Chapter 10
Water, Electrolyte, and Acid-Base Metabolism

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DEFINITIONS

Anion gap—The anion gap is the difference between the measured cations and anions in serum, plasma, or urine. For serum, it is estimated by subtracting the sum of the chloride and bicarbonate anions from the sodium cations and is usually expressed in mmol/L or mEq/L:

$$\left[Na^+\right]-\left(\left[Cl^-\right]+\left[HCO_3^-\right]\right)$$

Bowman space—This is the capsular-shaped space that surrounds the glomerulus at the beginning of the tubular nephron in the kidney. It receives the initial glomerular filtrate.

Effective intravascular volume—This is the proportion of the intravascular volume that is effective in determining the filling pressure of the ventricles and is usually directly related to the central venous pressure. This may not always correlate with the *actual* intravascular volume.

Extracellular fluid—The body fluid that exists outside of cells. It contains approximately one third of the volume of total body water.

Fractional excretion of sodium—This is the amount of sodium excreted in the urine, expressed as a percentage of the sodium that is filtered by the kidney:

$$\%E / F_{Na} = 100\left\{\left(\left[Na^+\right]_{Urine}\left[Cr\right]_{Serum}\right) / \left(\left[Na^+\right]_{Serum}\left[Cr\right]_{Urine}\right)\right\}$$

where $[Na^+]_{Urine}$ is the concentration of sodium in the urine. $[Na^+]_{Serum}$ is the concentration of sodium in the serum, $[Cr]_{Serum}$ is the concentration of creatinine in the serum, and $[Cr]_{Urine}$ is the concentration of creatinine in the urine.

Henderson-Hasselbalch—An equation for calculating the pH of an acid or buffered solution. A modification of this

equation may be used to calculate the pH of blood as follows:

$$pH = pK_{a\,H_2CO_3} + \log\left\{\left[HCO_3^-\right] / \left[k_{HCO_2}\left(PCO_2\right)\right]\right\}$$

where pK_a H_2CO_3 = 6.1, HCO_3^- = concentration of bicarbonate in the blood, kH CO_2 = 0.03 mmol/mm Hg.

Intracellular fluid—The body fluid that exists inside of cells. It contains approximately two thirds of the volume of total body water.

Intravascular volume—This is the same as blood volume and includes intravascular water, as well as plasma, plasma proteins, and other blood products such as red cells.

Metabolic acidosis—Acidosis resulting from increase in acids other than carbonic acid or resulting from

the inability of the body to form bicarbonate in the kidney.

Metabolic alkalosis—Alkalosis in which plasma bicarbonate is increased directly, or indirectly as a result of decreased hydrogen ion concentration.

Oncotic pressure—The osmotic pressure exerted by proteins in solution, usually pulling water into the intravascular space. This is also commonly called the *colloid osmotic pressure.*

Orthostatic hypotension—A decrease in perfusion that is caused by a change from a supine to a standing position. This is generally diagnosed by a decrease in systolic blood pressure of more than 20 mm Hg, or a decrease in diastolic blood pressure of more than 10 mm Hg, and is further suggested by a pulse increase of more than 30 bpm.

Osmotic pressure—The pressure that is needed to prevent water flow between two solutions of different concentrations that are separated by a semipermeable membrane.

Plasma osmolality—The measure of solute per kilogram of plasma. For the purposes of this chapter, this is used interchangeably with plasma *osmolarity,* which is the measure of solute per *liter* of plasma. This can be estimated for normal plasma:

$$P_{OSM} = 2\left[Na^{+}\right] + [glucose] + [urea]$$

Respiratory acidosis—Acidosis secondary to decreased ventilation, usually with a proportionate increase in plasma carbon dioxide.

Respiratory alkalosis—Alkalosis secondary to increased ventilation, usually with a proportionate decrease in plasma carbon dioxide.

Specific gravity—This is the ratio of the density of a substance to the density of water. Under most conditions encountered, this is equal to the *apparent* specific gravity, which is the ratio of the weight of a substance to the weight of an equal volume of water.

Proper management of fluids and electrolytes in the gynecologic surgical patient is of extreme importance. Gynecologic surgical patients can differ in age, baseline nutritional status, and in the complexity of medical problems that they possess. The stresses of surgery and the bodies' complex responses to that stress need to be understood to best care for these patients. The tendency to standardize postoperative care for all patients should be avoided.

This chapter focuses on the clinical aspects of water and electrolyte balance, and an understanding of basic renal physiology is a prerequisite.

CLINICAL ASSESSMENT OF DISORDERS OF WATER AND ELECTROLYTE METABOLISM

Disorders of extracellular fluid (ECF) electrolyte composition may be detected by measurement of the serum electrolyte concentrations. Identification of the process (or processes) behind the disturbance of electrolyte composition and the planning of subsequent therapy are critically dependent on the clinician's ability to accurately assess whether the disturbance in ECF electrolyte composition is associated with volume expansion, volume contraction, or a normal volume.

In the evaluation of a patient's ECF volume status, it must be kept clearly in mind that the critical volume that is effective in determining cardiac output is the effective intravascular volume (IVV). The most effective IVV is that which maintains an optimal cardiac output and thus maximizes tissue perfusion. Although the actual IVV and the effective IVV are the same in many clinical situations and can be expected to change in direct proportion, in a

number of important clinical states, the actual IVV is different from the effective IVV. For example, in acute metabolic acidosis, increased venoconstriction can develop, resulting in an abnormal increase in central venous pressure (CVP) and cardiac output. Under this circumstance, the actual IVV could be less than normal, whereas the effective IVV is greater than normal. Because of the increase in venous tone, an IVV that is lower than normal can maintain a normal effective IVV.

Acute changes in venous tone induced by drugs (e.g., morphine, furosemide, norepinephrine), changes in acid-base status, and the presence of bacterial endotoxin also can disrupt the normal relation between the actual IVV and the effective IVV.

The most reliable clinical means for assessing the status of the effective IVV is the pulmonary capillary wedge pressure. This measurement is an estimate of the pulmonary capillary pressure, which is a measure of the filling pressure of the left ventricle. Factors that increase pulmonary capillary wedge pressure tend to increase cardiac output by increasing capillary outflux. When effective IVV is considered within these constraints, it becomes clear that under virtually any physiologic or pathophysiologic circumstance, an optimal effective IVV is one that results in a pulmonary capillary wedge pressure that is high enough to promote optimal cardiac output but low enough to prevent pulmonary edema.

Fortunately, in most clinical situations, it is not necessary to resort to measuring pulmonary wedge pressure to assess whether a disturbance of ECF composition is associated with an effective IVV that is abnormally high, abnormally low, or normal. Instead, an accurate assessment of the effective IVV usually can be made by a careful clinical assessment using the criteria listed in **Table 10.1**. This table lists the bedside and laboratory means to assess volume status according to whether the findings are consistent with an effective IVV that is less than normal or an effective IVV that is nearly normal or expanded.

Also shown in **Table 10.1** are the conditions under which the given means for evaluating the IVV must be qualified (i.e., the conditions that may render the meaning of the finding indeterminate with respect to the evaluation of IVV). For example, the relation between an increase in weight and a change in IVV is rendered indeterminate if, at the same time, the patient has developed a third space, as in bowel obstruction. In this instance, the entire weight gain could be caused by the accumulation of fluid outside the IVV. Thus, the finding of weight gain in this setting cannot be used as evidence of an increase in effective IVV. Whenever a finding can be significantly qualified,

it should not be used in the assessment of the effective IVV. As many independent means as practical should be used to assess the effective IVV to minimize the effect of possible error on the final decision. The greater the number of independent, unqualified findings that agree in favor of a given clinical decision, the more likely it is that the decision is correct. If such a systematic approach to clinical decision making is used, it should be possible to arrive at an accurate evaluation of volume status in most circumstances.

TABLE 10.1 Assessment of Effective Intravascular Volume

SUGGESTIVE EVIDENCE	QUALIFYING CONDITIONS[a]
Significantly decreased effective IVV	
History of fluid and electrolyte deprivation or loss (e.g., vomiting, diarrhea)	Difficulty in establishing by history whether the magnitude of loss or deprivation is sufficient to result in negative balance of water and electrolytes

Decrease in body weight below normal not explained by inadequate caloric intake	None
Blood pressure less than usual for the patient with orthostatic hypotension	1. The patient receiving methyldopa (Aldomet), prazosin (Minipress), minoxidil (Loniten), or other drugs that interfere with vascular α-receptors 2. Autonomic insufficiency as in diabetics, quadriplegics, and after prolonged bed rest
Elevated serum creatinine associated with concentrated urine (U_{osm}/P_{osm} >1.5) and Na^+ conservation: (U_{Na} <20 mEq/L) or $\%E/F_{Na}$ <1%	Decreased renal perfusion owing to (a) severe hepatic failure (hepatorenal syndrome) and (b) severe cardiac failure. Acute, high-grade urinary tract obstruction (see text)
Low CVP or pulmonary capillary wedge pressure	See text
Decreased tissue turgor	See text
Hematocrit above normal	Presence of conditions that may cause erythrocytosis
Nearly normal or expanded effective IVV (i.e., absence of significant intravascular volume depletion)	
Hypertension with the patient in sitting or standing position and no orthostatic fall in blood pressure	None
Presence of cardiac failure: left ventricular failure: audible third heart sound or pulmonary edema	Patients with markedly reduced cardiac output and very large left ventricles may have decreased effective IVV despite an audible third heart sound
Right ventricular failure: peripheral edema with increased venous pressure (neck vein distention, increased intravenous pressure)	Right ventricular failure but normal left ventricular function (see text)
Increase in weight above normal not explained by increased caloric intake	1. Significant hypoalbuminemia 2. Development of third spaces (e.g., ascites, bowel obstruction)
Increased CVP	See text
Increased pulmonary capillary wedge	See text

	pressure	
	Edema, ascites, or pleural effusion	See text
	Hematocrit less than normal	Presence of conditions that can cause loss, destruction, or decreased production of red blood cells

[a]Qualifying conditions are circumstances that can render the meaning of the finding indeterminate with respect to the evaluation of the effective IVV.
$\%E/F_{Na}$, percentage of excretion of filtered sodium (see text).

