respiratory acidosis, in this instance—and it is unnecessary to proceed to the third step.

The third step requires determining whether the patient's compensation is appropriate. It is assumed that the primary disorder was

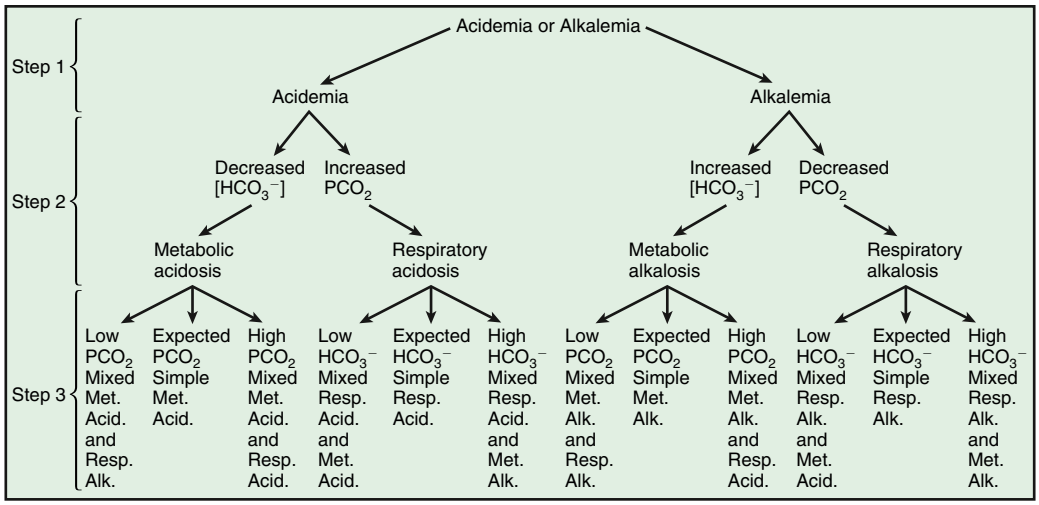

Fig. 73.10 Three-step process for interpreting acid-base disturbances. In step 1, determine whether the pH is low (acidemia) or high (alkalemia). In step 2, establish an explanation for the acidemia or alkalemia. In step 3, calculate the expected compensation (see Table 73.11) and determine whether a mixed disturbance is present. Met. Acid., metabolic acidosis; Met. Alk., metabolic alkalosis; Resp. Acid., respiratory acidosis; Resp. Alk., respiratory alkalosis.

diagnosed in the second step, and the expected compensation is calculated (see Table 73.11). If the compensation is appropriate, a simple acid-base disorder is present. If the compensation is not appropriate, a mixed disorder is present. The identity of the second disorder is determined by deciding whether the compensation is too little or too much compared with what was expected (see Fig. 73.10).

The history is always useful in evaluating and diagnosing patients with acid-base disturbances. It is especially helpful in a respiratory process. The expected metabolic compensation for a respiratory process changes according to whether the process is **acute** or **chronic**, which can be deduced only from the history. The metabolic compensation for an acute respiratory acidosis is less than that for a chronic respiratory acidosis. In a patient with a respiratory acidosis, a small increase in $[HCO_3^-]$ would be consistent with a simple acute respiratory acidosis or a mixed disorder (a chronic respiratory acidosis and a metabolic acidosis). Only the history can differentiate among the possibilities. Knowledge of the length of the respiratory process and the presence or absence of a risk factor for a metabolic acidosis (diarrhea) allows the correct conclusion to be reached.

An alternative to the **physiologic** approach just described (which includes calculation of the anion gap; see later) is the **physiochemical** approach, often called the **Stewart method**. Some view this approach as superior to the physiologic approach, but it requires multiple calculations and additional laboratory values and is thus more challenging to use in the clinical setting. The physiochemical approach requires measurement of the blood pH and P_{CO_2} and calculation of the apparent strong ion difference (SIDa), the effective strong ion difference (SIDe), the strong ion gap (SIG), and the total concentration of weak acids (A_{TOT}).

METABOLIC ACIDOSIS

Metabolic acidosis occurs frequently in hospitalized children; diarrhea is the most common etiology. For a patient with an unknown medical problem, the presence of a metabolic acidosis is often helpful diagnostically, because it suggests a relatively narrow differential diagnosis.

Patients with a metabolic acidosis have a low serum $[HCO_3^-]$, although not every patient with a low serum $[HCO_3^-]$ has a metabolic acidosis. The exception is the patient with a respiratory alkalosis, which causes a decrease in the serum $[HCO_3^-]$ as part of appropriate renal compensation. In a patient with an isolated metabolic acidosis, there is a predictable decrease in the blood $[CO_2]$, as follows:

$$PCO_2 = 1.5 \times [HCO_3^-] + 8 \pm 2$$

A mixed acid-base disturbance is present if the respiratory compensation is not appropriate. If the P_{CO_2} is greater than predicted, the patient has a concurrent respiratory acidosis. A lower P_{CO_2} than predicted indicates a concurrent respiratory alkalosis or, less frequently, an isolated respiratory alkalosis. Because the appropriate respiratory compensation for a metabolic acidosis never normalizes the patient's pH, the presence of a normal pH and a low $[HCO_3^-]$ occurs only if some degree of respiratory alkalosis is present. In this situation, distinguishing an isolated chronic respiratory alkalosis from a mixed metabolic acidosis and acute respiratory alkalosis may be possible only clinically. In contrast, the combination of a low serum pH and a low $[HCO_3^-]$ occurs only if a metabolic acidosis is present.

Etiology and Pathophysiology

There are many causes of a metabolic acidosis (Table 73.13), resulting from three basic mechanisms:

1. Loss of bicarbonate from the body
2. Impaired ability to excrete acid by the kidney
3. Addition of acid to the body (exogenous or endogenous)

Diarrhea, the most common cause of metabolic acidosis in children, causes a loss of bicarbonate from the body. The amount of bicarbonate lost in the stool depends on the volume of diarrhea and $[HCO_3^-]$ of the stool, which tends to increase with more severe diarrhea. The kidneys attempt to balance the losses by increasing acid secretion, but metabolic acidosis occurs when this compensation is inadequate. Diarrhea often causes volume depletion because of losses of sodium and water, potentially exacerbating the acidosis by causing shock and a lactic acidosis. In addition, diarrheal losses of potassium lead to hypokalemia. Moreover, the volume depletion causes increased production of aldosterone. This increase stimulates renal retention of sodium, helping to maintain intravascular volume, but also leads to increased urinary losses of potassium, exacerbating the hypokalemia.

There are four forms of renal tubular acidosis (RTA): distal (type I), proximal (type II), mixed (type III), and hyperkalemic (type IV) (see Chapter 569). In **distal** RTA, children may have accompanying hypokalemia, hypercalciuria, nephrolithiasis, and nephrocalcinosis. Failure

Table 73.13 Causes of Metabolic Acidosis

NORMAL ANION GAP
Diarrhea
RTA
Distal (type I) RTA (OMIM 179800/602722/267300/611590)*
Proximal (type II) RTA (OMIM 604278)†
Mixed (type III) RTA (OMIM 259730)
Hyperkalemic (type IV) RTA (OMIM 201910/264350/177735/145260)‡
Urinary tract diversions
Posthypocapnia
Ammonium chloride intake
INCREASED ANION GAP
Lactic Acidosis
Tissue hypoxia
Shock
Hypoxemia
Severe anemia
Liver failure
Malignancy
Intestinal bacterial overgrowth
Inborn errors of metabolism
Medications
Nucleoside reverse transcriptase inhibitors
Metformin
Propofol
Linezolid
Ketoacidosis
Diabetic ketoacidosis
Starvation ketoacidosis
Alcoholic ketoacidosis
Kidney Failure
Poisoning
Ethylene glycol
Methanol
Salicylate
Toluene
Paraldehyde

*Along with these genetic disorders, distal RTA may be secondary to renal disease or medications.
†Most cases of proximal RTA are not caused by this primary genetic disorder. Proximal RTA is usually part of Fanconi syndrome, which has multiple etiologies.
‡Hyperkalemic RTA can be secondary to a genetic disorder (some of the more common are listed) or other etiologies.
OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim); RTA, renal tubular acidosis.

to thrive because of chronic metabolic acidosis is the most common presenting complaint. Patients with distal RTA cannot acidify their urine and thus have a urine pH >5.5 despite a metabolic acidosis.

Proximal RTA is rarely present in isolation. In most patients, proximal RTA is part of **Fanconi syndrome**, a generalized dysfunction of the proximal tubule. The dysfunction leads to glycosuria, aminoaciduria, and excessive urinary losses of phosphate and uric acid. The presence of a low serum uric acid level, glycosuria, and aminoaciduria is helpful diagnostically. Chronic hypophosphatemia leads to rickets in children (see Chapter 69). Rickets and/or failure to thrive may be the presenting complaint. The ability to acidify the urine is intact in proximal RTA; thus untreated patients have a urine pH <5.5. However, bicarbonate therapy increases bicarbonate losses in the urine, and the urine pH increases. A mixed RTA (combined distal and proximal) occurs in patients with autosomal recessive osteopetrosis caused by pathologic variants in the gene for carbonic anhydrase II.

In **hyperkalemic** RTA, renal excretion of acid and potassium is impaired. Hyperkalemic RTA is the result of hyperkalemia, absence of aldosterone, or inability of the kidney to respond to aldosterone. In severe **aldosterone deficiency**, as occurs with congenital adrenal hyperplasia because of 21α-hydroxylase deficiency, the hyperkalemia and metabolic acidosis are accompanied by hyponatremia and volume depletion from renal salt wasting. Incomplete aldosterone deficiency causes less severe electrolyte disturbances; children may have isolated hyperkalemic RTA, hyperkalemia without acidosis, or isolated hyponatremia. Patients may have aldosterone deficiency caused by decreased renin production by the kidney; renin normally stimulates aldosterone synthesis. Children with hyporeninemic hypoaldosteronism usually have either isolated hyperkalemia or hyperkalemic RTA. The manifestations of aldosterone resistance depend on the severity of the resistance. In the autosomal recessive form of **pseudohypoaldosteronism** type I, which is the result of an absence of the sodium channel that normally responds to aldosterone, there is often severe salt wasting and hyponatremia. In contrast, the aldosterone resistance in kidney transplant recipients usually produces either isolated hyperkalemia or hyperkalemic RTA; hyponatremia is unusual. Similarly, the medications that cause hyperkalemic RTA do not cause hyponatremia. Pseudohypoaldosteronism type II, an autosomal dominant disorder also known as **Gordon syndrome**, is a unique cause of hyperkalemic RTA because the genetic defect causes volume expansion and hypertension.

Children with abnormal urinary tracts, usually secondary to congenital malformations, may require diversion of urine through intestinal segments. Ureterosigmoidostomy, anastomosis of a ureter to the sigmoid colon, almost always produces a metabolic acidosis and hypokalemia. Consequently, ileal conduits are the more commonly used procedure, although there is still a risk of a metabolic acidosis.

The appropriate metabolic compensation for a chronic respiratory alkalosis is a decrease in renal acid excretion. The resultant decrease in the serum [HCO_3^-] lessens the alkalemia caused by the respiratory alkalosis. If the respiratory alkalosis resolves quickly, the patient continues to have a decreased serum [HCO_3^-], causing acidemia as the result of a metabolic acidosis. This resolves over 1-2 days through increased acid excretion by the kidneys.

Lactic acidosis (L-lactic) typically occurs when inadequate oxygen delivery to the tissues leads to anaerobic metabolism and excess production of lactic acid. Lactic acidosis may be secondary to shock, severe anemia, or hypoxemia. When the underlying cause of the lactic acidosis is alleviated, the liver is able to metabolize the accumulated lactate into bicarbonate, correcting the metabolic acidosis. There is normally some tissue production of lactate metabolized by the liver. In children with severe liver dysfunction, impairment of lactate metabolism may produce a lactic acidosis. Rarely, a metabolically active malignancy grows so fast that its blood supply becomes inadequate, with resultant anaerobic metabolism and lactic acidosis. Patients who have **short bowel syndrome** resulting from small bowel resection can have bacterial overgrowth. In these patients, excessive intestinal bacterial metabolism of glucose into *D-lactic acid* can cause a lactic acidosis. Lactic acidosis occurs in a variety of **inborn errors of metabolism**, especially those affecting mitochondrial oxidation (see Chapters 107.4 and 108). **Medications** also can cause lactic acidosis. Nucleoside reverse transcriptase inhibitors that are used to treat HIV infection inhibit mitochondrial replication; lactic acidosis is a rare complication, although elevated serum lactate concentrations without acidosis are quite common. Metformin, used to treat type 2 diabetes mellitus, is most likely to cause a lactic acidosis in patients with chronic kidney disease. High dosages and prolonged use of propofol can cause lactic acidosis. Propylene glycol is a diluent in a variety of oral and IV medications; excessive intake causes a lactic acidosis, principally from accumulation of D-lactic acid. Linezolid is another medication that may cause a lactic acidosis

In **insulin-dependent diabetes mellitus**, inadequate insulin leads to hyperglycemia and DKA (see Chapter 629). Production of acetoacetic acid and β-hydroxybutyric acid causes the metabolic acidosis. Administration of insulin corrects the underlying metabolic problem and permits conversion of acetoacetate and β-hydroxybutyrate into bicarbonate, which helps correct the metabolic acidosis. However, in some patients, urinary losses of acetoacetate and β-hydroxybutyrate may be substantial, preventing rapid regeneration of bicarbonate. In these patients, full correction of the metabolic acidosis requires renal regeneration of bicarbonate, a slower process. The hyperglycemia causes an osmotic diuresis, usually producing volume depletion, along with substantial losses of potassium, sodium, and phosphate.

In **starvation ketoacidosis** the lack of glucose leads to ketoacid production, which in turn can produce a metabolic acidosis, although it is usually mild as a result of increased acid secretion by the kidney. In **alcoholic ketoacidosis**, which is much less common in children than in adults, the acidosis usually follows a combination of an alcoholic binge with vomiting and poor intake of food. The acidosis is potentially more severe than with isolated starvation, and the blood glucose level may be low, normal, or high. Hypoglycemia and acidosis also suggest an inborn error of metabolism.

Kidney failure causes a metabolic acidosis because of the need for the kidneys to excrete the acid produced by normal metabolism. With mild or moderate chronic kidney disease, the remaining nephrons are usually able to compensate by increasing acid excretion. When the GFR is <20–30% of normal, the compensation is inadequate, and a metabolic acidosis develops. In some children, especially those with chronic kidney disease because of tubular damage, the acidosis develops at a higher GFR because of a concurrent defect in acid secretion by the distal tubule (distal RTA).

A variety of **toxic ingestions** can cause a metabolic acidosis (see Chapter 94). **Salicylate** intoxication is now much less common because aspirin is no longer recommended for fever control in children. Acute salicylate intoxication occurs after a large overdose. Chronic salicylate intoxication is possible with gradual buildup of the drug. Especially in adults, respiratory alkalosis may be the dominant acid-base disturbance. In children, the metabolic acidosis is usually the more significant finding. Other symptoms of salicylate intoxication are fever, seizures, lethargy, and coma. Hyperventilation may be particularly marked. Tinnitus, vertigo, and hearing impairment are more likely with chronic salicylate intoxication.

Ethylene glycol, a component of antifreeze, is converted in the liver to glyoxylic and oxalic acids, causing a severe metabolic acidosis. Excessive oxalate excretion causes calcium oxalate crystals to appear in the urine, and calcium oxalate precipitation in the kidney tubules can cause kidney failure. The toxicity of **methanol** ingestion also depends on liver metabolism; formic acid is the toxic end product that causes the metabolic acidosis and other sequelae, which include damage to the optic nerve and CNS. Symptoms may include nausea, emesis, visual impairment, and altered mental status. **Toluene** inhalation and **paraldehyde** ingestion are other potential causes of a metabolic acidosis.

Many **inborn errors of metabolism** cause a metabolic acidosis (see Chapters 104-107). The metabolic acidosis may be the result of excessive production of ketoacids, lactic acid, and other organic anions. Some patients have accompanying hypoglycemia or hyperammonemia. In most patients, the acidosis occurs episodically during acute decompensations, which may be precipitated by ingestion of specific dietary substrates, the stress of a mild illness, or poor compliance with dietary or medical therapy. In a few inborn errors of metabolism, patients have a chronic metabolic acidosis.

Clinical Manifestations

The underlying disorder usually produces most of the signs and symptoms in children with a mild or moderate metabolic acidosis. The clinical manifestations of the acidosis are related to the degree of acidemia; patients with appropriate respiratory compensation and less severe acidemia have fewer manifestations than those with a concomitant respiratory acidosis. At a serum pH <7.2, there may be impaired cardiac contractility and an increased risk of arrhythmias, especially if underlying heart disease or other predisposing electrolyte disorders are present. With acidemia, there may be a decrease in the cardiovascular response to catecholamines, potentially exacerbating hypotension in children with volume depletion or shock. Acidemia causes vasoconstriction of the pulmonary vasculature, which is especially problematic in newborn infants with **persistent pulmonary hypertension** (see Chapter 130).

The normal respiratory response to metabolic acidosis—compensatory hyperventilation— may be subtle with mild metabolic acidosis, but it causes discernible increased respiratory effort with worsening acidemia. The acute metabolic effects of acidemia include insulin resistance, increased protein degradation, and reduced ATP synthesis. Chronic metabolic acidosis causes failure to thrive in children. Acidemia causes potassium to move from the ICS to the ECS, thereby increasing the serum [K^+]. Severe acidemia impairs brain metabolism, eventually resulting in lethargy and coma.

Diagnosis

The etiology of a metabolic acidosis is often apparent from the history and physical examination. Acutely, diarrhea and shock are common causes of a metabolic acidosis. Shock, which causes a lactic acidosis, is usually apparent on physical examination and can be secondary to dehydration, acute blood loss, sepsis, or heart disease. Failure to thrive suggests a chronic metabolic acidosis, as with renal insufficiency or RTA. New onset of polyuria occurs in children with undiagnosed diabetes mellitus and DKA. Metabolic acidosis with seizures and/or a depressed sensorium, especially in an infant, warrants consideration of an inborn error of metabolism. Meningitis and sepsis with lactic acidosis are more common explanations for metabolic acidosis with neurologic signs and symptoms. Identification of a toxic ingestion (e.g., ethylene glycol, methanol) is especially important because of the potentially excellent response to specific therapy. A variety of medications can cause a metabolic acidosis, whether prescribed or accidentally ingested. Hepatomegaly and metabolic acidosis may occur in children with sepsis, congenital or acquired heart disease, hepatic failure, or inborn errors of metabolism.

Basic laboratory tests in a child with a metabolic acidosis should include measurements of BUN, serum creatinine, serum glucose, urinalysis, and serum electrolytes. Metabolic acidosis, hyperglycemia, glycosuria, and ketonuria support a diagnosis of DKA. Starvation causes ketosis, but the metabolic acidosis, if present, is usually mild (HCO_3^- >18 mEq/L). Most children with ketosis from poor intake and metabolic acidosis have a concomitant disorder, such as gastroenteritis with diarrhea, that explains the metabolic acidosis. Alternatively, metabolic acidosis with or without ketosis occurs in inborn errors of metabolism; patients with these disorders may have hyperglycemia, normoglycemia, or hypoglycemia. Adrenal insufficiency may cause metabolic acidosis and hypoglycemia. Metabolic acidosis with hypoglycemia also occurs with liver failure. Metabolic acidosis, normoglycemia, and glycosuria occur in children when type II RTA is part of Fanconi syndrome; the defect in resorption of glucose by the proximal tubule of the kidney causes the glycosuria.

The serum [K^+] is often abnormal in children with a metabolic acidosis. Even though a metabolic acidosis causes potassium to move from the ICS to the ECS, many patients with a metabolic acidosis have a low serum [K^+] because of excessive body losses of K^+. With diarrhea, there are high stool losses of K^+ and, often, secondary renal losses of K^+, whereas in type I or type II RTA, there are increased urinary losses of K^+. In DKA, urinary losses of K^+ are high, but the shift of K^+ out of cells because of a lack of insulin and metabolic acidosis is especially significant. Consequently, the initial serum [K^+] can be low, normal, or high, even though total body K^+ is almost always decreased. The serum [K^+] is usually increased in patients with acidosis caused

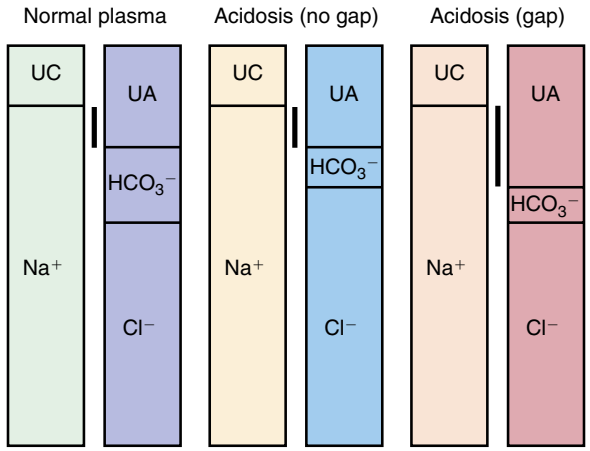

Fig. 73.11 Anion gap. The anion gap is the difference between the sodium concentration and the combined concentrations of chloride and bicarbonate *(vertical black bars)*. In both a gap and a nongap metabolic acidosis, there is a decrease in the bicarbonate concentration. There is an increase in unmeasured anions (UA) in patients with a gap metabolic acidosis. In a nongap metabolic acidosis, there is an increase in the serum chloride concentration. UC, Unmeasured cations.

by renal insufficiency; urinary K^+ excretion is impaired. The combination of metabolic acidosis, hyperkalemia, and hyponatremia occurs in patients with severe aldosterone deficiency (adrenogenital syndrome) or aldosterone resistance. Patients with less severe, type IV RTA often have only hyperkalemia and metabolic acidosis. Very ill children with metabolic acidosis may have an elevated serum K^+ because of a combination of renal insufficiency, tissue breakdown, and a shift of K^+ from the ICS to the ECS secondary to the metabolic acidosis.

The **plasma anion gap** is useful for evaluating patients with a metabolic acidosis. It divides patients into two diagnostic groups, those with normal anion gap and those with increased anion gap. The following formula determines the anion gap:

$$\text{Anion gap} = [Na^+] - ([Cl^-] + [HCO_3^-])$$

A normal anion gap is 4-11, although there is variation among laboratories. Approximately 11 mEq of the anion gap is normally secondary to albumin. A 1 g/dL decrease in the albumin concentration decreases the anion gap by approximately 2.5 mEq/L. Thus, if the albumin is not close to 4 g/dL, the anion gap should be corrected for the albumin concentration:

$$\text{Anion gap (corrected for albumin)} = [Na^+] - ([Cl^-] + [HCO_3^-]) + [2.5 \times (4 - \text{observed albumin})]$$

The number of serum anions must equal the number of serum cations to maintain electrical neutrality (Fig. 73.11). The anion gap is the difference between the measured cation (Na^+) and the measured anions (Cl^- + bicarbonate). The anion gap is also the difference between the unmeasured cations (K^+, magnesium, calcium) and the unmeasured anions (albumin, phosphate, urate, sulfate). An increased anion gap occurs when there is an increase in unmeasured anions. With a lactic acidosis, there is endogenous production of lactic acid, which is composed of positively charged hydrogen ions and negatively charged lactate anions. The hydrogen ions are largely buffered by serum bicarbonate, resulting in a decrease in $[HCO_3^-]$. The hydrogen ions that are not buffered by bicarbonate cause the serum pH to decrease. The lactate anions remain, causing the increase in the anion gap.

An increase in unmeasured anions, along with H^+ generation, is present in all causes of an increased gap metabolic acidosis (see Table 73.13). In DKA, the ketoacids β-hydroxybutyrate and acetoacetate are the unmeasured anions. In kidney failure there is retention of unmeasured anions, including phosphate, urate, and sulfate. The increase in unmeasured anions in kidney failure is usually less than the decrease in $[HCO_3^-]$. Kidney failure is thus a mix of an increased-gap and a normal-gap metabolic acidosis. The normal-gap metabolic acidosis is especially prominent in children with kidney failure because of tubular damage, as occurs with renal dysplasia or obstructive uropathy, because these patients have a concurrent RTA. The unmeasured anions in toxic ingestions vary: formate in methanol intoxication, glycolate in ethylene glycol intoxication, and lactate and ketoacids in salicylate intoxication. In inborn errors of metabolism, the unmeasured anions depend on the specific etiology and may include ketoacids, lactate, and other organic anions. In a few inborn errors of metabolism, the acidosis occurs without generation of unmeasured anions; thus the anion gap is normal.

A **normal–anion gap metabolic acidosis** occurs when there is a decrease in $[HCO_3^-]$ without an increase in the unmeasured anions. With diarrhea, there is a loss of bicarbonate in the stool, causing a decrease in the serum pH and $[HCO_3^-]$; the serum $[Cl^-]$ increases to maintain electrical neutrality (see Fig. 73.11). **Hyperchloremic metabolic acidosis** is an alternative term for a normal–anion gap metabolic acidosis. Calculation of the anion gap is more precise than using $[Cl^-]$ to differentiate between a normal-gap and an increased-gap metabolic acidosis, in that the anion gap directly determines the presence of unmeasured anions. Electrical neutrality dictates that the $[Cl^-]$ increases or decreases according to the serum $[Na^+]$, making $[Cl^-]$ a less reliable predictor of unmeasured anions than the more direct measure, calculation of the anion gap.

An increase in unmeasured cations, such as calcium, potassium, and magnesium, decreases the anion gap. Conversely, a decrease in unmeasured cations is a very unusual cause of an increased anion gap. Because of these variables, the broad range of a normal anion gap, and other variables, the presence of a normal or an increased anion gap is not always reliable in differentiating among the causes of a metabolic acidosis, especially when the metabolic acidosis is mild. In some patients, there is more than one explanation for the metabolic acidosis, such as the child with diarrhea and lactic acidosis as a result of poor perfusion. The anion gap should not be interpreted in dogmatic isolation; consideration of other laboratory abnormalities and the clinical history improves its diagnostic utility.

Treatment

The most effective therapeutic approach for patients with a metabolic acidosis is repair of the underlying disorder, if possible. The administration of insulin in DKA and the restoration of adequate perfusion with IV fluids in lactic acidosis because of hypovolemia or shock eventually result in normalization of the acid-base balance. In other diseases, the use of bicarbonate therapy is indicated because the underlying disorder is irreparable. Children with metabolic acidosis caused by RTA or chronic kidney disease require long-term base therapy. Patients with acute kidney injury and metabolic acidosis may need base therapy until their kidneys' ability to excrete hydrogen normalizes. In other disorders the cause of the metabolic acidosis eventually resolves, but base therapy may be necessary during the acute illness. In salicylate poisoning, alkali administration increases renal clearance of salicylate and decreases the amount of salicylate in brain cells. Short-term base therapy is often necessary in other poisonings (ethylene glycol, methanol) and inborn errors of metabolism (pyruvate carboxylase deficiency, propionic acidemia). Some inborn errors of metabolism require long-term base therapy.

The use of base therapy in DKA with lactic acidosis is controversial; *there is little evidence that it improves patient outcome, and it has a variety of potential side effects.* The risks of giving sodium bicarbonate

include the possibility of causing hypernatremia or volume overload. Furthermore, the patient may have overcorrection of the metabolic acidosis once the underlying disorder resolves, because metabolism of lactate or ketoacids generates bicarbonate. The rapid change from acidemia to alkalemia can cause a variety of problems, including hypokalemia and hypophosphatemia. Bicarbonate therapy increases the generation of CO_2, which can accumulate in patients with respiratory failure. Because CO_2 readily diffuses into cells, the administration of bicarbonate can lower the intracellular pH, potentially worsening cell function. Base therapy is usually reserved for children with severe acute lactic acidosis and severe DKA.

Oral base therapy is given to children with chronic metabolic acidosis. Sodium bicarbonate tablets are available for older children. Younger children generally take citrate solutions; the liver generates bicarbonate from citrate. Citrate solutions are available as sodium citrate, potassium citrate, and a 1:1 mix of sodium citrate and potassium citrate. The patient's potassium needs dictate the choice. Children with type I or type II RTA may have hypokalemia and benefit from potassium supplements, but most children with chronic kidney failure cannot tolerate additional potassium.

Oral or IV base can be used in acute metabolic acidosis; IV therapy is generally used when a rapid response is necessary. Sodium bicarbonate may be given as a bolus, usually at a dose of 1 mEq/kg, in an emergency situation. Another approach is to add sodium bicarbonate or sodium acetate to the patient's IV fluids, remembering to remove an equal amount of sodium chloride from the solution to avoid giving an excessive sodium load. Careful monitoring is mandatory so that the dose of base can be titrated appropriately. Tris(hydroxymethyl) aminomethane (**tromethamine, THAM**) is an option in patients with a metabolic acidosis and a respiratory acidosis, because it neutralizes acids without releasing CO_2. THAM also diffuses into cells and therefore provides intracellular buffering.

Hemodialysis is another option for correcting a metabolic acidosis, and it is an appropriate choice in patients with renal insufficiency, especially if significant uremia or hyperkalemia is also present. Hemodialysis is advantageous for correcting the metabolic acidosis caused by methanol or ethylene glycol intoxication, because hemodialysis efficiently removes the offending toxin. In addition, these patients often have a severe metabolic acidosis that does not respond easily to IV bicarbonate therapy. Peritoneal dialysis is another option for correcting the metabolic acidosis due to chronic kidney disease.

Many causes of metabolic acidosis require specific therapy. Administration of a glucocorticoid and a mineralocorticoid is necessary in patients with adrenal insufficiency. Patients with DKA require insulin therapy, whereas patients with lactic acidosis respond to measures that alleviate tissue hypoxia. Along with correction of acidosis, patients with methanol or ethylene glycol ingestion should receive an agent that prevents the breakdown of the toxic substance to its toxic metabolites. Fomepizole has supplanted ethanol as the treatment of choice. These agents work by inhibiting alcohol dehydrogenase, the enzyme that performs the first step in the metabolism of ethylene glycol or methanol. There are a variety of disease-specific therapies for patients with a metabolic acidosis resulting from an inborn error of metabolism.