DATABASE FOR ASSESSMENT OF EFFECTIVE INTRAVASCULAR VOLUME

Body Weight

All patients should be weighed on admission to the hospital and then periodically during their hospital stay. In patients undergoing surgery, or in whom problems in fluid and electrolyte balance are anticipated, weight must be measured daily.

Alterations in body weight are the result of changes in body water content plus solid tissue content (fat, protein, bone). Gains or losses of solid tissue are almost always related to changes in caloric intake and seldom exceed 0.25 kg/24 hours. For example, a patient who takes no calories for 24 hours is forced to consume her endogenous stores of fat and protein to meet the energy requirements for continued life. The complete oxidation of fat yields 9 cal/g, and protein yields 4 cal/g. It can be readily calculated that the complete oxidation of 0.25 kg of solid tissue (in starvation, a mixture of about 87% fat, 13% protein) yields enough calories to meet basal daily energy needs. Thus, changes in weight exceeding 0.25 kg/24 hours are almost always attributable to changes in water balance. Although the relation between body weight and effective IVV can be variable, usually the relation between changes in body weight and IVV can be correctly assessed by the application of the guidelines. The first is that a decrease in body weight below normal (for the patient), and not explained on the basis of inadequate caloric intake, can be assumed

to be accompanied by a decrease in IVV. The second is that an increase in body weight above normal not explained by increased nutrition can be assumed to be accompanied by an increase in IVV except when the weight gain develops in association with the following conditions:

- Significant hypoalbuminemia: serum albumin less than 2.5 g/dL
- Venous obstruction or congestion
- Development of third spaces (e.g., obstructed or ischemic bowel)

Under these three general conditions, an increase in body weight may not reflect an increase in the effective IVV.

Renal Function

Creatinine, a by-product of muscle energy metabolism, is produced at a constant rate that is related to muscle mass. Nearly all of the creatinine produced is excreted by glomerular filtration. Therefore, changes in the concentration of serum creatinine reflect changes in the glomerular filtration rate (GFR), and the clearance of creatinine is an index of the GFR.

Normally, as muscle mass increases, the GFR increases proportionately less. Therefore, on the average, children have lower serum creatinine values than do adults, and large adults have higher serum creatinine levels than do small adults. Because of these considerations, a single range of serum creatinine values cannot be applied to everyone.

The following guidelines are suggested for the evaluation of the IVV in light of the state of renal function. Azotemia can be assumed to result from decreased renal perfusion if the serum creatinine level is elevated, the urine is concentrated (specific gravity higher than 1.015), and renal sodium conservation is present (urine sodium level <20 mEq/L) on a random and untimed urine sample. If the fractional excretion of sodium is below 1%, azotemia can be attributed to decreased IVV, unless the patient has severe liver or cardiac disease causing end-organ hypoperfusion. If severe cardiac failure and severe liver failure (hepatorenal syndrome) can be excluded, the decreased renal perfusion can be assumed to be caused by a decreased effective IVV.

Edema, Ascites, and Pleural Effusion

Effective IVV is increased when edema, pleural effusion, or ascites occurs in the setting of congestive heart failure (CHF). Increased effective IVV cannot be assumed in the presence of edema, ascites, or pleural effusion if there is significant hypoalbuminemia or venous obstruction or if the accumulation of fluid is in a relatively small area of capillary injury (e.g., pleural effusion caused by pulmonary infarction).

Tissue Turgor

Tissue turgor is a function of the elasticity of the solid components of tissue and the degree of distention of the tissues by interstitial fluid. If tissue is depleted of interstitial fluid, it becomes less elastic (i.e., it less readily returns to its original shape after being deformed). Skin turgor is best assessed on the forehead and anterior chest. In patients less than 50 years of age, the turgor of the dorsum of the hand also can be used. In older patients, the elasticity of the solid components of tissue is decreased, and the turgor of the skin becomes unreliable in interpreting changes in interstitial volume.

Central Venous Pressure

The measurement of CVP is a relatively simple but useful means for monitoring cardiac function and cardiovascular status. For the valid measurement of CVP, the catheter must be placed in the large intrathoracic veins near the right atrium (as assessed by chest radiograph), and the catheter must be patent (as assessed by the cyclic variation of CVP with ventilatory movements: decreased CVP during inspiration, increased CVP during expiration).

In normal adults, CVP is about 5 to 12 cm H_2O. CVPs below 3 cm H_2O are commonly seen in children and young adults who have no evidence of a decreased effective IVV. In older adults and elderly persons, CVP of less than 3 cm H_2O can be assumed to reflect a significant decrease in effective IVV.

Central venous pressure is an index of the filling pressure of the right atrium, which, in turn, is an index of the filling pressure of the right ventricle. In uncomplicated circumstances, expansion of the IVV results in increased CVP, whereas contraction of the IVV results in decreased CVP. Central venous pressure cannot be used to assess the adequacy of left ventricular function in patients in whom left ventricular function may be impaired relative to right ventricular function. Central venous pressure also is unreliable when lung disease is present, because it is commonly falsely elevated. In such patients, left ventricular function can be monitored by observing for signs and symptoms of left ventricular failure (dyspnea, development of an audible third heart sound, or pulmonary edema), or by direct measurement of pulmonary capillary wedge pressure. Under normal circumstances, the pulmonary capillary wedge pressure is about equal to the CVP plus 6 mm Hg.

Pulmonary Capillary Wedge Pressure

Technical refinements of the Swan-Ganz catheter make it possible to measure pulmonary artery systolic and diastolic pressure, CVP, pulmonary wedge pressure, and cardiac output using the thermodilution technique with the same catheter. This permits a definitive assessment of the volume status of the patient, because it can be determined whether the cardiac output is appropriate for a given pulmonary wedge pressure. Specific guidelines for the interpretation of the relation between pulmonary wedge pressure and cardiac output are discussed in the following sections.

Patients with Normal Volume Status

Pulmonary wedge pressure can be expected to be between 8 and 12 mm Hg in a patient with a normal cardiopulmonary system and a normal effective IVV. Cardiac output is normal. Pulmonary wedge pressure can be less than 8 mm Hg without indicating volume contraction; in this circumstance, the cardiac output is normal despite the unusually low pulmonary wedge pressure.

Patients Who Are Volume Contracted

Patients who have a normal cardiopulmonary system but who are significantly volume depleted usually have a pulmonary wedge pressure below 8 mm Hg and their cardiac output is less than normal. In patients with chronic pulmonary hypertension (e.g., those with chronic left ventricular failure), a higher than normal pulmonary wedge pressure is needed to drive a satisfactory cardiac output. Thus, in such patients, pulmonary wedge pressure can be above the normal range but be inappropriately low for the patient. This situation can be identified by showing that: (a) cardiac output is less than normal, despite the elevated pulmonary wedge pressure; (b) volume infusion causes an increase in cardiac output toward a more favorable range; and (c) despite further increase in pulmonary wedge pressure with volume expansion, pulmonary function does not deteriorate. (Pao_2 does not decrease, $PaCO_2$ does not increase, and pulmonary compliance does not worsen.)

Patients Who Are Volume Expanded

In patients with a normal cardiopulmonary system, pulmonary wedge pressure usually is above 18 mm Hg when volume expansion is substantial. Cardiac output is above normal. If cardiac function is impaired, cardiac output will be inappropriately low for the level of pulmonary wedge pressure.

When a given pulmonary wedge pressure is being interpreted, the serum albumin level also should be taken into consideration, because this opposes the effect of capillary hydrostatic pressure to cause migration of fluid from the capillary lumen to the interstitial space. Thus, at any given elevated pulmonary wedge pressure, pulmonary edema develops more rapidly in a patient who is hypoalbuminemic than in one who has a normal serum albumin concentration. In some patients, it is not possible to obtain a reliable pulmonary wedge pressure. In most of these patients, the pulmonary artery diastolic pressure is a good estimate of the pulmonary wedge pressure. If pulmonary hypertension is present, then pulmonary vascular resistance is increased; thus, pulmonary artery diastolic pressure may not be a good index of the pulmonary wedge pressure. In such patients, it is important to be able to obtain a wedge pressure. Finally, in patients who are being ventilated with high levels of positive end-expiratory pressure, pulmonary wedge pressure may become an unreliable index of left atrial filling pressure because the high intrapulmonary pressures may cause obstruction of the catheter orifice. Patients must be briefly taken off the ventilator for accurate measurements. Other circumstances in which pulmonary artery wedge pressure measurements may be inaccurate include the presence of mitral stenosis or pulmonary venous obstruction.

Blood Pressure

The following guidelines are suggested for the evaluation of the effective IVV from measurement of blood pressure.

1. A nearly normal or expanded effective IVV can be assumed in patients with hypertension that is demonstrated in the sitting or standing position.

2. Effective IVV may be decreased in patients who previously were hypertensive but who have become normotensive.

3. Effective IVV may be decreased in patients who develop orthostatic hypotension (a drop in systolic pressure greater than 10 mm Hg in changing from the supine to the sitting or standing position).

Orthostatic hypotension also can be present, in the absence of volume contraction, as a result of prolonged bed rest, during the use of such antihypertensive agents as methyldopa (Aldomet) or of vasodilators (prazosin, minoxidil). If the pulse rate does not rise as blood pressure falls when a patient stands, autonomic neuropathy should be considered as a cause of postural hypotension.