METABOLIC ALKALOSIS

Metabolic alkalosis in children is most often secondary to emesis or diuretic use. The serum bicarbonate concentration is increased with a metabolic alkalosis, although a respiratory acidosis also leads to a compensatory elevation of the serum [HCO_3^-]. With a simple metabolic alkalosis, however, the pH is elevated; alkalemia is present. Patients with a respiratory acidosis are acidemic. Decreasing ventilation causes appropriate respiratory compensation for a metabolic alkalosis. P_{CO_2} increases by 7 mm Hg for each 10 mEq/L increase in the serum [HCO_3^-]. Appropriate respiratory compensation never exceeds a P_{CO_2} of 55-60 mm Hg. The patient has a concurrent respiratory alkalosis if the P_{CO_2} is lower than the expected compensation. A greater than expected P_{CO_2} occurs with a concurrent respiratory acidosis.

Table 73.14 Causes of Metabolic Alkalosis

CHLORIDE-RESPONSIVE (URINARY CHLORIDE <15 MEQ/L)
Gastric losses
Emesis
Nasogastric suction
Diuretics (loop or thiazide)
Chloride-losing diarrhea (OMIM 214700)
Low chloride formula
Cystic fibrosis (OMIM 219700)
Posthypercapnia
CHLORIDE-RESISTANT (URINARY CHLORIDE >20 MEQ/L)
High Blood Pressure
Adrenal adenoma or hyperplasia
Glucocorticoid-remediable aldosteronism/Familial hyperaldosteronism type I (OMIM 103900)
Familial hyperaldosteronism type II (OMIM 605635)
Familial hyperaldosteronism type III (OMIM 613677)
Familial hyperaldosteronism type IV (OMIM 617027)
Renovascular disease
Renin-secreting tumor
17α-Hydroxylase deficiency (OMIM 202110)
11β-Hydroxylase deficiency (OMIM 202010)
Cushing syndrome
11β-Hydroxysteroid dehydrogenase deficiency (OMIM 218030)
Licorice ingestion
Liddle syndrome (OMIM 177200)
Normal Blood Pressure
Gitelman syndrome (OMIM 263800)
Bartter syndrome (OMIM 241200/607364/602522/601678/300971/601198/613090)
Autosomal dominant hypoparathyroidism (OMIM 146200)
EAST syndrome (OMIM 612780)
Hyperuricemia, Pulmonary Hypertension, Renal Failure in Infancy and Alkalosis, HUPRA Syndrome (OMIM 613845)
Autosomal dominant kidney hypomagnesemia due to *RRAGD* variant (OMIM not assigned)
Base administration

EAST, Epilepsy, ataxia, sensorineural hearing loss, and tubulopathy; OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

Etiology and Pathophysiology

The kidneys normally respond promptly to a metabolic alkalosis by increasing base excretion. Two processes are therefore usually present to produce a metabolic alkalosis: (1) the generation of the metabolic alkalosis, which requires the addition of base to the body, and (2) the maintenance of the metabolic alkalosis, which requires impairment in the kidney's ability to excrete base.

The etiologies of a metabolic alkalosis are divided into two categories based on the urinary chloride level (Table 73.14). The alkalosis in patients with a low urinary [Cl^-] is maintained by **volume depletion**; thus volume repletion is necessary for correction of the alkalosis. The volume depletion in these patients is caused by losses of Na^+ and K^+, but the loss of Cl^- is usually greater than the losses of Na^+ and K^+ combined. Because Cl^- losses are the dominant cause of the volume depletion, these patients require Cl^- to correct the volume depletion and metabolic alkalosis; they are said to have **Cl^--responsive metabolic alkalosis.** In contrast, the alkalosis in a patient with an elevated urinary [Cl^-] does not respond to volume repletion and so is termed **Cl^--resistant metabolic alkalosis.**

Emesis or nasogastric suction results in **loss of gastric fluid**, which has a high content of HCl. Generation of H^+ by the gastric mucosa causes simultaneous release of bicarbonate into the bloodstream. Normally, the hydrogen ions in gastric fluid are reclaimed in the small intestine (by neutralizing secreted bicarbonate); thus there is no net loss of acid. With loss of gastric fluid, this does not occur, and a metabolic alkalosis develops. This period is the *generation phase* of the metabolic alkalosis.

The *maintenance phase* of the metabolic alkalosis from gastric losses is caused by the volume depletion ("chloride depletion" from gastric loss of HCl). Volume depletion interferes with urinary loss of bicarbonate, the normal renal response to a metabolic alkalosis. During volume depletion, several mechanisms prevent renal bicarbonate loss. First, there is a reduction in the GFR, so less bicarbonate is filtered. Second, volume depletion increases resorption of sodium and bicarbonate in the proximal tubule, limiting the amount of bicarbonate that can be excreted in the urine. This effect is mediated by angiotensin II and adrenergic stimulation of the kidney, both of which are increased in response to volume depletion. Third, the increase in aldosterone during volume depletion increases bicarbonate resorption and H^+ secretion in the collecting duct.

In addition to volume depletion, gastric losses are usually associated with hypokalemia as a result of both gastric loss of K^+ and, most importantly, increased urinary K^+ losses. The increased urinary losses of K^+ are mediated by aldosterone, through volume depletion, and by the increase in intracellular K^+ secondary to the metabolic alkalosis, which causes K^+ to move into the cells of the kidney, causing increased K^+ excretion. Hypokalemia contributes to the maintenance of the metabolic alkalosis by decreasing bicarbonate loss. Hypokalemia increases H^+ secretion in the distal nephron and stimulates ammonia production in the proximal tubule. Ammonia production enhances renal excretion of H^+.

A metabolic alkalosis can develop in patients receiving **loop** or **thiazide diuretics.** Diuretic use leads to volume depletion, which increases angiotensin II, aldosterone, and adrenergic stimulation of the kidney. Diuretics increase the delivery of sodium to the distal nephron, further enhancing acid excretion. Moreover, these diuretics cause hypokalemia, which increases acid excretion by the kidney. The increase in renal acid excretion generates the metabolic alkalosis, and the decrease in bicarbonate loss maintains it. In addition, patients who are receiving diuretics have a "contraction alkalosis." Diuretic use causes fluid loss without bicarbonate; thus the remaining body bicarbonate is contained in a smaller total body fluid compartment. The $[HCO_3^-]$ increases, helping to generate the metabolic alkalosis.

Diuretics are often used in patients with edema, such as those with nephrotic syndrome, heart failure, or liver failure. In many of these patients, metabolic alkalosis resulting from diuretic use develops despite the continued presence of edema. This is because the effective intravascular volume is low, and it is the effective intravascular volume that stimulates the compensatory mechanisms that cause and maintain a metabolic alkalosis. Many of these patients have a decreased effective intravascular volume before they begin diuretic therapy, increasing the likelihood of diuretic-induced metabolic alkalosis.

Diuretic use increases chloride excretion in the urine. Consequently, while a patient is receiving diuretics, the urine $[Cl^-]$ is typically high (>20 mEq/L). After the diuretic effect has worn off, the urinary $[Cl^-]$ is low (<15 mEq/L) because of appropriate renal Cl^- retention in response to volume depletion. Thus categorization of diuretics because of urinary $[Cl^-]$ depends on the timing of the measurement. However, the metabolic alkalosis from diuretics is Cl^- responsive; it is corrected after adequate volume repletion. This is the rationale for including this process among the chloride-responsive causes of a metabolic alkalosis.

Most patients with diarrhea have a metabolic acidosis because of stool losses of bicarbonate. In **chloride-losing diarrhea**, an autosomal recessive disorder, there is a defect in the normal intestinal exchange of bicarbonate for chloride, causing excessive stool losses of chloride (see Chapter 385). In addition, stool losses of H^+ and K^+ cause metabolic alkalosis and hypokalemia, both of which are exacerbated by increased renal H^+ and K^+ losses from volume depletion. Treatment is with oral supplements of K^+ and NaCl. Use of a gastric proton pump inhibitor (PPI), by decreasing gastric HCl production, reduces both the volume of diarrhea and the need for electrolyte supplementation.

Formulas with extremely low Cl^- content have led to Cl^- deficiency and volume depletion. There is secondary metabolic alkalosis and hypokalemia. **Cystic fibrosis** can rarely cause metabolic alkalosis, hypokalemia, and hyponatremia because of excessive NaCl losses in sweat (see Chapter 454). The volume depletion causes the metabolic alkalosis and hypokalemia through increased urinary losses, whereas the hyponatremia, a less common finding, is secondary to Na^+ loss combined with renal water conservation in an effort to protect the intravascular volume ("appropriate" ADH production).

A **posthypercapnic metabolic alkalosis** occurs after the correction of a chronic respiratory acidosis. This is typically seen in patients with chronic lung disease who are started on mechanical ventilation. During chronic respiratory acidosis, appropriate renal compensation leads to an increase in the serum $[HCO_3^-]$. Because it is still present after acute correction of the respiratory acidosis, the elevated $[HCO_3^-]$ causes a metabolic alkalosis. The metabolic alkalosis persists because the patient with a chronic respiratory acidosis is intravascularly depleted because of the Cl^- loss that occurred during the initial metabolic compensation for the primary respiratory acidosis. In addition, many children with a chronic respiratory acidosis receive diuretics, which further decrease the intravascular volume. The metabolic alkalosis responds to correction of the intravascular volume deficit.

The **chloride-resistant** causes of metabolic alkalosis can be subdivided according to blood pressure status. Patients with **hypertension** either have increased aldosterone levels or act as if they do. Aldosterone levels are elevated in children with adrenal adenomas or hyperplasia. Aldosterone causes renal retention of sodium, with resultant hypertension. Metabolic alkalosis and hypokalemia result from aldosterone-mediated renal excretion of H^+ and K^+. The urinary Cl^- level is not low because these patients are volume overloaded, not volume depleted. The volume expansion and hypertension allow normal excretion of Na^+ and Cl^- despite the presence of aldosterone. This is known as the *mineralocorticoid escape phenomenon.*

In **glucocorticoid-remediable aldosteronism**, an autosomal dominant disorder, excess production of aldosterone results from the presence of an aldosterone synthase gene regulated by adrenocorticotropic hormone (ACTH) (see Chapter 616.8). Glucocorticoids effectively treat this disorder by inhibiting ACTH production by the pituitary, downregulating the inappropriate aldosterone production. Familial hyperaldosteronism type II, which causes elevated aldosterone levels, responds to spironolactone. Familial hyperaldosteronism type III typically requires bilateral adrenalectomy due to the severity of the hyperaldosteronism. Renovascular disease and renin-secreting tumors both cause excessive renin, leading to an increase in aldosterone, although hypokalemia and metabolic alkalosis are less common findings than hypertension. In two forms of **congenital adrenal hyperplasia**, 11β-hydroxylase deficiency and 17α-hydroxylase deficiency, there is excessive production of the mineralocorticoid 11-deoxycorticosterone (see Chapters 616.2 and 616.4). Hypertension, hypokalemia, and metabolic alkalosis are more likely in 17α-hydroxylase deficiency than in 11β-hydroxylase deficiency. These disorders respond to glucocorticoids because the excess production of 11-deoxycorticosterone is under the control of ACTH.

Cushing syndrome frequently causes hypertension. Cortisol has *some* mineralocorticoid activity, and high levels can produce hypokalemia and metabolic alkalosis in patients with Cushing syndrome.

Cortisol can bind to the mineralocorticoid receptors in the kidney and function as a mineralocorticoid. This binding normally does not occur because 11β-hydroxysteroid dehydrogenase in the kidney converts cortisol to cortisone, which does not bind to the mineralocorticoid receptor. In the autosomal recessive disorder 11β-hydroxysteroid dehydrogenase deficiency, also called **apparent mineralocorticoid excess**, cortisol is not converted in the kidney to cortisone. Cortisol is therefore available to bind to the mineralocorticoid receptor in the kidney and act as a mineralocorticoid. Patients with this deficiency, despite low levels of aldosterone, are hypertensive and hypokalemic, and they have a metabolic alkalosis. The same phenomenon can occur with excessive intake of natural licorice, a component of which, glycyrrhizic acid, inhibits 11β-hydroxysteroid dehydrogenase. The autosomal dominant disorder **Liddle syndrome** is secondary to an activating variant in the gene for the sodium channel in the distal nephron (see Chapter 571.3). Upregulation of this sodium channel is one of the principal actions of aldosterone. Because this Na^+ channel is continuously open, children with Liddle syndrome have the features of hyperaldosteronism, including hypertension, hypokalemia, and metabolic alkalosis, but low serum levels of aldosterone.

Bartter and Gitelman syndromes are autosomal recessive disorders associated with normal blood pressure, elevated urinary Cl^-, metabolic alkalosis, and hypokalemia (see Chapter 571). In **Bartter syndrome**, patients have a defect in Na^+ and Cl^- resorption in the loop of Henle. This leads to excessive urinary losses of Na^+ and Cl^-, and as in patients receiving loop diuretics, volume depletion and secondary hyperaldosteronism occur, causing hypokalemia and metabolic alkalosis. **Gitelman syndrome** is usually milder than Bartter syndrome. Patients have renal Na^+ and Cl^- wasting with volume depletion caused by variants in the gene encoding the thiazide-sensitive Na^+-Cl^- transporter in the distal tubule. As in patients receiving a thiazide diuretic, affected patients have volume depletion and secondary hyperaldosteronism with hypokalemia and metabolic alkalosis. Children with Gitelman syndrome have hypocalciuria and hypomagnesemia. Some patients with autosomal dominant hypoparathyroidism have hypokalemia and metabolic alkalosis from impaired Na^+ and Cl^- resorption in the loop of Henle. **EAST syndrome** causes hypokalemia, metabolic alkalosis, and hypomagnesemia.

Excessive base intake can cause a metabolic alkalosis. Affected patients do not have low urine $[Cl^-]$, unless there is associated volume depletion. In the absence of volume depletion, excess base is rapidly corrected via renal excretion of bicarbonate. Rarely, massive base intake can cause a metabolic alkalosis by overwhelming the kidney's ability to excrete bicarbonate. This may occur in infants who are given baking soda as a "home remedy" for colic or stomach upset. Each teaspoon of baking soda has 42 mEq of sodium bicarbonate. Infants have increased vulnerability because of a lower GFR, limiting the rate of compensatory renal bicarbonate excretion. A metabolic alkalosis may also occur in patients who receive a large amount of sodium bicarbonate during cardiopulmonary resuscitation. Blood products are anticoagulated with citrate, which is converted into bicarbonate by the liver. Patients who receive large amounts of blood products may have a metabolic alkalosis. Iatrogenic metabolic alkalosis can occur because of acetate in TPN. Aggressive use of bicarbonate therapy in a child with a lactic acidosis or DKA may cause a metabolic alkalosis. This is especially likely in a patient in whom the underlying cause of the lactic acidosis is successfully corrected (restoration of intravascular volume in a patient with severe dehydration). Once the cause of the lactic acidosis resolves, lactate can be converted by the liver into bicarbonate, which when combined with infused bicarbonate can create a metabolic alkalosis. A similar phenomenon can occur in a child with DKA because the administration of insulin allows ketoacids to be metabolized, producing bicarbonate. However, this phenomenon rarely occurs because of judicious use of bicarbonate therapy in DKA and because there are usually significant pretreatment losses of ketoacids in the urine, preventing massive regeneration of bicarbonate. Base administration is most likely to cause a metabolic alkalosis in patients who have an impaired ability to excrete bicarbonate in the urine. This impairment occurs in patients with concurrent volume depletion or renal insufficiency.