Systemic Vascular Resistance

Normal values are 50 to 150 dyne-s/cm for pulmonary vascular resistance and 800 to 1,200 dyne-s/cm for systemic vascular resistance. Pulmonary vascular resistance is elevated in hypovolemic shock, cardiogenic shock, pulmonary embolism, or airway obstruction; it is diminished in septic shock. Systemic vascular resistance is elevated in hypovolemic shock, cardiogenic shock, pulmonary embolism, and sometimes in right ventricular infarct and cardiac tamponade; it is decreased in end-stage liver disease and septic shock.

CLINICAL ASSESSMENT OF DISORDERS OF EXTRACELLULAR FLUID COMPOSITION

Hyponatremia

The schema for the evaluation of a hyponatremic patient depends on the assessment of volume status. That is, it must first be determined whether the patient's hyponatremia is associated with an effective IVV that is decreased, normal, or increased. Once this is decided on the basis of the assessment of IVV, a further separation, based only on the state of renal sodium and water excretion, is made. Each of the final categories contains relatively few diagnostic possibilities, and the presence or absence of each of these conditions in a given patient usually can be readily determined. The scheme for the evaluation of a hypernatremic patient is analogous, except that it depends on the assessment of the state of renal water excretion.

Clinical Assessment

In the discussion that follows, only patients with true hyponatremia are considered (i.e., hyponatremia in which serum osmolality is decreased in proportion to the reduction in serum sodium concentration, after appropriate correction for any elevation in the plasma urea nitrogen). By making this distinction, hyponatremia caused by accumulation of ECF solutes such as glucose or mannitol can be excluded. In this type of hyponatremia, the decreased concentration of ECF sodium is the result of the shift of water from cells to the ECF in response to the osmotic gradient caused by the accumulation of the solute. As a consequence, the hyponatremia is associated with an increased plasma osmolality. These patients also can be readily identified either by the presence of hyperglycemia sufficient to explain the decrease in serum sodium concentration or by a history of administration of large amounts of mannitol (0.100 g in adults), usually in the presence of a decreased capacity to excrete mannitol (decreased GFR).

Also to be excluded are patients with spurious hyponatremia that results from the abnormal accumulation of plasma lipids or proteins. In such circumstances, the concentration of sodium in plasma water is normal;

however, the concentration of sodium expressed per liter of whole plasma is reduced because an abnormally large volume of whole plasma is occupied by the lipids or proteins, which do not contain plasma water and electrolytes. Thus, when aliquots of hyperlipemic or hyperproteinemic plasma are analyzed, a lower amount of sodium is determined to be present in a given volume of whole plasma. Plasma osmolality, however, is normal because lipids and proteins do not contribute importantly to plasma osmolality (see section on osmotic forces). Patients with spurious hyponatremia can be readily identified by the presence of markedly elevated total serum protein levels (e.g., multiple myeloma) or grossly lipemic serum. The distinction can be readily made if lipemic serum is subjected to centrifugation and the lipoprotein layer is removed before evaluation, if flame photometry is being used for measurement of serum Na^+. Spurious hyponatremia is no longer a consideration in most laboratories, because serum Na^+ concentration is determined by ion-specific electrodes, and increased levels are not affected by lipemic serum. Symptoms of hyponatremia include increased tendon reflexes, lethargy, mental confusion, and muscle twitching, which are followed by convulsions, coma, and possibly death if levels fall below 115 mEq/L.

Hyponatremia and Volume Depletion Associated with Renal Sodium Wasting

The normal renal response to volume depletion and hyponatremia is the virtual elimination of sodium from the urine

(**Fig. 10.1**; see section on sodium balance). Thus, the presence of an excessive amount of urinary sodium under these conditions indicates that renal sodium loss is the cause or a major contributing factor to the state of sodium depletion. A spot urine sodium concentration greater than 40 mEq/L, a $\%E/F^{Na}$ above 1%, or a urinary sodium excretion rate greater than intake indicates such renal sodium wasting. The conditions discussed in the following sections are associated with hyponatremia, IVV depletion, and renal sodium wasting.

Chronic Renal Disease

All types of renal disease can be associated with renal salt wasting. In adults with such a disorder, the serum creatinine level is virtually always above 2 mg and usually much higher before a significant salt leak develops. These azotemic patients usually require 85 to 170 mEq of sodium daily (5 to 10 g of sodium chloride) to maintain salt balance at a normal effective IVV. Thus, if sodium intake is decreased in azotemic patients by anorexia or vomiting, or if additional sodium losses occur (e.g., diarrhea or diuretic therapy), the inability of the diseased kidneys to conserve sodium and water normally may rapidly lead to the development of significant sodium and water deficits. Water intake usually continues; therefore, sodium balance is more adversely affected than is water balance. As a consequence, the patient becomes volume contracted with hyponatremia. With the onset of CHF or the nephrotic syndrome, the salt leak of chronic renal failure usually disappears, and salt intake must be restricted.

Diuretic Therapy

The diuretics include thiazide agents or loop diuretics, such as furosemide, bumetanide, and ethacrynic acid. Diuretics induce a renal salt-wasting state, and if the urinary output of sodium exceeds intake, sodium depletion ensues. Rarely, diuretics cause hyponatremia without evidence of volume depletion if severe potassium depletion has resulted from their use (**Fig. 10.1**).

Adrenal Insufficiency (Addison Disease)

Destruction of the adrenal gland or sudden withdrawal of chronic, daily glucocorticoid therapy results in inadequate adrenal function. The lack of mineralocorticoid causes wasting of renal salt but retention of renal potassium and leads to sodium depletion. The lack of glucocorticoid results in a decreased capacity to excrete a

water load and leads to hyponatremia but not to volume depletion or hyperkalemia.

Hyponatremia and Volume Depletion Associated with Renal Sodium Conservation

A spot urine sodium concentration of less than 20 mEq/L or a $\%E/F_{Na}$ below 1% in a hyponatremic, volume-contracted patient is evidence of normal renal sodium conservation and indicates that the cause of the sodium depletion is nonrenal in origin or that it occurred during previous diuretic therapy. The fact that the serum sodium concentration is lower than normal indicates that water balance is less negative than is sodium

balance. The conditions discussed in the following sections can result in volume depletion and hyponatremia as a result of extrarenal losses of sodium.

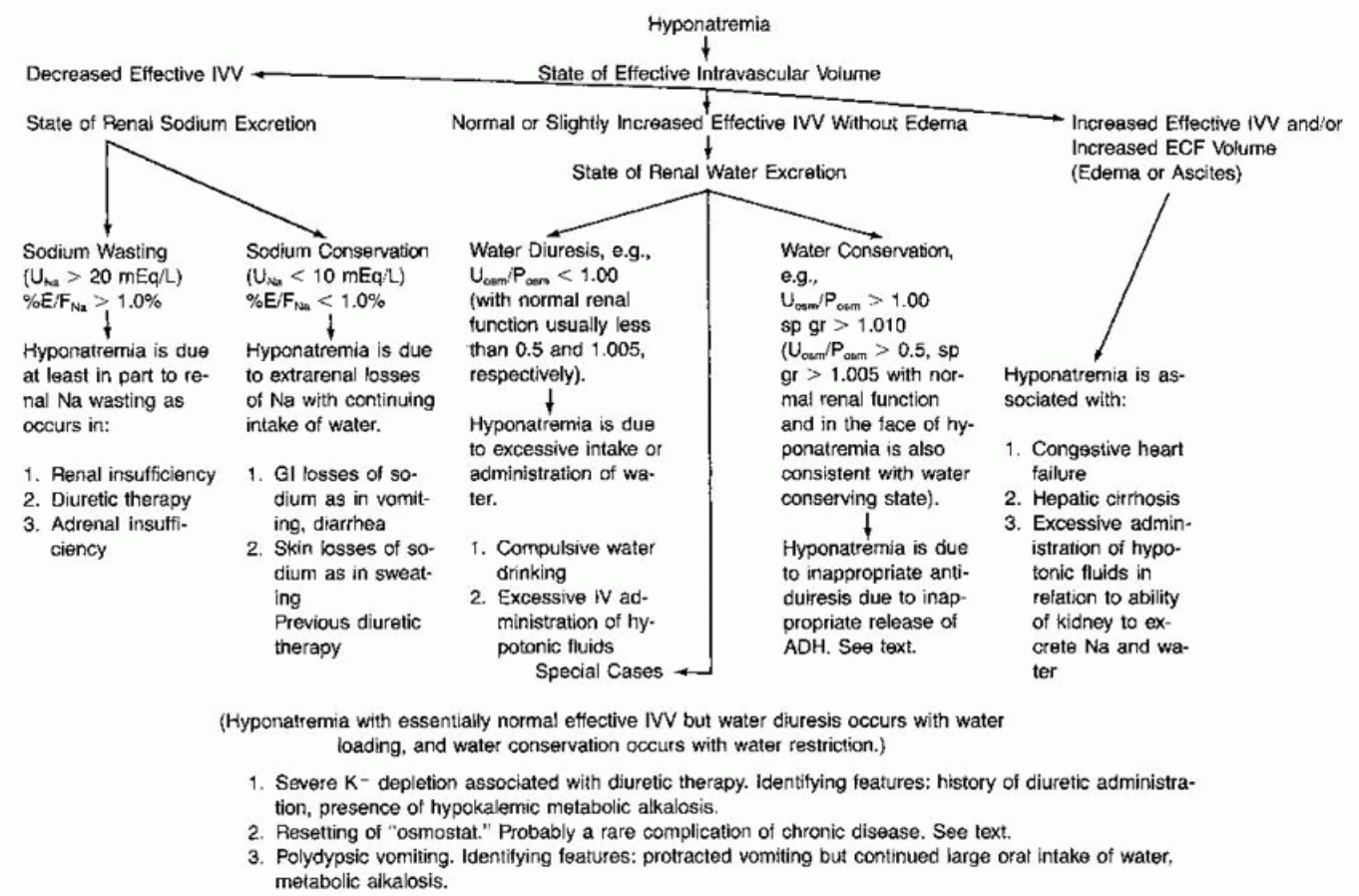

FIGURE 10.1 Approach to the assessment of a hyponatremic patient.This approach considers only patients with true hyponatremia (i.e., in nonazotemic patients, serum osmolality is reduced in proportion to the decrease in serum sodium). Thus, patients are excluded who have lowered concentrations of serum sodium because of hyperlipidemia, hyperproteinemia, or the abnormal accumulations of solutes in the extracellular fluid (ECF), such as glucose or mannitol. ADH, antidiuretic hormone; ECT, extracellular fluid; $\%E/F_{Na}$, fractional excretion of sodium; GI, gastrointestinal; IVV, intravascular volume.

Gastrointestinal Losses

If losses of fluid from the upper gastrointestinal tract (e.g., vomiting, gastric aspiration) cause the hyponatremia, and if the gastric juice is normally acid, metabolic alkalosis is present. If diarrheal losses cause the hyponatremia, metabolic acidosis may be present. In patients with gastric achlorhydria, upper gastrointestinal losses also can lead to metabolic acidosis.

Losses of Sodium from the Skin

Sweat contains about 50 mEq/L of sodium and is a hypotonic fluid. If sweat losses are not replaced, then

hypernatremia can develop. In most situations, the water losses from the skin are replaced more adequately than are the sodium losses. Thus, most patients with significant sodium losses that are due to sweating become hyponatremic. Skin losses of fluid and electrolytes also can occur after burns or other skin injuries. These are isotonic losses of sodium and lead to hyponatremia if the water losses are more adequately replaced than are the sodium losses.

Losses of Sodium from Prior Diuretic Therapy

The natriuretic action of most diuretics lasts less than 24 hours. Hyponatremia is made worse if water intake is excessive.

Hyponatremia and Normal Volume Status Associated with Water Diuresis

In a patient with normal renal function who has become hyponatremic as a result of the administration or ingestion of excessive amounts of water, intravascular and ECF volume are normal to slightly expanded, and high rates of urine flow in association with maximally, or nearly maximally, dilute urine can be expected. In a patient with preexisting renal functional impairment, water loading also increases urine flow rate and dilution of the urine; however, maximally dilute urine cannot be formed. Hyponatremia secondary to water loading may occur in compulsive water drinkers, who usually are severely neurotic or psychotic, or after excessive IV administration of hypotonic fluids. Many of these patients also have high levels of antidiuretic hormone (ADH) for various reasons (e.g., drugs, psychosis). Without this elevation of ADH, presuming normal renal function, consumption of 20 L of water a day would be necessary for development of frank hyponatremia.

Hyponatremia and Normal to Slightly Elevated Volume Status Associated with Water Conservation

As discussed, it is appropriate to observe a brisk water diuresis in a patient with normal renal function who is hyponatremic and has evidence of normal or slightly elevated IVV without edema. When high flow rates of hypotonic urine are not observed, the patient is exhibiting an inappropriate antidiuresis. This may result from the inappropriate release of ADH, although other mechanisms also can be involved (e.g., decreased renal blood flow, certain drugs). Another characteristic of such patients is that administered sodium is promptly excreted in the urine, perhaps because of the effect of atrial natriuretic factors. On the other hand, when sodium intake is curtailed, renal sodium conservation is observed. These patients also exhibit normal adrenal and renal function and are not edematous. The syndrome of inappropriate antidiuresis has been associated with various clinical states, including malignant tumors (e.g., in the lung or pancreas), central nervous system (CNS) disorders (e.g., head trauma, meningitis), infections (e.g., tuberculosis, bacterial pneumonias), the postoperative state, hypopituitarism, and myxedema, as well as with many drugs (**Table 10.2**). Infusion of oxytocin to induce uterine contraction also can cause hyponatremia because of the antidiuretic effects of oxytocin.

Within the category of hyponatremia associated with normal IVV are three special categories. The feature that sets these apart is that patients may exhibit evidence of water conservation when water is withdrawn or an appropriate or nearly appropriate water diuresis when water is administered. That is, it appears that osmoregulation has been reset to “defend” a lowered plasma osmolality. The first special category includes patients who have an unusual response to diuretic therapy, characterized by hyponatremia, severe potassium depletion, and metabolic alkalosis. Despite the hyponatremia and normal IVV, exchangeable sodium is nearly normal, suggesting intracellular movement of sodium. Magnesium levels should be assessed, and potassium replacement must be accomplished before specific treatment of hyponatremia. The second category involves patients with an unusual manifestation of a chronic illness, such as pulmonary tuberculosis, that resets the osmostat. The third category includes patients with sodium depletion resulting from any cause in whom the decrease in effective IVV is minimized by excessive water intake and retention. This effect of excessive water intake can occur in any of the causes of sodium depletion.

Hyponatremia Associated with Increased Effective Intravascular Volume or Increased Extracellular Fluid Volume (Edema or Ascites)

Congestive Heart Failure

When hyponatremia develops spontaneously in the course of chronic CHF (i.e., is not the result of excessive water administration or diuretic therapy), it usually is indicative of severe cardiac insufficiency and has a poor prognosis. The cause of the hyponatremia in such patients has been ascribed to a decreased capacity to increase renal free water clearance perhaps because of (a) increased fractional reabsorption of glomerular filtrate proximal to the renal diluting sites of the distal nephron and (b) an elevated ADH level.

Cirrhosis of the Liver

Patients with cirrhosis and ascites have a decreased capacity to excrete a water load, possibly because of the same mechanisms at work in patients with CHF.

Excessive Administration of Hypotonic Fluids

This usually is an iatrogenic situation and must be especially guarded against

in postoperative patients whose ADH levels are elevated because of stress, pain, hypovolemia, or drugs, as well as in elderly patients who are unable to maximally dilute their urine.

TABLE 10.2 Antidiuretic Drugs

Sulfonylureas (chlorpropamide, tolbutamide)
Cytotoxic agents (vincristine, cyclophosphamide)
Nicotine
Morphine
Barbiturates
Carbamazepine
Psychotropics (tricyclics)
Clofibrate
Isoproterenol
Nonsteroidals
Salicylates
Acetaminophen

Vasopressin

Oxytocin

Hypernatremia

All patients with hypernatremia are volume contracted, except those in whom the disorder develops as a result of excessive administration of hypertonic saline or sodium bicarbonate and the rare patients with essential hypernatremia (**Fig. 10.2**). The following discussion considers only the first group of patients; the latter section on treatment discusses all forms of hypernatremia. Patients with hypernatremia usually have CNS deficits, and they may also have confusion and neuroseizures. Autopsy findings often reveal hemorrhages or thromboses of brain tissue.

Hypernatremia Associated with Formation of Concentrated Urine

The normal renal response to decreased intake of water or increased extrarenal losses of water is the formation of maximally concentrated urine. In most clinical situations in which hypernatremia is the result of water depletion, the expected renal response is a U_{osm}:P_{osm} ratio greater than 1.5 and a specific gravity above 1.015. Thus, the finding of hypernatremia with evidence of renal conservation of water indicates that the hypernatremia is caused by excessive nonrenal losses of water or solute diuresis.

Excessive Nonrenal Water Loss

Hypernatremia typically develops in patients with accelerated rates of nonrenal water loss owing to a hot environment, fever, or hyperventilation, and in whom water losses are not replaced because the patient cannot perceive or communicate thirst. Despite the hypernatremia, sodium deficits usually are present because initially, as water deficits develop, renal sodium excretion increases to maintain normal plasma osmolality and serum sodium concentration.

When more than about 15% of ECF volume is lost, renal conservation of sodium occurs; if the water losses continue, hypernatremia develops. The presence of volume deficits is indicated by the signs of IVV depletion, as previously described. Urine flow rate usually is less than 35 mL/h.

Solute Diuresis

The amount of water that must accompany the excretion of a given amount of solute in the urine is determined by the osmolality of the renal medullary interstitial fluid (with which the collecting duct fluid must equilibrate) and the plasma level of ADH activity (which determines the permeability of the collecting duct to water and, therefore, the rate at which water moves from the collecting duct to medullary interstitial fluid to achieve osmotic equilibrium). Hypernatremia results if water intake does not keep pace with renal water losses, because although renal sodium excretion also is increased in solute diuresis, renal sodium reabsorption is affected proportionately less than is water reabsorption. Large amounts of mannitol infused intravenously or high-protein mixtures fed by nasogastric tube (each gram of protein yields 8 mOsm as urea, phosphate, and potassium) can cause a solute diuresis sufficient to cause hypernatremia if water intake is inadequate. In solute diuresis, urine volume usually is greater than 35 mL/h.

Hypernatremia Associated with Formation of Dilute Urine

The finding of hypernatremia in combination with isotonic or hypotonic urine indicates that, at least in part, the hypernatremia results from failure of normal renal conservation of water. Failure to concentrate the urine under

these conditions may result from the lack of ADH (hypothalamic-pituitary diabetes insipidus) or impaired renal tubular function that interferes with the development of a hypertonic medullary interstitium (renal tubular damage).