Clinical Manifestations

The symptoms in patients with a metabolic alkalosis are often related to the underlying disease and associated electrolyte disturbances. Children with Cl^--responsive causes of metabolic alkalosis often have symptoms related to volume depletion, such as thirst and lethargy. In contrast, children with Cl^--unresponsive causes may have symptoms related to hypertension.

Alkalemia causes potassium to shift into the ICS, producing a decrease in the extracellular $[K^+]$. Alkalemia leads to increased urinary losses of K^+. Increased K^+ losses are present in many of the conditions that cause a metabolic alkalosis. Therefore most patients with a metabolic alkalosis have hypokalemia, and their symptoms may be related to the hypokalemia (see Chapter 73.4).

The symptoms of a metabolic alkalosis are caused by the associated alkalemia. The magnitude of the alkalemia is related to the severity of the metabolic alkalosis and the presence of concurrent respiratory acid-base disturbances. During alkalemia, the ionized calcium concentration decreases because of increased binding of calcium to albumin. The decrease in the ionized calcium concentration may cause symptoms of **tetany** (**carpopedal spasm**).

Arrhythmias are a potential complication of a metabolic alkalosis, and the risk for arrhythmia increases if there is concomitant hypokalemia. Alkalemia increases the risk of digoxin toxicity, and antiarrhythmic medications are less effective in the presence of alkalemia. In addition, alkalemia may decrease cardiac output. A metabolic alkalosis causes a compensatory increase in the P_{CO_2} by decreasing ventilation. The decrease in ventilatory drive can cause hypoxia.

Diagnosis

Measurement of the urine $[Cl^-]$ is the most helpful test in differentiating among the causes of a metabolic alkalosis. The urine $[Cl^-]$ is low in patients with a metabolic alkalosis resulting from volume depletion, unless there is a defect in renal handling of Cl^-. The urine $[Cl^-]$ is superior to the urine $[Na^+]$ in assessment of volume status in patients with a metabolic alkalosis because the normal renal response to a metabolic alkalosis is to excrete bicarbonate. Because bicarbonate is negatively charged, it can only be excreted with cations, usually Na^+ and K^+. Therefore a patient with a metabolic alkalosis may excrete Na^+ in the urine despite the presence of volume depletion, which normally causes avid Na^+ retention. The urine $[Cl^-]$ is usually a good indicator of volume status, and it differentiates Cl^--resistant and Cl^--responsive causes of a metabolic alkalosis.

Diuretics and gastric losses are the most common causes of metabolic alkalosis and are usually apparent from the patient history. Occasionally, metabolic alkalosis, usually with hypokalemia, may be a clue to the presence of bulimia or surreptitious diuretic use (see Chapter 41). Patients with bulimia have a low urine Cl^- level, indicating that they have volume depletion because of an extrarenal etiology, but there is no alternative explanation for their volume depletion. Surreptitious diuretic use may be diagnosed by obtaining a urine toxicology screen for diuretics. The urine $[Cl^-]$ is increased while a patient is using diuretics but is low when the patient stops taking them. *Rarely, children with mild Bartter or Gitelman syndrome are misdiagnosed as having bulimia or abusing diuretics.* The

urine [Cl^-] is always elevated in Bartter and Gitelman syndromes, and the urine toxicology screen for diuretics has a negative result. Metabolic alkalosis with hypokalemia is occasionally the initial manifestation of cystic fibrosis. An elevated sweat Cl^- finding is diagnostic.

Patients with a metabolic alkalosis and a high urinary [Cl^-] are subdivided according to blood pressure status. Children with normal blood pressure may have Bartter or Gitelman syndrome. Excess base administration is another diagnostic possibility, but it is usually apparent from the history. In patients with sodium bicarbonate ingestion (baking soda), which may be unreported by the parent, the metabolic alkalosis usually occurs with significant hypernatremia. In addition, unless volume depletion is superimposed, the metabolic alkalosis from base ingestion resolves itself once the source of base is eliminated.

Measuring serum concentrations of renin and aldosterone differentiates children with a metabolic alkalosis, a high urinary [Cl^-], and elevated blood pressure. Both renin and aldosterone are elevated in children with either renovascular disease or a renin-secreting tumor. Aldosterone is high and renin is low in patients with adrenal adenomas or hyperplasia and glucocorticoid-remediable aldosteronism. Renin and aldosterone are low in children with Cushing syndrome, Liddle syndrome, licorice ingestion, and 17α-hydroxylase, 11β-hydroxylase, and 11β-hydroxysteroid dehydrogenase deficiencies. An elevated 24-hour urine cortisol value is diagnostic of Cushing syndrome, which is suspected from the presence of the other classic features of this disease (see Chapter 619). Elevations of 11-deoxycorticosterone values are seen in 17α-hydroxylase and 11β-hydroxylase deficiency.

Treatment

The approach to treatment of metabolic alkalosis depends on the severity of the alkalosis and the underlying etiology. In children with a mild metabolic alkalosis ([HCO_3^-] <32 mEq/L), intervention is often unnecessary, although this depends on the specific circumstances. In a child with congenital heart disease who is receiving a stable dose of a loop diuretic, a mild alkalosis does not require treatment. In contrast, intervention may be appropriate in a child with a worsening mild metabolic alkalosis because of nasogastric suction. The presence of a concurrent respiratory acid-base disturbance also influences therapeutic decision-making. A patient with a concurrent respiratory acidosis should have some increase in bicarbonate from metabolic compensation; thus the severity of the pH elevation is more important than [HCO_3^-]. In contrast, a patient with respiratory alkalosis and a metabolic alkalosis is at risk for severe alkalemia; treatment may be indicated, even if the increase in bicarbonate value is only mild.

Intervention is usually necessary in children with moderate or severe metabolic alkalosis. The most effective approach is to address the underlying etiology. In some children, nasogastric suction may be decreased or discontinued. Alternatively, the addition of a gastric PPI reduces gastric secretion and losses of HCl. Diuretics are an important cause of metabolic alkalosis, and if a change is tolerated, they should be eliminated or the dose reduced. Adequate potassium supplementation or the addition of a potassium-sparing diuretic is also helpful in a child with a metabolic alkalosis from diuretics. Potassium-sparing diuretics not only decrease renal K^+ losses but, by blocking the action of aldosterone, also decrease H^+ secretion in the distal nephron, increasing urinary bicarbonate excretion. Many children cannot tolerate discontinuation of diuretic therapy; hence, potassium supplementation and potassium-sparing diuretics are the principal therapeutic approach. Arginine HCl may also be used to treat chloride-responsive metabolic acidosis if sodium or potassium salts are not appropriate. Arginine HCl may raise the serum K^+ levels during administration. Rarely, in cases of severe metabolic alkalosis, acetazolamide is an option. A carbonic anhydrase inhibitor, acetazolamide decreases resorption of bicarbonate in the proximal tubule, causing significant bicarbonate loss in the urine. The patient receiving this drug must be monitored closely, because acetazolamide produces major losses of potassium in the urine and increases fluid losses, potentially necessitating a reduction in dosage of other diuretics.

Most children with a metabolic alkalosis have one of the **chloride-responsive** etiologies. In these situations, administration of sufficient sodium chloride and potassium chloride to correct the volume deficit and the potassium deficit is necessary to correct the metabolic alkalosis. This approach may not be an option in the child who has volume depletion due to diuretics, because volume repletion may be contraindicated. Adequate replacement of gastric losses of sodium and potassium in a child with a nasogastric tube can minimize or prevent the development of the metabolic alkalosis. With adequate intravascular volume and a normal serum [K^+], the kidney excretes the excess bicarbonate within 2 days.

In children with the **chloride-resistant** causes of a metabolic alkalosis that are associated with hypertension, volume repletion is contraindicated because it would exacerbate the hypertension and would not repair the metabolic alkalosis. Ideally, treatment focuses on eliminating the excess aldosterone effect. Adrenal adenomas can be resected, licorice intake can be eliminated, and renovascular disease can be repaired. Glucocorticoid-remediable aldosteronism, 17α-hydroxylase deficiency, and 11β-hydroxylase deficiency respond to the administration of glucocorticoids. The mineralocorticoid effect of cortisol in 11β-hydroxysteroid dehydrogenase deficiency can be decreased with the use of spironolactone, which blocks the mineralocorticoid receptor. In contrast, the metabolic alkalosis in children with Liddle syndrome does not respond to spironolactone; however, either triamterene or amiloride is effective therapy because both agents block the sodium channel that is constitutively active in Liddle syndrome.

In children with Bartter or Gitelman syndrome, therapy includes oral potassium and sodium supplementation; potassium-sparing diuretics may be helpful in select cases. Children with Gitelman syndrome often require magnesium supplementation, whereas children with severe Bartter syndrome often benefit from indomethacin.

RESPIRATORY ACIDOSIS

A respiratory acidosis is an inappropriate increase in blood carbon dioxide tension (P_{CO_2}). CO_2 is a by-product of metabolism and is removed from the body by the lungs. During a respiratory acidosis, the effectiveness of CO_2 removal by the lungs is decreased. A respiratory acidosis is secondary to either pulmonary disease, such as severe bronchiolitis, or nonpulmonary disease, such as a narcotic overdose (see Chapter 86). Even though body production of CO_2 can vary, normal lungs are able to accommodate this variation; excess production of CO_2 is not an isolated cause of a respiratory acidosis. With impairment of alveolar ventilation, the rate of body production of CO_2 may affect the severity of the respiratory acidosis, but this is usually not a significant factor.

A respiratory acidosis causes a decrease in the blood pH, but there is normally a metabolic response that partially compensates, minimizing the severity of the acidemia. The acute metabolic response to a respiratory alkalosis occurs within minutes. The metabolic compensation for an *acute* respiratory acidosis is secondary to titration of acid by nonbicarbonate buffers. This buffering of H^+ causes a predictable increase in the serum [HCO_3^-]: Plasma bicarbonate increases by 1 for each 10 mm Hg increase in the P_{CO_2} (acute compensation).

With a *chronic* respiratory acidosis, there is more significant metabolic compensation and thus less severe acidemia than in an acute respiratory acidosis with the same increase in P_{CO_2}. During a chronic respiratory acidosis, the kidneys increase acid excretion. This response occurs over 3-4 days and causes a predictable increase in the serum [HCO_3^-]: Plasma bicarbonate increases by 3.5 for each 10 mm Hg increase in the P_{CO_2} (chronic compensation).

The increase of serum [HCO_3^-] during a chronic respiratory acidosis is associated with a decrease in body chloride. After acute correction of a chronic respiratory acidosis, the plasma bicarbonate continues to

Table 73.15 Causes of Respiratory Acidosis

CENTRAL NERVOUS SYSTEM DEPRESSION
- Encephalitis
- Head trauma
- Brain tumor
- Central sleep apnea
- Primary pulmonary hypoventilation (Ondine curse)
- Stroke
- Hypoxic brain damage
- Obesity-hypoventilation (Pickwickian) syndrome
- Increased intracranial pressure
- Medications
  - Narcotics
  - Barbiturates
  - Anesthesia
  - Benzodiazepines
  - Propofol
  - Alcohols

DISORDERS OF SPINAL CORD, PERIPHERAL NERVES, OR NEUROMUSCULAR JUNCTION
- Diaphragmatic paralysis
- Guillain-Barré syndrome
- Poliomyelitis
- Acute flaccid myelitis
- Spinal muscular atrophies
- Tick paralysis
- Botulism
- Myasthenia
- Multiple sclerosis
- Spinal cord injury
- Medications
  - Vecuronium
  - Aminoglycosides
  - Organophosphates (pesticides)

RESPIRATORY MUSCLE WEAKNESS
- Muscular dystrophy
- Hypothyroidism
- Malnutrition
- Hypokalemia
- Hypophosphatemia
- Medications
  - Succinylcholine
  - Corticosteroids

PULMONARY DISEASE
- Pneumonia
- Pneumothorax
- Asthma
- Bronchiolitis
- Pulmonary edema
- Pulmonary hemorrhage
- Acute respiratory distress syndrome
- Neonatal respiratory distress syndrome
- Cystic fibrosis
- Bronchopulmonary dysplasia
- Hypoplastic lungs
- Meconium aspiration
- Pulmonary thromboembolus
- Interstitial fibrosis

UPPER AIRWAY DISEASE
- Aspiration
- Laryngospasm
- Angioedema
- Obstructive sleep apnea
- Tonsillar hypertrophy
- Vocal cord paralysis
- Extrinsic tumor
- Extrinsic or intrinsic hemangioma

MISCELLANEOUS
- Flail chest
- Cardiac arrest
- Kyphoscoliosis
- Decreased diaphragmatic movement due to ascites or peritoneal dialysis

be increased, and the patient has a metabolic alkalosis. Because of the Cl^- deficit, this is a chloride-responsive metabolic alkalosis; it corrects once the patient's Cl^- deficit is replaced.

A **mixed disorder** is present if the metabolic compensation is inappropriate. A higher than expected bicarbonate value occurs in the setting of a concurrent metabolic alkalosis, and a lower than expected bicarbonate value occurs in the setting of a concurrent metabolic acidosis. Evaluating whether compensation is appropriate during a respiratory acidosis requires clinical knowledge of the acuity of the process, because the expected compensation is different, depending on whether the process is acute or chronic.

The P_{CO_2} cannot be interpreted in isolation to determine whether a patient has a respiratory acidosis. A respiratory acidosis is always present if a patient has acidemia and an elevated P_{CO_2}. However, an elevated P_{CO_2} also occurs as appropriate respiratory compensation for a simple metabolic alkalosis. The patient is *alkalemic*; this is not a respiratory acidosis. During a mixed disturbance, a patient can have a respiratory acidosis and a normal or even low P_{CO_2}. This condition may occur in a patient with a metabolic acidosis. A respiratory acidosis is present if the patient does not have appropriate respiratory compensation (the P_{CO_2} is higher than expected from the severity of the metabolic acidosis).

Etiology and Pathophysiology

The causes of a respiratory acidosis are either pulmonary or nonpulmonary (Table 73.15). CNS disorders can decrease the activity of the central respiratory center, reducing ventilatory drive. A variety of medications and illicit drugs suppress the respiratory center. The signals from the respiratory center need to be transmitted to the respiratory muscles via the nervous system. Respiratory muscle failure can be secondary to disruption of the signal from the CNS in the spinal cord, the phrenic nerve, or the neuromuscular junction. Disorders directly affecting the muscles of respiration can prevent adequate ventilation, causing a respiratory acidosis.

Mild or moderate lung disease often causes a respiratory alkalosis as a result of hyperventilation secondary to hypoxia or stimulation of lung mechanoreceptors or chemoreceptors. Only more severe lung disease causes a respiratory acidosis. Upper airway diseases, by impairing air entry into the lungs, may decrease ventilation, producing a respiratory acidosis.

Increased production of CO_2 is never the sole cause of a respiratory acidosis, but it can increase the severity of the disease in a patient with decreased ventilation of CO_2. Increased production of CO_2 occurs in patients with fever, hyperthyroidism, excess caloric intake, and high levels of physical activity. Increased respiratory muscle work also increases CO_2 production.

Clinical Manifestations

Patients with a respiratory acidosis are often tachypneic in an effort to correct the inadequate ventilation. Exceptions include patients with a respiratory acidosis resulting from CNS depression and patients who are on the verge of complete respiratory failure secondary to fatigue of the respiratory muscles.

The symptoms of respiratory acidosis are related to the severity of the **hypercarbia**. Acute respiratory acidosis is usually more symptomatic than chronic respiratory acidosis. Symptoms are also increased by concurrent hypoxia or metabolic acidosis. In a patient breathing room air, hypoxia is always present if a respiratory acidosis is present. The potential CNS manifestations of respiratory acidosis include anxiety, dizziness, headache, confusion, asterixis, myoclonic jerks, hallucinations, psychosis, coma, and seizures.

Acidemia, no matter the etiology, affects the cardiovascular system. An arterial pH <7.2 impairs cardiac contractility and the normal response to catecholamines in both the heart and the peripheral vasculature. Hypercapnia causes vasodilation, most dramatically in the cerebral vasculature, but hypercapnia produces vasoconstriction of the pulmonary circulation. Respiratory acidosis increases the risk of cardiac **arrhythmias**, especially in a child with underlying cardiac disease.

Diagnosis

The history and physical findings often point to a clear etiology. For the obtunded patient with poor respiratory effort, evaluation of the CNS is often indicated. This may include imaging studies (CT or MRI) and, potentially, a lumbar puncture for cerebrospinal fluid analysis. A toxicology screen for illicit drugs may also be appropriate. A response to naloxone is both diagnostic and therapeutic. In many of the diseases affecting the respiratory muscles, there is evidence of weakness in other muscles. Stridor is a clue that the child may have upper airway disease. Along with a physical examination, a chest radiograph is often helpful in diagnosing pulmonary disease.

In many patients, respiratory acidosis may be multifactorial. A child with bronchopulmonary dysplasia, an intrinsic lung disease, may worsen because of respiratory muscle dysfunction caused by severe hypokalemia resulting from long-term diuretic therapy. Conversely, a child with muscular dystrophy, a muscle disease, may worsen because of aspiration pneumonia.

For a patient with respiratory acidosis, calculation of the gradient between the alveolar oxygen concentration and the arterial oxygen concentration, the A-a O_2 gradient, is useful for distinguishing between poor respiratory effort and intrinsic lung disease. The A-a O_2 gradient is increased if the hypoxemia is caused by intrinsic lung disease (see Chapter 421).

Treatment

Respiratory acidosis is best managed by treatment of the underlying etiology. In some patients, the response is very rapid, such as after the administration of naloxone to a patient with a narcotic overdose. In contrast, in the child with pneumonia, a number of days of antibiotic therapy may be required before the respiratory status improves. In many children with a chronic respiratory acidosis, there is no curative therapy, although an acute respiratory illness superimposed on a chronic respiratory condition is usually reversible.

All patients with an *acute* respiratory acidosis are hypoxic and therefore need to receive supplemental oxygen. Mechanical ventilation is necessary in some children with respiratory acidosis. Children with significant respiratory acidosis caused by CNS disease usually require mechanical ventilation because such a disorder is unlikely to respond quickly to therapy. In addition, hypercarbia causes cerebral vasodilation, and the increase in ICP can be dangerous in a child with an underlying CNS disease. Readily reversible CNS depression, as from a narcotic overdose, may not require mechanical ventilation. Decisions on mechanical ventilation for other patients depend on a number of factors. Patients with severe hypercarbia (P_{CO_2} >75 mm Hg) usually require mechanical ventilation (see Chapter 86.1). The threshold for intubation is lower if there is concomitant metabolic acidosis, a slowly responsive underlying disease, or hypoxia that responds poorly to oxygen, or if the patient appears to be tiring and respiratory arrest seems likely.

In patients with a *chronic* respiratory acidosis, the respiratory drive is often less responsive to hypercarbia and more responsive to hypoxia. Thus, with chronic respiratory acidosis, excessive use of oxygen can blunt the respiratory drive and therefore increase the P_{CO_2}. In these patients, oxygen must be used cautiously.

When possible, it is best to avoid mechanical ventilation in a patient with chronic respiratory acidosis because extubation is often difficult. However, an acute illness may necessitate mechanical ventilation in a child with a chronic respiratory acidosis. When intubation is necessary, the P_{CO_2} should be lowered only to the patient's normal baseline, and this should be done gradually. These patients normally have an elevated serum [HCO_3^-] as a result of metabolic compensation for their respiratory acidosis. A rapid lowering of the P_{CO_2} can cause a severe metabolic alkalosis, potentially leading to complications, including cardiac arrhythmias, decreased cardiac output, and decreased cerebral blood flow. In addition, prolonged mechanical ventilation at a normal P_{CO_2} causes the metabolic compensation to resolve. When the patient is subsequently extubated, the patient will no longer benefit from metabolic compensation, causing a more severe acidemia because of the respiratory acidosis.

RESPIRATORY ALKALOSIS

A respiratory alkalosis is an inappropriate reduction in the blood CO_2 concentration. This is usually secondary to hyperventilation, initially causing removal of CO_2 to surpass production. Eventually, a new steady state is achieved, with removal equaling production, although at a lower CO_2 tension (P_{CO_2}). A respiratory alkalosis that is not the result of hyperventilation may occur in children receiving extracorporeal membrane oxygenation, with CO_2 lost directly from the blood in the extracorporeal circuit.

With a simple respiratory alkalosis, the pH increases, but there is a normal metabolic response that attenuates some of the change in the blood pH. A metabolic response to an acute respiratory alkalosis occurs within minutes, mediated by hydrogen ion release from nonbicarbonate buffers. The metabolic response to an acute respiratory alkalosis is predictable: Plasma bicarbonate falls by 2 for each 10 mm Hg decrease in the P_{CO_2} (acute compensation).

A chronic respiratory alkalosis leads to more significant metabolic compensation because of the actions of the kidneys, which decrease acid secretion, producing a decrease in the serum [HCO_3^-]. Both the proximal and distal tubules decrease acid secretion. Metabolic compensation for a respiratory alkalosis develops gradually and takes 2-3 days to produce the full effect: Plasma bicarbonate falls by 4 for each 10 mm Hg decrease in the P_{CO_2} (chronic compensation).

A chronic respiratory alkalosis is the only acid-base disturbance in which appropriate compensation may *normalize the pH,* although >7.4.

A **mixed disorder** is present if the metabolic compensation is inappropriate. A higher than expected HCO_3^- level occurs in the setting of a concurrent metabolic alkalosis, and a lower than expected HCO_3^- level occurs in the setting of a concurrent metabolic acidosis. Evaluating whether compensation is appropriate during a respiratory alkalosis requires clinical knowledge of the acuity of the process, because the expected compensation differs according to whether the process is acute or chronic.

A low P_{CO_2} value does not always indicate a respiratory alkalosis. The P_{CO_2} also decreases as part of the appropriate respiratory compensation for a metabolic acidosis; this is not a respiratory alkalosis.

Table 73.16 Causes of Respiratory Alkalosis

HYPOXEMIA OR TISSUE HYPOXIA
Pneumonia
Pulmonary edema
Cyanotic heart disease
Congestive heart failure
Asthma
Severe anemia
High altitude
Laryngospasm
Aspiration
Carbon monoxide poisoning
Pulmonary embolism
Interstitial lung disease
Hypotension
LUNG RECEPTOR STIMULATION
Pneumonia
Pulmonary edema
Asthma
Pulmonary embolism
Hemothorax
Pneumothorax
Respiratory distress syndrome (adult or infant)
CENTRAL STIMULATION
Central nervous system disease
Subarachnoid hemorrhage
Encephalitis or meningitis
Trauma
Brain tumor
Stroke
Fever
Pain
Anxiety (panic attack)
Psychogenic hyperventilation or anxiety
Liver failure
Sepsis
Pregnancy
Mechanical ventilation
Hyperammonemia
Extracorporeal membrane oxygenation or hemodialysis
Medications
Salicylate intoxication
Theophylline
Progesterone
Exogenous catecholamines
Caffeine

A metabolic acidosis is the dominant acid-base disturbance in a patient with acidemia and a low P_{CO_2}, even though there could still be a concurrent respiratory alkalosis. In contrast, a respiratory alkalosis is always present in a patient with alkalemia and a low P_{CO_2}. Even a normal P_{CO_2} value may be consistent with a respiratory alkalosis in a patient with a metabolic alkalosis, because an elevated P_{CO_2} is expected as part of appropriate respiratory compensation for the metabolic alkalosis.

Etiology and Pathophysiology

A variety of stimuli can increase the ventilatory drive and cause a respiratory alkalosis (Table 73.16). Arterial hypoxemia or tissue **hypoxia** stimulates peripheral chemoreceptors to signal the central respiratory center in the medulla to increase ventilation. The resultant greater respiratory effort increases the oxygen content of the blood (P_{O_2}) but depresses the P_{CO_2}. The effect of hypoxemia on ventilation begins when the arterial oxygen saturation (Sa_{O_2}) decreases to approximately 90% (P_{O_2} = 60 mm Hg), and hyperventilation increases as hypoxemia worsens. Acute hypoxia is a more potent stimulus for hyperventilation than chronic hypoxia; thus chronic hypoxia, as occurs in cyanotic heart disease, causes a much less severe respiratory alkalosis than an equivalent degree of acute hypoxia. The many causes of hypoxemia or tissue hypoxia include primary lung disease, severe anemia, and carbon monoxide (CO) poisoning.

The lungs contain chemoreceptors and mechanoreceptors that respond to irritants and stretching and send signals to the respiratory center to increase ventilation. Aspiration or pneumonia may stimulate the chemoreceptors, whereas pulmonary edema may stimulate the mechanoreceptors. Most of the diseases that activate these receptors may also cause hypoxemia and can therefore potentially lead to hyperventilation by two mechanisms. Patients with primary lung disease may initially have a respiratory alkalosis, but worsening of the disease, combined with respiratory muscle fatigue, often causes respiratory failure and the development of a respiratory acidosis.

Hyperventilation in the absence of lung disease occurs with direct stimulation of the central respiratory center. This occurs with CNS diseases such as meningitis, hemorrhage, and trauma. Central hyperventilation caused by lesions, such as infarcts or tumors near the central respiratory center in the midbrain, increases the rate and depth of the respiratory effort. This respiratory pattern portends a poor prognosis because these midbrain lesions are frequently fatal. Systemic processes may cause centrally mediated hyperventilation. Although the exact mechanisms are not clear, liver disease causes a respiratory alkalosis that is usually proportional to the degree of liver failure. **Pregnancy** causes a chronic respiratory alkalosis, probably mediated by progesterone acting on the respiratory centers. **Salicylates**, although often causing a concurrent metabolic acidosis, directly stimulate the respiratory center to produce a respiratory alkalosis. The respiratory alkalosis during sepsis is probably caused by cytokine release.

Hyperventilation may be secondary to an underlying disease that causes pain, stress, or anxiety. In psychogenic hyperventilation or in **panic attacks**, there is no disease process accounting for the hyperventilation. This disorder may occur in a child who has had an emotionally stressful experience. Alternatively, it may be part of a panic disorder, especially if there are repeated episodes of hyperventilation. In such a patient, the symptoms of acute alkalemia increase anxiety, potentially perpetuating the hyperventilation.

A respiratory alkalosis is quite common in children receiving mechanical ventilation because the respiratory center is not controlling ventilation. In addition, these children may have a decreased metabolic rate and thus less CO_2 production because of sedation and paralytic medications. Normally, decreased CO_2 production and the resultant hypocapnia decrease ventilation, but this physiologic response cannot occur in a child who cannot reduce ventilatory effort.

Clinical Manifestations

The disease process causing the respiratory alkalosis is usually more concerning than the clinical manifestations. Chronic respiratory alkalosis is usually asymptomatic because metabolic compensation decreases the magnitude of the alkalemia.

Acute respiratory alkalosis may cause chest tightness, palpitations, lightheadedness, circumoral numbness, and paresthesias of the extremities. Less common manifestations include tetany, seizures, muscle cramps, and syncope. The lightheadedness and syncope probably result from the reduction in cerebral blood flow caused by hypocapnia. The reduction in cerebral blood flow is the rationale for using hyperventilation to treat children with increased intracranial pressure (ICP). The paresthesias, tetany, and seizures may be partially related to the reduction in ionized calcium that occurs because alkalemia causes more calcium to bind to albumin. A respiratory alkalosis also causes a mild reduction in the serum potassium level. Patients with psychogenic hyperventilation tend to be symptomatic because of the respiratory alkalosis, and these symptoms, along with a sensation of breathlessness, exacerbate the hyperventilation.

Diagnosis

In many patients, hyperventilation producing a respiratory alkalosis is not clinically detectable, even with careful observation of the patient's

respiratory effort. Metabolic compensation for a respiratory alkalosis causes a low serum [HCO_3^-]. When hyperventilation is not appreciated and only serum electrolytes are evaluated, there is often a presumptive diagnosis of a metabolic acidosis. If a respiratory alkalosis is suspected, only ABG determination can make the diagnosis.

Hyperventilation does not always indicate a primary respiratory disorder. In some patients, the hyperventilation is appropriate respiratory compensation for a metabolic acidosis. With a primary metabolic acidosis, acidemia is present, and the serum HCO_3^- level is usually quite low if there is clinically detectable hyperventilation. In contrast, the serum HCO_3^- level never goes below 17 mEq/L as part of the metabolic compensation for acute respiratory alkalosis, and simple acute respiratory alkalosis causes alkalemia.

The etiology of a respiratory alkalosis is often apparent from the physical examination or history, and it may consist of lung disease, neurologic disease, or cyanotic heart disease. **Hypoxemia** is a common cause of hyperventilation, and it is important to diagnose because it suggests a significant underlying disease that requires expeditious treatment. Hypoxemia may be detected on physical examination (cyanosis) or by pulse oximetry. However, normal pulse oximetry values do not eliminate hypoxemia as the etiology of the hyperventilation. There are two reasons why pulse oximetry is not adequate for eliminating hypoxemia as a cause of a respiratory alkalosis. First, pulse oximetry is not very sensitive at detecting a mildly low arterial P_{O_2} (Pa_{O_2}). Second, the hyperventilation during a respiratory alkalosis causes Pa_{O_2} to increase, possibly to a level that is not identified as abnormal by pulse oximetry. Only ABG measurement can eliminate hypoxia as an explanation for a respiratory alkalosis. Along with hypoxemia, it is important to consider processes that cause **tissue hypoxia without necessarily causing hypoxemia**. Examples are CO or cyanide poisoning, severe anemia, and heart failure.