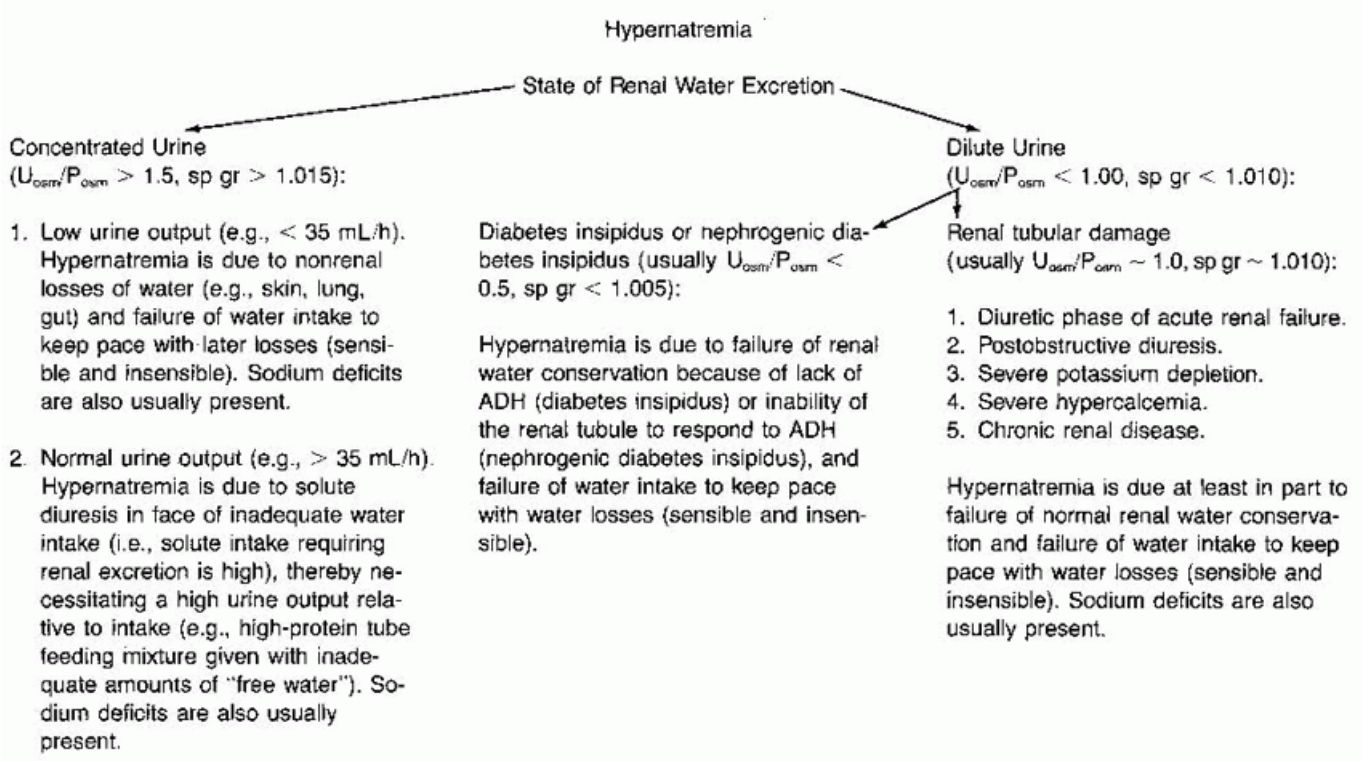

FIGURE 10.2 Approach to the assessment of a hypernatremic patient. This approach does not consider patients with hypernatremia secondary to excessive administration of hypertonic saline. ADH, antidiuretic hormone.

Central diabetes insipidus or nephrogenic diabetes insipidus should be suspected immediately in a patient with hypernatremia when the urine is very dilute (a U_{osm}:P_{osm} ratio <0.5, or specific gravity <1.005).

In patients with renal tubular damage, the ability to concentrate and dilute the urine is decreased. As a result, under all conditions, the urine is isotonic or nearly isotonic with plasma. Hypernatremia can supervene when water losses exceed sodium losses and water intake does not keep pace with water losses. Despite the hypernatremia, significant sodium deficits usually are present because renal sodium wasting also usually is a feature of these disorders. The following sections are examples of clinical situations in which renal tubular damage can be associated with hypernatremia.

Diuretic Phase of Acute Renal Failure

Occasionally, in a patient recovering from acute renal injury, tubular function is more severely affected than is glomerular function. Thus, an inordinately large fraction of the glomerular filtrate escapes reabsorption, resulting in high urine flow rates. The period of inappropriate diuresis can persist for a few days to several weeks.

Postobstructive Diuresis

The sudden release of chronic urinary tract obstruction often is followed by several days or weeks in which urine flow rates are abnormally high. Shortlived nephrogenic diabetes insipidus develops in some patients.

MANAGEMENT OF WATER AND ELECTROLYTE BALANCE

Water requirements should be carefully monitored, especially in hospitalized patients. Patients with known fluid deficits or excesses should be approached as demonstrated in **Tables 10.3**

and 10.4. *Minimum* maintenance requirements can be calculated from two simple formulas.

TABLE 10.3 General Guidelines for Planning Fluid and Electrolyte Therapy in Complicated Cases

Volume-contracted patients (from water and electrolyte loss)

Deficit Replacement

Moderate volume contraction (e.g., decreased effective IVV causing azotemia but not hypotension). Plan to replace deficits in about 24 h (e.g., 0.9% saline at 200-250 mL/h). If the patient is hypernatremic, 0.9% and 0.45% saline can be alternated.
Severe volume contraction (e.g., decreased effective IVV causing hypotension). Give 0.9% saline as rapidly as practicable until the hypotension is corrected.
Estimate maintenance needs, and add this amount to the fluids used to correct the preexisting water and electrolyte deficits.

For patients with normal renal function and no abnormal losses:

Maintenance	*Equivalent Intravenous Fluid Orders*
Water: 2,500-3,000 mL/24 h	Alternate:
Sodium: 150 mEq/24 h	5% dextrose in 0.45% saline with
Potassium: 40 mEq/24 h	5% dextrose in 0.25% saline Each day add: Multivitamins to first liter Potassium chloride 20 mEq to first and second liters Infuse at 100-125 mL/h

Nutrition (Short Term)
At least 400 carbohydrate calories/24 h

For patients with acute renal failure with no urine output and no abnormal losses:

Maintenance	*Equivalent Intravenous Fluid Orders*
Water: 600 mL/24 h	600 mL 20% glucose in water and multivitamins per 24 h
Sodium: 0	
Potassium: 0	

Nutrition (Long Term)
At least 400 carbohydrate calories/24 h
Monitor the patient frequently:
Weigh daily.

Measure serum creatinine and electrolyte levels daily or more frequently if necessary.
Measure CVP or pulmonary wedge pressure in complicated cases. If the patient has normal cardiopulmonary function, CVP is sufficient. If cardiac disease or pulmonary hypertension is suspected, pulmonary wedge pressure measurement is preferred.
Evaluate water and electrolyte needs daily or more frequently in patients with high rates of abnormal losses.

Volume-expanded patients (increased effective IVV)

Correct volume excess:
Mild (e.g., simple edema): Decrease NaCl intake.
Moderate (e.g., mild pulmonary vascular congestion): Induce diuresis with diuretic and allow the sodium and water losses to go unreplaced.
Severe volume excess (e.g., severe pulmonary edema): Steps 1 and 2 and phlebotomy or ultrafiltration (if the patient is anemic) and/or digitalis, vasodilators, if heart disease is present.
Estimate ongoing losses (as above) and begin replacing when volume excesses have been corrected.
Monitor the patient frequently.

CVP, central venous pressure; IVV, intravascular volume.

TABLE 10.4 Major Sources, Loss Rates, and Replacement Fluids in Abnormal Water and Electrolyte Loss

SOURCES	RATE OF LOSS	REPLACEMENT FLUID
Fever	Insensible water losses (normally 450 mL/24 h from the skin and 450 mL/24 h from the lung) increase by about 10% per degree Fahrenheit or 20% per degree Celsius for each degree of temperature above normal.	Replace with 5% dextrose in water
Hyperventilation	Doubling alveolar ventilation (i.e., 50% reduction in $PaCO_2$) increases insensible water losses from the lung by 50%. Thus, the increase in alveolar ventilation required to reduce $PaCO_2$ from 40 to 20 mm Hg increases insensible loss from the lung from 450 to 675 mL/24 h.	Replace with 5% dextrose in water
Gastric fluid	Rates of loss from nasogastric suction usually are 1-2 L/24 h but can be much greater. Normal composition of gastric juice is about H^+, 100 mEq/L; sodium, 40 mEq/L; potassium, 10 mEq/L; and chloride, 150 mEq/L.	Replace with 0.45 normal saline and potassium chloride (usually 20-40 mEq/L) as needed[a]
Diarrheal fluid	Losses can vary from trivial to several liters daily. In	Replace with 0.45

	adults, diarrheal fluid usually resembles ECF except that the bicarbonate concentration is higher (about 30-50 mEq/L) and chloride concentration is lower (about 80 mEq/L). Potassium concentration is variable (10-40 mEq/L)	normal saline and 50 mEq of sodium bicarbonate/liter and potassium chloride (usually 20 mEq/L), as needed[a]
Urine in acute renal failure	Because of tubular injury, urine sodium concentration usually is between 40 and 80 mEq/L and is largely independent of urine flow rate.	Replace with 0.45 normal saline and potassium chloride, as needed[a]

[a]The rate of potassium replacement usually is determined by the serum potassium concentration rather than the rates of potassium loss. For example, even though a patient in acute renal failure may be losing 30 mEq/24 h potassium in the urine, it may not be necessary to replace this amount, since potassium may be entering the extracellular fluid (ECF) at an even faster rate because of catabolism of cellular proteins. On the other hand, the potassium losses in gastric fluid may amount to only 10-20 mEq/24 h, yet far greater amounts of potassium may have to be administered to maintain a normal serum potassium level, since gastric aspiration may lead to metabolic alkalosis, causing renal potassium wasting and extensive diffusion of potassium into intracellular fluid.

The first is the 4-2-1 rule (**Table 10.5**). A more simplified method of calculation using this formula in adults would be to administer 60 mL/h of fluid for the first 20 kg of body weight. Subtract 20 from the patient's weight (in kilograms) and add this difference to calculate the hourly rate. For example, a patient who weighs 65 kg has a maintenance requirement of 105 mL/h. The 4-2-1 method was originally established in children, and characteristically overestimates fluid needs for adults since adults have lower body surface area per unit of weight and, as a result, less insensible losses.

The second method is to calculate the body surface area and multiply by 1,000. A patient with a body surface area of 1.5 m^2 would require 1,500 mL of fluid daily.

Intraoperative Fluid Administration

The guidelines for fluid replacement during the perioperative period are dictated by (maintenance) basal requirements, deficits, intraoperative losses, and third space losses. The basal requirement has been discussed. Deficits include actions of general or spinal anesthesia on effective blood volume, intestinal losses (bowel obstruction or diarrhea), perspiration, and blood loss. In some cases, a CVP or Swan-Ganz catheter may be needed to assess IVV.

Intraoperative losses of fluid occur through several routes. Evaporation from peritoneal surfaces occurs, but quantifying it is difficult. The most obvious source of fluid loss, blood loss, is first assessed by looking into the suction canister. Fluid from irrigation should be subtracted. A soaked lap pad contains about 50 mL of blood, and a 4 × 4 pad contains about 5 mL. These are crude approximations. For instance, a moistened lap pad absorbs less than a dry one. Most researchers recommend a replacement rate of 3 to 1 for blood loss using crystalloid suspension and 1 to 1 using colloid suspension. While anesthetized, patients experience third space loss. This phenomenon is the movement of isotonic fluid from the intravascular space to the interstitial space. A replacement of 2 to

4 mL/kg/h is usually adequate to accommodate third space losses. Actual total intraoperative losses may be difficult or impossible to monitor during long and difficult surgical procedures. Monitoring of vital signs and urine output (optimal, 0.5 mL/kg/h) is extremely important. Sometimes invasive monitoring can be used to guide the clinician.

TABLE 10.5 Maintenance Requirements by 4-2-1 Rule[a]

BODY WEIGHT CATEGORY	FLUID RATE (ML/KG)	WEIGHT CATEGORY (KG)	FLUID (ML/H)
0-10	4	10	40
11-20	2	10	20
21+	1	40	40

[a]Patient weighs 60 kg. Fluid requirement would be 100 mL/h.

TABLE 10.6 Composition of Parenteral Fluids[a]

	CATIONS				ANIONS		
SOLUTIONS	Na	K	Ca	Mg	Cl	HCO_3	OSMOLALITY (mOsm)
Extracellular fluid	142	4	5	3	103	27	280-310
Lactated Ringer solution	130	4	3	—	109	28[b]	273
0.9% sodium chloride	154	—	—	—	154	—	308
D_5 45% sodium chloride	77	—	—	—	77	—	407
D_5W	—	—	—	—	—	—	253
3% sodium chloride	513	—	—	—	513	—	1,026

[a]Electrolyte count in mEq/L.

[b]Present in solution as lactate that is converted to bicarbonate.

Crystalloid solutions contain only sugars and electrolytes (**Table 10.6**). Lactated Ringer solution is usually used

because its composition more closely resembles the extracellular component than does normal saline. Generally, solutions that contain less sodium than lactated Ringer solution does should not be used in the perioperative setting. Although D_5W solutions have an osmolality greater than 250, they are unsuitable as routine perioperative replacement because the sugar is metabolized. Normal saline is another popular crystalloid solution. It is preferred over lactated Ringer solutions in the perioperative period when the patient is hyponatremic or if brain injury is present. Hypertonic saline is rarely used in the perioperative setting. Because water tends to follow sodium, its theoretic advantage is that water is drawn into the intravascular space from the interstitial space; hence, smaller volumes of hypertonic solution than isotonic solution are needed to provide the same intravascular expansion. Crystalloid solutions are preferentially used over colloid solutions for perioperative fluid replacement.

Colloid solutions include albumin, hetastarch, and dextran. Blood is also a colloid but is discussed in another chapter. Colloids are used primarily when patients have a low colloid oncotic pressure or when large amounts of crystalloids have been infused. For example, if a patient has suffered a significant protein loss from ascites secondary to pelvic malignancy, colloids should be used early in the fluid replacement process. If a patient's blood pressure becomes difficult to maintain after infusion of sufficient crystalloid, colloids should be used.

Albumin, hetastarch, and dextran are three commonly used colloid solutions. Albumin is the most popular of the colloid solutions. It is a blood product but has the advantage of complete absence of infectious agents. In addition, it is treated with heat, eliminating the possibility of transmission of hepatitis or human immunodeficiency virus (HIV). It comes in 5% and 25% concentrations. In a prior Cochrane review, perioperative use of albumin in critically ill patients was shown to be associated with an increased risk of death. However, several subsequent studies in various populations, including septic and critically ill patients, have shown that albumin is safe and may reduce morbidity and mortality. Albumin may be especially useful when large volumes of fluid may be needed or if other blood products are limited or not available. Hetastarch consists of large polymer molecules and comes in a solution of saline. It is synthetic; therefore, its use does not affect the blood supply. There is no risk for viral transmission. Hetastarch is metabolized by the kidney and so must be used judiciously in those who have renal disease. Other disadvantages include potential volume overload, dilution hypoproteinemia, and decreased coagulation. The half-life of hetastarch can be as long as 13 days. More recently, serious safety concerns have arisen regarding the use of hetastarch. Hetastarch has been associated with an increased risk of mortality and kidney injury in critically ill and septic patients. In addition, several trials utilizing hetastarch have been retracted because of scientific misconduct. Given the associated risks, with questionable benefit, further use of hetastarch compounds should be limited to clinical trials. Dextran is similar to hetastarch in mode of action. Additional problems with this substance are interference with cross matching and histamine release.

In summary, crystalloids should be used primarily for perioperative volume replacement. Colloid solutions may be considered under the following conditions:

1. Large amounts of crystalloid are needed to maintain normal hemodynamics.
2. Assessment of circulatory status is difficult.
3. The patient has an elevated pulmonary capillary wedge pressure.
4. The colloid pressure is below 12 mm Hg.

Colloid oncotic pressure may be difficult to ascertain in a routine clinical setting; therefore, total protein or albumin levels can be used to give a rough approximation of colloid pressure. If blood loss is more than 25% of total blood volume, transfusion of red cells may be considered. Hemoglobin concentrations can be useful. Experience has shown that hemoglobin levels between 7 and 8 g/dL are generally well tolerated in healthy adults. If the patient has significant comorbidities, then transfusion may be considered to achieve a higher

hemoglobin level, especially prior to surgery.

Correction of Volume Deficits

Estimating the Magnitude of Sodium or Water Deficits

If the patient has been weighed daily, the magnitude of the water deficit owing to external losses of water can be estimated from the decrease in body weight. The coexisting

sodium deficits can be estimated by examining the weight deficits in light of the serum sodium concentration. For example, if the patient has acutely lost 3 kg and the serum sodium concentration is within 10% either way of normal serum sodium concentration (i.e., 126 to 154 mEq/L), little error is incurred by assuming that the patient has lost 3 L of ECF (i.e., isotonic saline); therefore, replacement therapy should be about 3 L of 0.9% saline (155 mEq/L). Using an equivalent amount of lactated Ringer solution offers no advantage, because the kidneys adjust electrolyte excretion to make up for small differences between the composition of the ECF and the isotonic saline.

In patients in whom sodium and water deficits cannot be documented by changes in body weight, or in whom the losses are from the IVV into internal third spaces, approximate but useful guidelines are available to estimate the magnitude of the IVV deficit. These guidelines are as follows:

1. A loss equivalent to 15% of ECF volume (about 2 to 3 L in the average adult) results in a decrease in tissue turgor, but blood pressure and renal function, as judged by serum creatinine level, usually are normal.
2. Losses of sodium and water in excess of 15% of ECF volume usually are accompanied by decreased tissue turgor, orthostatic or frank hypotension, and significant elevation of serum creatinine level.

Correction Rates and Criteria for Assessment

Sodium and water losses great enough to result in hypotension represent a medical emergency, and rapid IV administration of isotonic saline is indicated until the hypotension is reversed. Thereafter, the rate of IV therapy is guided by the adequacy of the IVV as assessed by other criteria, particularly the measurement of blood pressure and pulse in the supine and sitting positions, urine flow rate, and CVP. In patients with less severe degrees of volume depletion, salt and water deficits often can be corrected by increasing oral intake. Salt can be added to food (the salt packets commonly present on hospital trays provide slightly more than 1 g of sodium chloride), or plain sodium chloride tablets can be given, with unrestricted water allowance, letting the patient's thirst mechanism dictate water intake. As a guide to the amount of sodium chloride that should be added to the diet to restore the deficits, 1 L of ECF contains 140 mEq of sodium, or about 9 g of sodium chloride. The adequacy of replacement therapy can be assessed over the ensuing days by measurement of change in body weight and blood pressure and by the decrease in serum creatinine level.

Correction of Volume Excess

Expansion of effective IVV sufficient to precipitate pulmonary edema is a medical emergency and requires the usual treatment of pulmonary edema, including placement of the patient in the sitting position or elevation of the head of the bed and administration of oxygen, vasodilators—such as nitrates, hydralazine, or angiotensin-converting enzyme inhibitors (e.g., captopril, enalapril, lisinopril)—digitalis, and loop diuretics, as needed. If the pulmonary edema does not improve, then phlebotomy may be required to relieve the vascular congestion. If the volume excess is less severe (e.g., simple edema), the problem usually can be controlled by decreasing salt intake, adding a diuretic drug, or both. The effectiveness of treatment can be guided by the decrease in body weight and periodic measurement of serum electrolyte and creatinine levels.

Correction of Hyponatremia

The approach to the correction of hyponatremia depends on (a) whether the patient has significant CNS symptoms as a result of the hyponatremia (coma or seizures) and (b) the cause of the hyponatremia. If the patient has coma or seizures as a result of hyponatremia, the serum sodium level is commonly below 125 mEq/L and the reduction usually has occurred rapidly, over a few hours to days. In these situations, regardless of the cause of the hyponatremia, the serum sodium level should be rapidly raised toward normal by the IV administration of 3% saline. The serum sodium level should be raised to 125 mEq/L at a rate of 1 to 2 mEq/h. The rate of replacement can be slowed once the serum sodium level reaches 125 mEq/L, because neurologic symptoms are rare above this concentration. Rapid elevation of the serum sodium concentration to normal or hypernatremic levels must be avoided, because it may cause central pontine myelinolysis. The correction using 3% saline (513 mEq/L) can be calculated as follows:

volume TBW = 0.6 H total body weight in kg

$$\text{volume TBW} \times \left(\text{desired}\left[Na^+\right] - \text{actual}\left[Na^+\right]\right) = \text{total } Na^+ \text{ (mEq)}$$

where:

$[Na^+]$ is expressed in mEq/L; and TBW = total body water.