Lung disease without hypoxemia may cause hyperventilation. Although lung disease is often apparent by history or physical examination, a chest radiograph may detect more subtle disease. The patient with a pulmonary embolism may have benign chest radiograph findings, normal Pa_{O_2}, and isolated respiratory alkalosis, although hypoxia may eventually occur. Diagnosis of a pulmonary embolism requires a high index of suspicion and should be considered in children without another explanation for respiratory alkalosis, especially if risk factors are present, such as prolonged bed rest and a hypercoagulable state (e.g., nephrotic syndrome, lupus anticoagulant).

Treatment

There is seldom a need for specific treatment of respiratory alkalosis. Rather, treatment focuses on the underlying disease. Mechanical ventilator settings are adjusted to correct **iatrogenic** respiratory alkalosis, unless the hyperventilation has a therapeutic purpose (e.g., treatment of increased ICP).

For the patient with hyperventilation secondary to anxiety, efforts should be undertaken to reassure the child, usually enlisting the parents. Along with reassurance, patients with **psychogenic hyperventilation** may benefit from benzodiazepines. During an acute episode of psychogenic hyperventilation, rebreathing into a paper bag increases the patient's P_{CO_2}. Using a paper bag instead of a plastic bag allows adequate oxygenation but permits [CO_2] in the bag to increase. The resultant increase in the patient's P_{CO_2} decreases the symptoms of the respiratory alkalosis that tend to perpetuate the hyperventilation. Rebreathing should be performed only when other causes of hyperventilation have been eliminated; pulse oximetry during the rebreathing is prudent.

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Chapter 74

Maintenance and Replacement Therapy

Larry A. Greenbaum

Maintenance intravenous (IV) fluids are used in a child who cannot be fed enterally. Along with maintenance fluids, children may require concurrent **replacement fluids** if they have continued excessive losses, as may occur with drainage from a nasogastric (NG) tube or with high urine output because of nephrogenic diabetes insipidus. If dehydration is present, the patient also needs to receive **deficit** replacement (see Chapter 75). A child awaiting surgery may need only maintenance fluids, whereas a child with diarrheal dehydration needs maintenance and deficit therapy and also may require replacement fluids if significant diarrhea continues.

MAINTENANCE THERAPY

Children normally have large variations in their daily intake of water and electrolytes. The only exceptions are patients who receive fixed dietary regimens orally, via a gastric tube, or as IV total parenteral nutrition (TPN). Healthy children can tolerate significant variations in intake because of the many homeostatic mechanisms that can adjust absorption and excretion of water and electrolytes (see Chapter 73). The calculated water and electrolyte need that form the basis of maintenance therapy are not absolute requirements. Rather, these calculations provide reasonable guidelines for a *starting point to estimate IV therapy*. Children do not need to be started on IV fluids simply because their intake is being monitored in a hospital and they are not taking "maintenance fluids" orally, unless there is a pathologic process present that necessitates high fluid intake.

Maintenance fluids are most often necessary in preoperative and postoperative surgical patients; many nonsurgical patients also require maintenance fluids. It is important to recognize when it is necessary to begin maintenance fluids. A normal teenager who is given nothing by mouth (NPO) overnight for a morning procedure does not require maintenance fluids because a healthy adolescent can easily tolerate 12-18 hours without oral intake. In contrast, a 6-month-old child waiting for surgery should begin receiving IV fluids within 8 hours of the last feeding. Infants become dehydrated more quickly than older patients. A child with obligatory high urine output from nephrogenic diabetes insipidus should begin receiving IV fluids soon after being classified as NPO.

Maintenance fluids are composed of a solution of water, glucose, sodium (Na^+), and potassium (K^+). This solution has the advantages of simplicity, long shelf life, low cost, and compatibility with peripheral IV administration. Such a solution accomplishes the major objectives of maintenance fluids (Table 74.1). Patients lose water, Na^+, and K^+ in their urine and stool; water is also lost from the skin and lungs. Maintenance fluids replace these losses, thereby avoiding the development of dehydration and Na^+ or K^+ deficiency.

Table 74.1 Goals of Maintenance Fluids

- Prevent dehydration
- Prevent electrolyte disorders
- Prevent ketoacidosis
- Prevent protein degradation

The glucose in maintenance fluids provides approximately 20% of the normal caloric needs of the patient, prevents the development of starvation ketoacidosis, and diminishes the protein degradation that would occur if the patient received no calories. Maintenance fluids do not provide adequate calories, protein, fat, minerals, or vitamins. This fact is typically not problematic for a patient receiving IV fluids for a few days. A patient receiving maintenance IV fluids is receiving inadequate calories and will lose 0.5–1% of weight each day. It is imperative that patients not remain on maintenance therapy indefinitely; TPN should be used for children who cannot be fed enterally for more than a few days, especially patients with underlying malnutrition.

Prototypical maintenance fluid therapy does not provide electrolytes such as calcium, phosphorus, magnesium, and bicarbonate. For most patients, this lack is not problematic for a few days, although there are patients who will not tolerate this omission, usually because of excessive losses. A child with proximal renal tubular acidosis wastes bicarbonate in urine. Such a patient will rapidly become acidemic unless bicarbonate (or another base) is added to the maintenance fluids. It is important to remember the limitations of maintenance fluid therapy.

MAINTENANCE WATER

Water is a crucial component of maintenance fluid therapy because of the obligatory daily water losses. These losses are both measurable (urine, stool) and not measurable (**insensible losses** from the skin and lungs). Failure to replace these losses leads to a child who is thirsty, uncomfortable, and ultimately dehydrated.

The goal of maintenance water is to provide enough water to replace these losses. Although urinary losses are approximately 60% of the total, the normal kidney can greatly modify water losses, with daily urine volume potentially varying by more than a factor of 20. Maintenance water is designed to provide enough water so that the kidney does not need to significantly dilute or concentrate the urine. It also provides a margin of safety so that normal homeostatic mechanisms can adjust urinary water losses to prevent overhydration and dehydration. This adaptability obviates the need for absolute precision in determining water requirements. This fact is important, given the absence of absolute accuracy in the formulas for calculation of water needs.

Table 74.2 provides a system for calculating maintenance water on the basis of the patient's weight and emphasizes the high water needs of smaller, less mature patients. This approach is reliable, although calculations based on weight do overestimate the water needs of an overweight child, in whom it is better to base the calculations on the lean body weight, which can be estimated by using the 50th percentile of body weight for the child's height. It is also important to remember that there is an upper limit of 2.4 L/24 hr in adult-sized patients. IV fluids are written as an hourly rate. The formulas in Table 74.3 enable rapid calculation of the rate of maintenance fluids.

Table 74.2 Body Weight Method for Calculating Daily Maintenance Fluid Volume

BODY WEIGHT	FLUID PER DAY
0-10 kg	100 mL/kg
11-20 kg	1,000 mL + 50 mL/kg for each kg >10 kg
>20 kg	1,500 mL + 20 mL/kg for each kg >20 kg*

*The maximum total fluid per day is normally 2,400 mL.

Table 74.3 Hourly Maintenance Water Rate

For body weight 0-10 kg: 4 mL/kg/hr
For body weight 10-20 kg: 40 mL/hr + 2 mL/kg/hr × (wt − 10 kg)
For body weight >20 kg: 60 mL/hr + 1 mL/kg/hr × (wt − 20 kg)*

*The maximum fluid rate is normally 100 mL/hr.

INTRAVENOUS SOLUTIONS

The components of available solutions are shown in Table 74.4. These solutions are available with 5% dextrose (D5), 10% dextrose (D10), or without dextrose. Except for Ringer lactate (lactated Ringer, LR), they are also available with added potassium (10 or 20 mEq/L). A *balanced IV fluid* contains a base (lactate or acetate), a more physiologic chloride concentration than normal saline (NS), and additional physiologic concentrations of electrolytes such as potassium, calcium, and magnesium. Examples include LR and Plasma-Lyte, and there is evidence suggesting benefit versus NS in some but not all clinical situations. A hospital pharmacy can also prepare custom-made solutions with different concentrations of sodium or potassium. In addition, other electrolytes, such as calcium, magnesium, phosphate, acetate, and bicarbonate, can be added to IV solutions. Custom-made solutions take time to prepare and are much more expensive than commercial solutions. The use of custom-made solutions is necessary only for patients who have underlying disorders that cause significant electrolyte imbalances. The use of commercial solutions saves time and expense.

A normal plasma osmolality is 285-295 mOsm/kg. Infusing an IV solution peripherally with a much lower osmolality can cause water to move into red blood cells, leading to hemolysis. Thus IV fluids are generally designed to have an osmolality that is either close to 285 or greater (fluids with moderately higher osmolality do not cause problems). Thus 0.2NS (osmolality = 68) should not be administered peripherally, but D5 0.2NS (osmolality = 346) or D5 1/2NS + 20 mEq/L potassium chloride (KCl) with an osmolality of 472 can be administered.

Hypotonic fluids seem more physiologic given the low Na^+ content of breast milk and formula (~7 mEq/L). However, hospitalized children often have impaired water excretion because of volume depletion or nonosmotic stimuli for antidiuretic hormone (ADH) production, such as respiratory disease, central nervous system disease, stress, pain, nausea, and medications (e.g., narcotics). Hypotonic fluids increase the risk of hyponatremia, which may have serious sequelae; *hence, isotonic fluids with D5 are recommended as standard maintenance fluid except in neonates <28 days of age.*

GLUCOSE

Maintenance fluids usually contain D5, which provides 17 calories/100 mL and nearly 20% of the daily caloric needs. This level is enough to prevent ketone production and helps minimize protein degradation, but the child will lose weight on this regimen. Maintenance fluids are also lacking in such crucial nutrients as protein, fat, vitamins, and minerals. Hence, a patient needs to be started on TPN after a few days of maintenance fluids if enteral feedings are still not possible.

SELECTION OF MAINTENANCE FLUIDS

An isotonic fluid (NS, LR, Plasma-Lyte) with D5 and KCl (10-20 mEq/L is usually added to NS) is recommended for maintenance IV fluids. Surgical patients typically receive isotonic fluids (NS, LR) during surgery and in the recovery room for 6-8 hours postoperatively; the rate is typically approximately two thirds the calculated maintenance rate, with dextrose added if clinically indicated. Subsequent maintenance fluids have the addition of D5 and 10-20 mEq/L KCl based on the serum K^+ and the clinical setting. Electrolytes should be measured at least daily in all children receiving >50% of maintenance fluids intravenously unless the child is receiving prolonged IV fluids (TPN).

These guidelines assume that no disease process is present that would require an adjustment in either the volume or the electrolyte composition of maintenance fluids. Neonates, and especially premature infants, are outside the scope of these guidelines given their unique physiology. Children with renal insufficiency may be hyperkalemic or unable to excrete K^+ and may not tolerate 10 or 20 mEq/L of potassium. Patients with persistent ADH production because of an underlying disease process (syndrome of inappropriate ADH secretion, congestive heart failure, nephrotic syndrome, liver disease) should receive less

Table 74.4 Composition of Intravenous Solutions*

FLUID	[NA^+]	[CL^-]	[K^+]	[CA^{2+}]	[LACTATE$^-$]
Normal saline (0.9% NaCl)	154	154	—	—	—
Half-normal saline (0.45% NaCl)	77	77	—	—	—
0.2 normal saline (0.2% NaCl)	34	34	—	—	—
Ringer lactate	130	109	4	3	28

*Electrolyte concentrations in mEq/L.

than maintenance fluids. Children with meningitis are fluid restricted unless intravascular volume depletion is present (see Chapter 643.1). Treatment is individualized, and careful monitoring is critical.

In children with complicated pathophysiologic derangements, it may be necessary to adjust empirically the electrolyte composition and rate of maintenance fluids on the basis of electrolyte measurements and assessment of fluid balance. In all children it is critical to monitor weight, urine output, and electrolytes carefully to identify overhydration or underhydration, hyponatremia, and other electrolyte disturbances, and then adjust the rate or composition of the IV solution accordingly.

VARIATIONS IN MAINTENANCE WATER AND ELECTROLYTES

The calculation of maintenance water is based on standard assumptions regarding water losses. In some patients, however, these assumptions are incorrect. To identify such situations, it is helpful to understand the source and magnitude of normal water losses. Table 74.5 lists the three sources of normal water loss.

Urine is the most important contributor to normal water loss. Insensible losses represent approximately one third of total maintenance water (40% in infants; 25% in adolescents and adults). Insensible losses are composed of evaporative losses from the skin and lungs that cannot be quantitated. The evaporative losses from the skin *do not* include sweat, which would be considered an additional (sensible) source of water loss. Stool normally represents a minor source of water loss.

Maintenance water and electrolyte needs may be increased or decreased, depending on the clinical situation. This may be obvious, as in the infant with profuse diarrhea, or subtle, as in the patient who has decreased insensible losses while receiving mechanical ventilation. It is helpful to consider the sources of normal water and electrolyte losses and to determine whether any of these sources is being modified in a specific patient. It is then necessary to adjust maintenance water and electrolyte calculations.

Table 74.6 lists a variety of clinical situations that modify normal water and electrolyte losses. The skin can be a source of very significant water loss, particularly in neonates, especially premature infants, who are under radiant warmers or are receiving phototherapy. Very low birthweight infants can have insensible losses of 100-200 mL/kg/24 hr. Burns can result in massive losses of water and electrolytes, and there are specific guidelines for fluid management in children with burns (see Chapter 89). Sweat losses of water and electrolytes, especially in a warm climate, can also be significant. Children with cystic fibrosis and some children with pseudohypoaldosteronism have increased sodium losses from the skin.

Fever increases evaporative losses from the skin. These losses are somewhat predictable, leading to a 10–15% increase in maintenance water needs for each 1°C (1.8°F) increase in temperature above 38°C (100.4°F). These guidelines are for a patient with a persistent fever; a 1-hour fever spike does not cause an appreciable increase in water needs.

Tachypnea or a tracheostomy increases evaporative losses from the lungs. A humidified system (nasal cannula, mask, ventilator) causes a decrease in insensible losses from the lungs and can even lead to water absorption via the lungs; a ventilated patient has a decrease in maintenance water requirements. It may be difficult to quantify the changes that take place in the individual patient in these situations.

Table 74.5 Sources of Water Loss

- Urine: 60%
- Insensible losses: ≈35% (skin and lungs)
- Stool: 5%

REPLACEMENT FLUIDS

The gastrointestinal (GI) tract is potentially a source of considerable water loss. GI water losses are accompanied by electrolytes and thus may cause disturbances in intravascular volume and electrolyte concentrations. GI losses are often associated with loss of potassium, leading to hypokalemia. Because of the high bicarbonate concentration in stool, children with diarrhea usually have a **metabolic acidosis**, which may be accentuated if volume depletion causes hypoperfusion and a concurrent lactic acidosis. Emesis or losses from an NG tube can cause a **metabolic alkalosis** (see Chapter 73).

In the absence of vomiting, diarrhea, or NG drainage, GI losses of water and electrolytes are usually quite small. All GI losses are considered excessive, and the increase in the water requirement is equal to the volume of fluid losses. Because GI water and electrolyte losses can be precisely measured, an appropriate replacement solution can be used.

It is impossible to predict the losses for the next 24 hours; it is better to replace excessive GI losses as they occur. The child should receive an appropriate maintenance fluid that does not consider the GI losses. The losses should then be replaced after they occur, with use of a solution with a similar electrolyte concentration as the GI fluid. The losses are usually replaced every 1-6 hours, depending on the rate of loss, with very rapid losses being replaced more frequently.

Diarrhea is a common cause of fluid loss in children and can result in dehydration and electrolyte disorders. In the unusual patient with significant diarrhea and a limited ability to take oral fluid, it is important to have a plan for replacing excessive stool losses. The volume of stool should be measured, and an equal volume of replacement solution should be given. Data are available on the average electrolyte composition of diarrhea in children (see Table 74.7). With this information, an appropriate replacement solution can be designed. The solution shown in Table 74.7 replaces stool losses of Na^+, K^+, chloride (Cl^-), and bicarbonate. Each 1 mL of stool should be replaced by 1 mL of this solution. The average electrolyte composition of diarrhea is just an average, and there may be considerable variation. It is therefore advisable to consider measuring the electrolyte composition of a patient's diarrhea if the amount is especially excessive or if the patient's serum electrolyte levels are problematic.

Loss of gastric fluid, through emesis or NG suction, is also likely to cause dehydration, in that most patients with either condition have impaired oral intake of fluids. Electrolyte disturbances, particularly hypokalemia and metabolic alkalosis, are also common. These complications can be avoided by judicious use of a replacement solution. The composition of gastric fluid shown in Table 74.8 is the basis for designing a replacement solution.

Table 74.6 Adjustments in Maintenance Water

SOURCE	CAUSES OF INCREASED WATER NEEDS	CAUSES OF DECREASED WATER NEEDS
Skin	Radiant warmer	Incubator (premature infant)
	Phototherapy	
	Fever	
	Sweat	
	Burns	
Lungs	Tachypnea	Humidified system (nasal cannula, mask, ventilator)
	Tracheostomy	
Gastrointestinal tract	Diarrhea	—
	Emesis	
	Nasogastric suction	
Renal	Polyuria	Oliguria/anuria
Miscellaneous	Surgical drain	—
	Third spacing	

Table 74.7 Replacement Fluid for Diarrhea

AVERAGE COMPOSITION OF DIARRHEA
Sodium: 55 mEq/L
Potassium: 25 mEq/L
Bicarbonate: 15 mEq/L
APPROACH TO REPLACEMENT OF ONGOING LOSSES
Solution: D5 1/2NS + 30 mEq/L sodium bicarbonate + 20 mEq/L KCl
Replace stool mL/mL every 1-6 hr

D5, 5% dextrose; NS, normal saline.

Table 74.8 Replacement Fluid for Emesis or Nasogastric Losses

AVERAGE COMPOSITION OF GASTRIC FLUID
Sodium: 60 mEq/L
Potassium: 10 mEq/L
Chloride: 90 mEq/L
APPROACH TO REPLACEMENT OF ONGOING LOSSES
Solution: normal saline + 10 mEq/L KCl
Replace output mL/mL every 1-6 hr

Patients with gastric losses frequently have hypokalemia, although the K^+ concentration of gastric fluid is relatively low. The associated urinary K^+ loss is an important cause of hypokalemia in this situation (see Chapter 73). These patients may need additional potassium either in their maintenance fluids or in their replacement fluids to compensate for prior or ongoing urinary losses. Restoration of the patient's intravascular volume, by decreasing aldosterone synthesis, lessens the urinary K^+ losses.

Urine output is normally the largest cause of water loss. Diseases such as renal failure and syndrome of inappropriate ADH secretion can lead to a decrease in urine volume. The patient with oliguria or anuria has a decreased need for water and electrolytes; continuation of maintenance fluids produces fluid overload. In contrast, postobstructive diuresis, the polyuric phase of acute tubular necrosis, diabetes mellitus, and diabetes insipidus increase urine production. To prevent dehydration, the patient must receive more than standard maintenance fluids when urine output is excessive. The electrolyte losses in patients with polyuria are variable. In diabetes insipidus, the urine electrolyte concentration is usually low, whereas children with diseases such as juvenile nephronophthisis and obstructive uropathy usually have increased losses of both water and sodium.

Table 74.9 Adjusting Fluid Therapy for Altered Renal Output

OLIGURIA/ANURIA
Replacement of insensible fluid losses (25–40% of maintenance) with D5 1/2NS
Replace urine output mL/mL with D5 1/2NS ± KCl
POLYURIA
Replacement of insensible fluid losses (25–40% of maintenance) with D5 1/2NS ± KCl
Measure urine electrolytes
Replace urine output mL/mL with solution based on measured urine electrolytes

D5, 5% dextrose; NS, normal saline.

The approach to decreased or increased urine output is similar (Table 74.9). The patient receives fluids at a rate to replace insensible losses. This is accomplished by a rate of fluid administration that is 25–40% of the normal maintenance rate, depending on the patient's age. Replacing insensible losses in the anuric child will theoretically maintain an even fluid balance, with the caveat that 25–40% of the normal maintenance rate is only an estimate of insensible losses. In the individual patient, this rate is adjusted on the basis of monitoring of the patient's weight and volume status. Most children with renal insufficiency receive little or no potassium because the kidney is the principal site of K^+ excretion.

For the **oliguric** child, it is important to add a urine replacement solution to prevent dehydration. This issue is especially important in the patient with acute kidney injury, in whom output may increase, potentially leading to volume depletion and worsening of kidney injury if the patient remains on only insensible fluids. A replacement solution of D5 1/2NS is usually appropriate initially, although its composition may have to be adjusted if urine output increases significantly.

Most children with **polyuria** (except in diabetes mellitus; see Chapter 629) should be started on replacement of insensible fluid plus urine losses. This approach avoids the need to attempt to calculate the volume of urine output that is "normal" so that the patient can be given

replacement fluid for the excess. In these patients, urine output is, by definition, excessive, and it is often helpful to measure Na^+ and K^+ concentrations of the urine to help in formulating the urine replacement solution.

Surgical drains and chest tubes can produce measurable fluid output. These fluid losses should be replaced when they are significant. They can be measured and replaced with an appropriate solution. **Third space losses**, which manifest as edema and ascites, are caused by a shift of fluid from the intravascular space into the interstitial space. Although these losses cannot be quantitated easily, third space losses can be large and may lead to intravascular volume depletion, despite the patient's weight gain. Replacement of third space fluid is empirical but should be anticipated in patients who are at risk, such as children who have burns or abdominal surgery. Third space losses and chest tube output are isotonic, so they usually require replacement with an isotonic fluid, such as NS or LR. Adjustments in the amount of replacement fluid for third space losses are based on continuing assessment of the patient's intravascular volume status. Protein losses from chest tube drainage can be significant, occasionally necessitating that 5% albumin be used as a replacement solution.

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Chapter 75

Deficit Therapy

Larry A. Greenbaum

Dehydration, most often caused by gastroenteritis, is a common problem in children. Most cases can be managed with oral rehydration (see Chapter 387). *Even children with mild to moderate hyponatremic or hypernatremic dehydration can be managed with oral rehydration.*

CLINICAL MANIFESTATIONS

The first step in caring for the child with dehydration is to assess the degree of dehydration (Table 75.1), which dictates both the urgency of the situation and the volume of fluid needed for rehydration. The infant with mild dehydration (3–5% of body weight dehydrated) has few clinical signs or symptoms. The infant may be thirsty; the alert parent may notice a decline in urine output. The history is most helpful. The infant with moderate dehydration has clear physical signs and symptoms. Intravascular volume depletion is evident from an increased heart rate and reduced urine output. This patient needs fairly prompt intervention. The infant with severe dehydration is gravely ill. The decrease in blood pressure indicates that vital organs may be receiving inadequate perfusion. Immediate and aggressive intervention is necessary. If possible, the child with severe dehydration should initially receive intravenous (IV) therapy. For older children and adults, mild, moderate, or severe dehydration represents a lower percentage of body weight lost. This difference occurs because water accounts for a higher percentage of body weight in infants (see Chapter 73).

Table 75.1 Clinical Evaluation of Dehydration

Mild dehydration (<5% in an infant; <3% in an older child or adult): Normal or increased pulse; decreased urine output; thirsty; normal physical findings
Moderate dehydration (5–10% in an infant; 3–6% in an older child or adult): Tachycardia; little or no urine output; irritable/lethargic; sunken eyes and fontanel; decreased tears; dry mucous membranes; mild delay in elasticity (skin turgor); delayed capillary refill (>1.5 sec); cool and pale
Severe dehydration (>10% in an infant; >6% in an older child or adult): Peripheral pulses either rapid and weak or absent; decreased blood pressure; no urine output; very sunken eyes and fontanel; no tears; parched mucous membranes; delayed elasticity (poor skin turgor); very delayed capillary refill (>3 sec); cold and mottled; limp, depressed consciousness

Clinical assessment of dehydration is only an estimate; thus the patient must be continually reevaluated during therapy. The degree of dehydration is underestimated in hypernatremic dehydration because the movement of water from the intracellular space (ICS) to the extracellular space (ECS) helps preserve the intravascular volume.

The history usually suggests the etiology of the dehydration and may predict whether the patient will have a normal sodium concentration (isotonic dehydration), hyponatremic dehydration, or hypernatremic dehydration. The neonate with dehydration caused by poor intake of breast milk often has hypernatremic dehydration. **Hypernatremic dehydration** is likely in any child with losses of hypotonic fluid and poor water intake, as may occur with diarrhea, and poor oral intake because of anorexia or emesis. **Hyponatremic dehydration** occurs in the child with diarrhea who is taking in large quantities of low-salt fluid, such as water or formula.

Some children with dehydration are appropriately thirsty, but in others the lack of intake is part of the pathophysiology of the dehydration. Even though decreased urine output is present in most children with dehydration, good urine output may be deceptively present if a child has an underlying renal defect, such as diabetes insipidus or a salt-wasting nephropathy, or in infants with hypernatremic dehydration.

Physical examination findings are usually proportional to the degree of dehydration. Parents may be helpful in assessment of the child for the presence of sunken eyes, because this finding may be subtle. Pinching and gently twisting the skin of the abdominal or thoracic wall detects tenting of the skin (turgor, elasticity). Tented skin remains in a pinched position rather than springing quickly back to normal. It is difficult to properly assess tenting of the skin in premature infants or severely malnourished children. Activation of the sympathetic nervous system causes **tachycardia** in children with intravascular volume depletion; diaphoresis may also be present. Postural changes in blood pressure are often helpful for evaluating and assessing the response to therapy in children with dehydration. **Tachypnea** in children with dehydration may be present secondary to a metabolic acidosis from stool losses of bicarbonate or lactic acidosis from shock (see Chapter 85).

LABORATORY FINDINGS

Several laboratory findings are useful for evaluating the child with dehydration. The serum sodium concentration determines the type of dehydration. **Metabolic acidosis** may be a result of stool bicarbonate losses in children with diarrhea, secondary **acute kidney injury** (see Chapter 572.1), or lactic acidosis from shock. The anion gap is useful for differentiating among the various causes of a metabolic acidosis (see Chapter 73). Emesis or nasogastric losses usually cause a **metabolic alkalosis**. The serum potassium (K^+) concentration may be low as a result of diarrheal losses. In children with dehydration as a result of emesis, gastric K^+ losses, metabolic alkalosis, and urinary K^+ losses all contribute to hypokalemia. Metabolic acidosis, which causes a shift of K^+ out of cells, and acute kidney injury may lead to hyperkalemia. A combination of mechanisms may be present; thus it may be difficult to predict the child's acid-base status or serum K^+ level from the history alone.

The blood urea nitrogen (BUN) value and serum creatinine concentration are useful in assessing the child with dehydration. Volume depletion without parenchymal kidney injury may cause a disproportionate increase in the BUN with little or no change in the creatinine concentration. This condition is secondary to increased passive resorption of urea in the proximal tubule as a result of appropriate renal conservation of sodium and water. The increase in the BUN with moderate or severe dehydration may be absent or blunted in the child with poor protein intake, because urea production depends on protein degradation. The BUN may be disproportionately increased in the child with increased urea production, as occurs with a gastrointestinal bleed or

with the use of glucocorticoids, which increase catabolism. A significant elevation of the creatinine concentration suggests acute kidney injury, although a small, transient increase can occur with dehydration. Decreased kidney perfusion is the most common etiology of acute kidney injury in a child with volume depletion, but occasionally the child may have previously undetected chronic kidney disease or an alternative explanation for the acute kidney injury. **Renal vein thrombosis** is a well-described sequela of severe dehydration in infants; findings may include thrombocytopenia and hematuria (see Chapter 562.2).

Hemoconcentration from dehydration causes increases in hematocrit, hemoglobin, and serum proteins. These values normalize with rehydration. A normal hemoglobin concentration during acute dehydration may mask an underlying anemia. A decreased albumin level in a dehydrated patient suggests a chronic disease, such as malnutrition, nephrotic syndrome, or liver disease, or an acute process, such as capillary leak. An acute or chronic protein-losing enteropathy may also cause a low serum albumin concentration.

CALCULATION OF THE FLUID DEFICIT

Determining the fluid deficit necessitates clinical determination of the percentage of dehydration and multiplication of this percentage by the patient's weight; a child who weighs 10 kg and is 10% dehydrated has a fluid deficit of 1 L.

APPROACH TO SEVERE DEHYDRATION

The child with dehydration needs acute intervention to ensure that there is adequate tissue perfusion. This resuscitation phase requires rapid restoration of the circulating intravascular volume and treatment of **shock** with an isotonic solution, such as normal saline (NS), Ringer lactate (lactated Ringer solution, LR), or Plasma-Lyte (see Chapter 85). The child is given a fluid bolus, usually 20 mL/kg of the isotonic fluid, over approximately 20 minutes. The child with severe dehydration may require multiple fluid boluses and may need to receive the boluses as fast as possible. In a child with a known or probable *metabolic alkalosis* (e.g., child with isolated vomiting), LR or Plasma-Lyte should not be used because the lactate or acetate would worsen the alkalosis. However, LR or Plasma-Lyte may be preferable to NS in shock since it is a balanced solution (see Chapters 74 and 85); NS may cause a hyperchloremic metabolic acidosis.

Colloids, such as blood, 5% albumin, and plasma, are rarely needed for fluid boluses. A crystalloid solution (NS or LR) is satisfactory, with both lower risk of infection and lower cost. Blood is obviously indicated in the child with significant anemia or acute blood loss. Plasma is useful for children with a coagulopathy. The child with hypoalbuminemia may benefit from 5% albumin, although there is evidence that albumin infusions increase mortality in adults. The volume and the infusion rate for colloids are generally modified compared with crystalloids (see Chapter 522).

The initial resuscitation and rehydration phase is complete when the child has an adequate intravascular volume. Typically, the child shows clinical improvement, including a lower heart rate, normalization of blood pressure, improved perfusion, better urine output, and a more alert affect.