The total amount of sodium required can then be replaced at a rate of 2 mEq/h using hypertonic saline. For example, if a 71-kg woman with neurologic symptoms has a serum sodium level of 113 mEq/L, correction to a serum sodium level of 125 mEq/L can be achieved as follows:

$$\text{volume TBW} = 0.6 \times 71 = 42.6$$
$$42.6 \times (125 - 113) = 511 \text{ mEq } Na^+$$

Therefore, since 1 L of 3% saline contains 513 mEq of sodium, this patient requires 1 L of 3% saline to raise her serum sodium level by 12 mEq. The liter of hypertonic saline is administered over 6 to 12 hours. Serum electrolyte levels should be checked every few hours and rates of replacement readjusted as necessary. The infusion of hypertonic saline results in diffusion of water from ICF to ECF until isosmotic conditions are restored. This results in reduction of cell volume and an increase of ICF osmolality toward normal as well as in an expansion of ECF volume. The expansion of the ECF by the hypertonic saline may precipitate or worsen CHF. Therefore, patients who receive hypertonic saline should be carefully observed for signs of pulmonary edema and, if such signs are present, vigorously treated with a loop diuretic.

Hyponatremia Associated with Volume Depletion

The administration of isotonic saline in amounts sufficient to replace existing sodium deficits usually results in complete correction of the hyponatremia, as discussed, in connection with the treatment of volume depletion, because restoration of effective IVV toward normal allows a water diuresis. If specific disease states, such as adrenal insufficiency or diarrhea, are associated with the development of the hyponatremia and volume depletion, these also require treatment.

Hyponatremia Associated with Normal Intravascular Volume

If the hyponatremia is associated with excessive intake of water, restricting water intake to normal corrects the problem.

If the hyponatremia is owing to an inappropriate antidiuresis, water intake must be restricted below normal—for example, to about 800 mL of measured liquid intake daily in an average-sized adult. This usually results in negative water balance, a decrease in body weight, and an increase in serum sodium concentration toward normal. If a specific cause for the inappropriate antidiuresis can be identified, it should be eliminated.

Hyponatremia Associated with Expanded Intravascular Volume and Extracellular Fluid

The spontaneous development of hyponatremia in the course of severe CHF or liver failure is an ominous sign. The hyponatremia usually does not cause any clinical symptoms, and although it can be successfully treated by water restriction, clinical improvement usually does not follow. Furthermore, during such treatment, patients complain bitterly of thirst. Thus, water restriction sufficient to raise the serum sodium concentration to normal is not indicated. Water intake should be restricted, however, to prevent the serum sodium concentration from decreasing to less than 120 mEq/L in an effort to prevent possible CNS symptoms of hyponatremia.

Correction of Hypernatremia

Hypernatremia Secondary to Water Depletion

The amount of water needed to correct the serum sodium concentration toward normal should be determined based on the clinical volume status of the patient. Hypotonic solutions can be used to correct hypernatremia over a period of 24 to 48 hours. Serial sodium levels should be used to avoid overcorrection and hyponatremia. Furosemide should not be used to correct hypernatremia or decreased urine output in a patient with decreased IVV.

Hypernatremia Secondary to Excessive Administration of Hypertonic Saline

In the rare instance of hypernatremia secondary to excessive administration of hypertonic saline, which occurs when intraamniotic infusion of hypertonic saline is used to induce abortion, hypernatremia is owing solely to positive sodium chloride balance. Therefore, treatment involves simply inducing a state of negative sodium chloride balance while maintaining a slightly positive water balance. If the hypernatremia is associated with impairment of CNS function (Na^+ usually exceeds 160 mEq/L), 2 to 3 L of 5% solution of glucose in water should rapidly be given IV, along with sufficient furosemide to induce a urine flow rate of about 10 to 20 mL/min. About 100 mg of IV furosemide is an appropriate initial dose. This results in the excretion of urine containing about 140 mEq/L of sodium and chloride and 10 mEq/L of potassium. If, at the same time, only the water and potassium are replaced (e.g., replacement of each 1,000 mL of urine with 1,000 mL of 5% solution of glucose in water plus 10 to 20 mEq of potassium chloride, given IV), the patient is selectively depleted of sodium chloride, and plasma electrolytes can be restored to normal within several hours. During this period of correction, serum and urine electrolyte levels must be monitored frequently to assess the adequacy of IV replacement therapy, particularly the rate of potassium administration.

POTASSIUM METABOLISM

Disorders of potassium metabolism frequently coexist with disorders of sodium and water balance. For example, sodium and potassium losses often accompany gastrointestinal losses of water and electrolytes. The recognition and management of potassium depletion under these circumstances were discussed earlier in connection with the management of disorders of sodium and water balance. Even small movements of potassium into and out of cells can cause significant changes in the serum potassium since more than 90% of potassium resides intracellularly. It also is important to recognize disorders in which disturbances of potassium balance are the primary abnormality or the major feature of the electrolyte disturbances.

Hyperkalemia

Hyperkalemia is defined as a serum potassium level greater than 5 mEq/L. Serum potassium levels between 5 and 6 mEq/L usually cause little or no functional abnormality, but such levels indicate that an abnormality of potassium regulation is present. This sign should be heeded and its cause investigated, because further small elevations in serum potassium concentration can seriously impair cardiac and skeletal muscle function. At a serum potassium level of 6 or 7 mEq/L, the electrocardiogram (ECG) begins to show tall, peaked T waves, and skeletal muscle weakness may be present. At a serum potassium level greater than 7 mEq/L, severe ECG abnormalities may be present, including complete suppression of atrial activity and an idioventricular rhythm that can then lead to ventricular tachycardia and fibrillation. Profound skeletal muscle weakness leading to respiratory arrest also may develop. If serious hyperkalemia is suspected, an ECG should be obtained immediately along with a blood specimen for potassium measurement. The ECG findings establish whether life-threatening hyperkalemia is present. **Table 10.7** lists the principal clinical conditions associated with hyperkalemia.

Pseudohyperkalemia can result from hemolysis of red blood cells as a result of the mechanical trauma of venipuncture. Such pseudohyperkalemia should be readily recognized, because both potassium and hemoglobin are released by the damaged cells. If the serum potassium level has been significantly raised by in vitro hemolysis, the serum is visibly pink because of the presence of free hemoglobin. Patients with extraordinarily high white blood cell counts or platelet counts also can exhibit pseudohyperkalemia as the result of excessive traumatic in vitro lysis of these cells. Pseudohyperkalemia can be avoided by drawing venous blood samples under low pressure into a heparinized syringe.

Management

Life-Threatening Hyperkalemia

Electrocardiogram shows sine waves or loss of atrial activity and a broad QRS complex. Serum potassium level usually is higher than 7 mEq/L.

1. Infuse 10 mL of 10% calcium gluconate intravenously over a few minutes with ECG monitoring to observe for reversal of ECG changes toward normal. The same infusion of 10 mL of 10% calcium gluconate can be repeated once. Calcium ion directly antagonizes the effects of potassium on myocardial metabolism. The onset of action is a few minutes. If the patient is taking digitalis, consider not giving the calcium and proceed on to the next step.

2. Infuse 50 g of glucose, 10 U of regular insulin, and 50 mEq of sodium bicarbonate. The onset of action is about 15 minutes. Additionally, an IV infusion of glucose, insulin, and sodium bicarbonate (e.g., 500 mL of 10% dextrose in water plus 15 units of regular insulin plus 50 mEq of sodium bicarbonate) may be started. Infuse over several hours. This maneuver causes potassium to

move intracellularly. The amount of glucose infused must be altered or omitted in hyperglycemic diabetic patients.

TABLE 10.7 Causes of Hyperkalemia

CAUSE	EFFECT
Excessive intake of potassium	Shortened life span of stored RBCs after transfusion leads to excessive release of RBC potassium to ECF. Plasma potassium of stored blood also is increased (30 mEq/L) after 14 days of storage.
Transfusion of	

blood stored for prolonged periods	
Excessive oral or intravenous intake of potassium	Acute ingestion of 500 mEq potassium chloride can cause fatal hyperkalemia with normal renal function. If renal function is impaired, even normal potassium intake can cause severe hyperkalemia.
Excessive release of intracellular stores of potassium	
Chemotherapy of malignancies Catabolism of hematomas Rhabdomyolysis	The potential for any of these conditions to cause serious hyperkalemia is greatly increased when they coexist with impaired renal function.
Succinylcholine action on muscle Sepsis with excessive catabolism of muscle protein Acute digitalis poisoning Familial hyperkalemic periodic paralysis Intravenous hypertonic glucose or mannitol	
Intravenous arginine Metabolic acidosis	H^+ displaces K^+ from intracellular sites, causing increased diffusion of K^+ into ECF.
Impaired renal capacity to excrete potassium	
Grossly reduced GFR	Almost all of filtered potassium is reabsorbed. Excreted potassium represents almost exclusively potassium secreted by the tubules. Nevertheless, grossly reduced GFR is associated with grossly reduced tubular function and hence the tendency to hyperkalemia.
Impaired tubular function	
Hyperkalemic renal	Some patients with normal or mildly reduced GFR can have substantial

tubular acidosis	impairment of potassium secretion (e.g., lupus patients with interstitial nephritis, mild obstructive uropathy).
Decreased aldosterone secretion	Aldosterone is necessary for normal potassium and H^+ secretion and normal Na^+ absorption in the distal renal tubule.
Addison disease Primary hypoaldosteronism	
Hyporeninemic hypoaldosteronism	Common in patients with diabetes mellitus or obstructive uropathy.
Drugs that suppress angiotensin formation	
β-Blocking agents (e.g., propranolol) Prostaglandin synthetase inhibitors (e.g., indomethacin, ibuprofen) Angiotensin-converting enzyme inhibitors (e.g., captopril, enalapril, lisinopril)	Angiotensin II causes aldosterone secretion; β-blockers and nonsteroidal anti-inflammatory drugs directly suppress angiotensin formation by suppressing renin production. Captopril prevents angiotensin II formation by blocking conversion of angiotensin I.
Drugs that interfere with renal potassium secretion	Spironolactone competitively inhibits the action of aldosterone. Triamterene and amiloride block potassium secretion even in the absence of aldosterone.
Ureteral implantation into jejunal loop	Increased reabsorption of potassium from jejunum causes predisposition to hyperkalemia.