With adequate intravascular volume, it is appropriate to plan the fluid therapy for the next 24 hours. A general approach is outlined in Table 75.2, with the caveat that there are many different approaches to correcting dehydration. A balanced solution can be substituted for NS. In isonatremic or hyponatremic dehydration, the entire fluid deficit is corrected over 24 hours; a slower approach is used for hypernatremic dehydration (discussed later). The volume of isotonic fluids that the patient has received is subtracted from this total. The remaining fluid volume is then administered over 24 hours. The potassium concentration may need to be decreased or, less frequently, increased, depending on the clinical situation. Potassium is not usually included in the IV fluids until the patient voids and normal renal function is documented by measurement of BUN and creatinine. Children with significant ongoing losses need to receive an appropriate replacement solution (see Chapter 74).

MONITORING AND ADJUSTING THERAPY

The formulation of a plan for correcting a child's dehydration is only the beginning of management. *All calculations in fluid therapy are only approximations.* This statement is especially true for the assessment of percentage dehydration. It is equally important to monitor the patient during treatment and to modify therapy on the basis of the clinical situation. Table 75.3 lists the cornerstones of patient monitoring. The patient's vital signs are useful indicators of intravascular volume status. The child with decreased blood pressure and an increased heart rate will probably benefit from a fluid bolus.

The patient's intake and output are critically important in the dehydrated child. The child who, after 8 hours of therapy, has more output than input because of continuing diarrhea needs to be started on a replacement solution. See the guidelines in Chapter 74 for selecting an appropriate replacement solution. Urine output is useful for evaluating the success of therapy. Good urine output indicates that rehydration has been successful.

Signs of dehydration on physical examination suggest the need for continued rehydration. Signs of fluid overload, such as edema and pulmonary congestion, are present in the child who is overhydrated. An accurate daily weight measurement is critical for the management of the dehydrated child. There should be a gain in weight during successful therapy.

Measurement of serum electrolyte levels at least daily is appropriate for any child who is receiving IV rehydration. Such a child is at risk for sodium, potassium, and acid-base disorders. It is always important to look at trends. For example, a sodium concentration ($[Na^+]$) of 144 mEq/L is normal; but if the $[Na^+]$ was 136 mEq/L 12 hours earlier, there is a distinct risk that the child will be hypernatremic in 12 or 24 hours. It is advisable to be proactive in adjusting fluid therapy.

Both hypokalemia and hyperkalemia are potentially serious (see Chapter 73). Because dehydration can be associated with acute kidney injury and hyperkalemia, potassium is withheld from IV fluids until the patient has voided. The potassium concentration in the patient's IV fluids is not rigidly prescribed. Rather, the patient's serum K^+ level and underlying kidney function are used to modify potassium delivery. The patient with an elevated creatinine value and K^+ level of 5 mEq/L does not receive any potassium until the serum K^+ level decreases.

Table 75.2 Fluid Management of Dehydration

1. Restore intravascular volume
   Isotonic fluid (NS or LR): 20 mL/kg over 20 min
   Repeat as needed
2. Calculate 24 hr fluid needs: maintenance + deficit volume
3. Subtract isotonic fluid already administered from 24 hr fluid needs
4. Administer remaining volume over 24 hr using 5% dextrose NS + 20 mEq/L KCl
5. Replace ongoing losses as they occur

LR, Ringer lactate; NS, normal saline.

Table 75.3 Monitoring Therapy

- Vital signs
  - Pulse
  - Blood pressure
- Intake and output
  - Fluid balance
  - Urine output
- Physical examination
  - Weight
  - Clinical signs of depletion or overload
- Electrolytes

Conversely, the patient with a K^+ level of 2.5 mEq/L may require additional potassium.

Metabolic acidosis can be quite severe in dehydrated children. Although normal kidneys eventually correct this problem, a child with renal dysfunction may be unable to correct a metabolic acidosis, and a portion of the patient's IV sodium chloride may have to be replaced with sodium bicarbonate, sodium lactate (as in LR), or sodium acetate.

The serum K^+ level is modified by the patient's acid-base status. Acidosis increases serum K^+ by causing intracellular K^+ to move into the ECS. Thus, as acidosis is corrected, the serum potassium concentration ($[K^+]$) decreases. Again, it is best to anticipate this problem and to monitor the serum $[K^+]$ and adjust potassium administration appropriately.

HYPONATREMIC DEHYDRATION

The pathogenesis of hyponatremic dehydration usually involves a combination of sodium and water loss and water retention to compensate for the volume depletion. The patient has a pathologic increase in fluid loss, and the lost fluid contains sodium. Most fluid that is lost has a lower sodium concentration, so patients with only fluid loss would have hypernatremia. Diarrhea has, on average, a sodium concentration of 50 mEq/L. Replacing diarrheal fluid with water, which has almost no sodium, causes a reduction in the serum $[Na^+]$ (see Chapter 74). The volume depletion stimulates synthesis of antidiuretic hormone, resulting in reduced renal water excretion. Therefore the body's usual mechanism for preventing hyponatremia, renal water excretion, is blocked. The risk of hyponatremia is further increased if the volume depletion is a result of loss of fluid with a higher sodium concentration, as may occur with renal salt wasting, third space losses, or diarrhea with high sodium content (cholera).

The initial goal in treating hyponatremia is correction of intravascular volume depletion with isotonic fluid. An overly rapid (>8-10 mEq/L over the first 24 hours) or overcorrection in the serum $[Na^+]$ (>135 mEq/L) is associated with an increased risk of **osmotic demyelination syndrome** (formerly *central pontine myelinolysis*) (see Chapter 73). Most patients with hyponatremic dehydration do well with the same basic strategy outlined in Table 75.2. Again, K^+ delivery is adjusted according to the initial serum K^+ level and the patient's renal function. Potassium is not given until the patient voids.

The patient's $[Na^+]$ is monitored closely to ensure appropriate correction, and the sodium concentration of the fluid is adjusted accordingly. Patients with ongoing losses require an appropriate replacement solution (see Chapter 74). Patients with neurologic symptoms (seizures) as a result of hyponatremia need to receive an acute infusion of hypertonic (3%) saline to increase the serum $[Na^+]$ rapidly (see Chapter 73).

HYPERNATREMIC DEHYDRATION

Hypernatremic dehydration is the most dangerous form of dehydration because of complications of hypernatremia itself and of its therapy. Hypernatremia can cause serious neurologic damage, including central nervous system hemorrhages and thrombosis. This damage appears to be secondary to the movement of water from the brain cells into the hypertonic extracellular fluid (ECF), causing brain cell shrinkage and tearing blood vessels within the brain (see Chapter 73).

The movement of water from the ICS to the ECS during hypernatremic dehydration partially protects the intravascular volume. Unfortunately, because the initial manifestations are milder, children with hypernatremic dehydration are often brought for medical attention with more profound dehydration.

Children with hypernatremic dehydration are often lethargic, and they may be irritable when touched. Hypernatremia may cause fever, hypertonicity, and hyperreflexia. More severe neurologic symptoms may develop if cerebral bleeding or thrombosis occurs.

Overly rapid treatment of hypernatremic dehydration may cause significant morbidity and mortality. **Idiogenic osmoles** are generated within the brain during the development of hypernatremia; they increase the osmolality within the cells of the brain, providing protection against brain cell shrinkage caused by movement of water out of the cells and into the hypertonic ECF. Idiogenic osmoles dissipate slowly during the correction of hypernatremia. With overly rapid lowering of the extracellular osmolality during the correction of hypernatremia, an osmotic gradient may be created that causes water movement from the ECS into the cells of the brain, producing cerebral edema. Symptoms of the resultant cerebral edema can range from seizures to brain herniation and death.

To minimize the risk of **cerebral edema** during the correction of hypernatremic dehydration, *the serum sodium concentration should not decrease by >10 mEq/L every 24 hours.* The deficits in severe hypernatremic dehydration may need to be corrected over 2-4 days (Fig. 75.1).

The initial resuscitation of hypernatremic dehydration requires restoration of the intravascular volume with NS. LR should not be used because it is more hypotonic than NS and may cause too rapid a decrease in the serum $[Na^+]$, especially if multiple fluid boluses are necessary.

To avoid cerebral edema during correction of hypernatremic dehydration, the fluid deficit is corrected slowly. The rate of correction depends on the initial sodium concentration (see Fig. 75.1). There is no general agreement on the choice or the rate of fluid administration for correcting hypernatremic dehydration; these factors are not nearly as important as vigilant monitoring of the serum $[Na^+]$ and adjustment of the therapy according to the result. The rate of decrease of the serum $[Na^+]$ is roughly related to the "free water" delivery, although there is considerable variation between patients. Free water is water without sodium. NS contains no free water, half-normal saline (½ NS) is 50% free water, and water is 100% free water. Smaller patients, to achieve the same decrease in the sodium concentration, tend to need higher amounts of free water delivery per kilogram because of **higher insensible fluid losses**. Five percent dextrose (D5) with ½ NS is usually an appropriate starting solution for correction of a patient with hypernatremic dehydration. Some patients, especially infants with ongoing high insensible water losses, may rarely need to receive D5 0.2NS, which should be used with great caution and constant monitoring. Others require D5 NS. A child with dehydration as a result of pure free water loss, as usually occurs with diabetes insipidus, usually needs a more hypotonic fluid than a child with depletion of both sodium and water from diarrhea.

Adjustment in the sodium concentration of the IV fluid is the most common approach to modify the rate of decrease in the serum concentration (see Fig. 75.1). For difficult-to-manage patients with severe hypernatremia, having two IV solutions (e.g., D5 ½ NS and D5 NS, both with the same concentration of potassium) at the bedside can facilitate this approach by allowing for rapid adjustments of the rates of the two fluids. If the serum $[Na^+]$ decreases too rapidly, the rate of D5 NS can be increased and the rate of D5 ½ NS can be decreased by the same amount. Adjustment in the total rate of fluid delivery is another approach to modifying free water delivery. For example, if the serum $[Na^+]$ is decreasing too slowly, the rate of a hypotonic IV fluid can be increased, thereby increasing the delivery of free water. There is limited flexibility in modifying the rate of the IV fluid because patients generally should receive 1.25-1.5 times the normal maintenance fluid rate. Nevertheless, in some situations, it can be a helpful adjustment.

Because increasing the rate of the IV fluid increases the rate of decline of the sodium concentration, signs of volume depletion are treated with additional isotonic fluid boluses. The serum $[K^+]$ and the level of renal function dictate the potassium concentration of the IV fluid; potassium is withheld until the patient voids. Patients with hypernatremic dehydration need an appropriate replacement solution if they have ongoing, excessive losses (see Chapter 74).

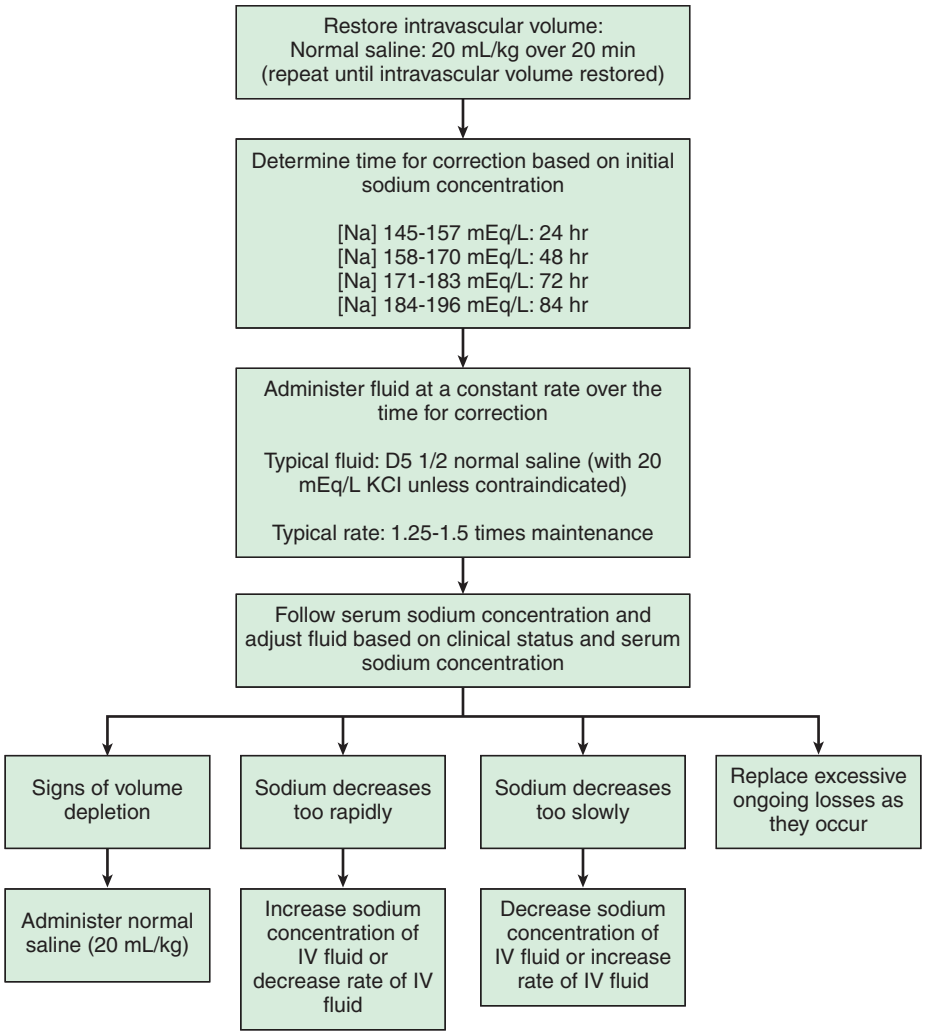

Fig. 75.1 Algorithm for the treatment of hypernatremic dehydration. *(From Londeree JT, Greenbaum LA. Dehydration and replacement therapy. In: Marcdante KJ, Kliegman RM, Schuh AM, eds. Nelson Essentials of Pediatrics, 9th ed. Philadelphia: Elsevier, 2023. Fig 33.1.)*

Seizures and a depressed level of consciousness are the most common manifestations of **cerebral edema** from an overly rapid decrease of the serum [Na^+] during correction of hypernatremic dehydration. Signs of increased intracranial pressure or impending herniation may develop quite rapidly (see Chapter 82). Acutely, increasing the serum [Na^+] through an infusion of 3% sodium chloride can reverse the cerebral edema. Each 1 mL/kg of 3% NaCl increases the serum [Na^+] by approximately 1 mEq/L. An infusion of 4 mL/kg often results in resolution of the symptoms. This strategy is similar to that used for treating symptomatic hyponatremia (see Chapter 73).

Many patients with mild to moderate hypernatremic dehydration as a result of gastroenteritis can be managed with oral rehydration (see Chapter 387). In patients with severe hypernatremia, oral fluids must be used cautiously. Infant formula, because of its low sodium concentration, has a high free water content, and especially if added to IV therapy, it may contribute to a rapid decrease in the serum [Na^+]. Less hypotonic fluid, such as an oral rehydration solution, may be more appropriate initially. If oral intake is allowed, its contribution to free water delivery must be taken into account, and adjustment in the IV fluid is usually appropriate. Judicious monitoring of the serum [Na^+] is critical.

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Chapter 76

Fluid and Electrolyte Treatment of Specific Disorders

ACUTE DIARRHEA

See Chapter 387.

PYLORIC STENOSIS

See Chapter 375.1.

PERIOPERATIVE FLUIDS

See Chapter 91.