ECF, extracellular fluid; GFR, glomerular filtration rate; RBCs, red blood cells.

3. Nebulized albuterol at a dose of 10 to 20 mg is recommended. The peak action is approximately 90 minutes.

4. As soon as practical, give sodium polystyrene sulfonate (Kayexalate) by mouth, nasogastric tube, or retention enema (e.g., 20 to 50 g of Kayexalate every 2 to 4 hours). An equal number of grams of sorbitol should be given if the Kayexalate is administered into the upper gastrointestinal tract. Sorbitol, a sugar that is poorly absorbed from the intestine, causes an osmotic diarrhea and prevents concretions of Kayexalate from forming within the gut. Kayexalate is an ion-exchange resin that removes potassium by binding potassium and releasing sodium into body fluids.

5. Hemodialysis may be required in patients in whom these measures fail.

TABLE 10.8 Causes of Hypokalemia

CAUSE	COMMENTS ON PATHOGENESIS
Decreased potassium intake	With 0 mEq potassium intake, stool potassium is about 10 mEq/2 h, urinary potassium is <30 mEq/24 h or is <20 mEq/L.
Excessive renal losses of potassium	Urinary potassium usually >30 mEq/24 h or 20 mEq/L.
Diuretic therapy	All diuretics except for spironolactone, triamterene, and amiloride cause renal potassium wasting. *Mechanism:* Diuretics cause increased sodium delivery to distal tubular sites where sodium is reabsorbed in exchange for potassium or hydrogen ion.
Diuretic phase of acute tubular necrosis and other causes of osmotic diuresis	*Mechanism:* Same as above.
Metabolic alkalosis	*Mechanism:* renal tubular cell potassium concentration increased resulting in enhanced potassium secretion.
Gentamicin or amphotericin B nephrotoxicity	Renal tubular damage presumably causes increased back flux of potassium into renal tubules in the case of amphotericin.
Increased renal mineralocorticoid effects	Increased activity of distal tubular site, which reabsorbs sodium in exchange for potassium or H^+.
Mineralocorticoid therapy (deoxycorticosterone acetate, 9 α-fludrocortisone) Primary aldosteronism Secondary aldosteronism (e.g., cirrhosis of the liver, renal artery stenosis, malignant hypertension) Cushing syndrome Excessive licorice or chewing tobacco (glycyrrhizic acid) Bartter syndrome	

Renal tubular acidosis	*Mechanism:* Distal: Possibly increased renal potassium secretion in exchange for sodium at the distal tubular site because of decreased availability of H^+ for secretion Proximal: Increased bicarbonate excretion leads to increased renal potassium excretion.
Excessive gastrointestinal losses of potassium	
Vomiting, gastric drainage, diarrhea, laxative abuse	Renal potassium excretion also increased in the case of vomiting or gastric drainage.
Villous adenoma of the rectum	Loss of potassium-rich mucus per rectum
Shift of potassium from the extracellular to the intracellular fluid	
Correction of metabolic acidosis	H^+ leaves cells, K^+ enters cells during correction of metabolic acidosis.
Correction of hyperglycemia	K^+ enters cells with glucose to provide cation to balance anion that forms during metabolism of glucose
Hypokalemic periodic paralysis	Unexplained familial disorder
Miscellaneous	
Ureterosigmoidostomy	Colonic secretion of HCO_3^- and K^+ with absorption of Na^+ and Cl^- results in hypokalemic metabolic acidosis.

Moderate Hyperkalemia

Electorocardiogram shows only peaked T waves; serum potassium level usually is below 7 mEq/L.

1. Reduce potassium intake (normal potassium intake is 60 to 100 mEq/24 h). Reducing dietary potassium to 50 to 60 mEq/24 h usually is sufficient to correct mild hyperkalemia.

2. Kayexalate may be needed periodically to control the serum potassium level.

3. Correct metabolic acidosis if present.

4. Stop administration of medications that can contribute to hyperkalemia, such as angiotensin-converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, and potassium-sparing diuretics.

Hypokalemia

Hypokalemia is defined as a serum potassium level below 3.5 mEq/L (**Table 10.8**). Significant symptoms usually do not result from hypokalemia unless the serum potassium level is less than 3 mEq/L. An important exception is in patients who are receiving digitalis preparations. In such patients, hypokalemia, or even low-normal serum potassium levels, can increase myocardial irritability and lead to serious arrhythmias. In addition to increasing myocardial irritability, hypokalemia can cause

profound muscle weakness and ileus. Chronic severe hypokalemia also can cause metabolic alkalosis and decreased capacity to concentrate the urine. The ECG in hypokalemia often shows U waves, although this finding is not diagnostic of hypokalemia.

Management

Mild Asymptomatic Hypokalemia

This usually can be corrected simply by eliminating the cause of the potassium wasting or by increasing potassium intake. If the hypokalemia is caused by diuretic therapy, potassium depletion usually can be avoided by administering spironolactone or triamterene. Potassium supplementation also can be used, but if the patient is on a low sodium chloride intake, the potassium supplement must be given as potassium chloride. The use of other, more palatable potassium salts (e.g., gluconate, citrate, acetate) and all forms of potassium in food is much less effective in correcting hypokalemia, and this treatment is used primarily in patients on a normal sodium chloride intake.

Severe or Symptomatic Hypokalemia

This usually requires IV administration of potassium chloride. In general, the use of IV solutions that contain more than 40 mEq/L of potassium should be avoided, because infusing high concentrations of potassium can cause hyperkalemia or cardiac disturbance. In correcting even severe potassium deficits, it is seldom necessary to infuse more than 120 to 160 mEq/24 hours of potassium chloride. When higher rates are used, frequent monitoring of the patient's ECG and serum potassium level is essential. Intravenous replacement of potassium should never run at a rate of greater than 10 mEq/h. The oral route of potassium replacement should be used whenever possible.

Calcium

Approximately *99%* of body calcium is contained in bone. Up to 40% of the extracellular calcium that circulates in the bloodstream is bound to plasma proteins. However, the unbound or ionized form of calcium is the form that exerts physiologic activity. Total calcium is a measure of both the bound and unbound or ionized form. Serum albumin levels affect the total serum calcium, as albumin is the plasma protein to which the majority of calcium is bound.

$$\text{corrected calcium in mg / dL} = \text{measured calcium} + \left[(4 - \text{albumin in g / dL}) \times 0.8\right]$$

Ionized or unbound calcium can be measured if specifically requested. Its concentration is affected by the serum pH. With alkalosis when the pH is increased, a decrease in ionized calcium results from the increased protein binding of calcium. Conversely, with acidosis, a decrease in protein binding causes an increase in ionized calcium.

The homeostasis of calcium is quite complex, and calcium serves many important functions. Calcium plays a role in regulation of muscle contraction and nerve conduction. Additionally, it functions in the coagulation cascade.

The majority of calcium is stored in bone; however, calcium is under the control of several other organ systems, including the integument, endocrine, and renal. Parathyroid hormone (PTH) appears to be the major hormone effecting calcium homeostasis. Vitamin D must be present, however, for it to exert its maximal effect. PTH causes the following.

- Mobilization of calcium and phosphorus from bone
- Increased renal tubular reabsorption of calcium
- Increased intestinal absorption of calcium
- Decreased renal tubular reabsorption of phosphorus

Hypocalcemia

Clinical manifestations of hypocalcemia (defined as a calcium level below 8 to 8.5 mg/dL) are characterized by neuromuscular irritability. Symptoms can include numbness, muscle cramping, paresthesias, Chvostek (twitching of facial muscles) and Trousseau (carpal spasm) signs, tetany, and seizures. Patients can also experience psychosis and memory loss. On physical examination, patients may have hyperactive deep tendon reflexes. ECG findings of hypocalcemia include a prolonged QT interval, which can lead to heart block or ventricular fibrillation. Causes of hypocalcemia are shown in **Table 10.9.**

Treatment of hypocalcemia should be directed at its underlying cause. A low total calcium level with a normal ionized calcium level signifies a low level of plasma proteins. These patients usually are asymptomatic, and calcium replacement in this setting usually is not necessary.

For patients with acute symptomatic hypocalcemia, calcium gluconate or chloride should be given intravenously. These may cause a local cellulitis or tissue necrosis if infiltration occurs. If infiltration occurs, especially with the chloride solution in emergent situations, 10 mL of 10% calcium gluconate can be administered intravenously over 15 minutes. In addition, 10 to 20 mL of calcium gluconate can be placed in 1 L of D_5W and administered over 24 hours. If the serum albumin level is below 2 mg/dL, then it may be prudent to replace albumin, especially if the urine output is low. Because albumin is heat treated, there is no risk of hepatitis or HIV exposure. In cases of symptomatic hypocalcemia, magnesium levels must be checked and corrected if necessary. In those patients with metabolic acidosis and hypocalcemia, the hypocalcemia should be treated initially followed by the correction of the acidosis.

Long-term treatment of hypocalcemia involves adequate nutritional supplementation of calcium, vitamin D, or both. If the serum phosphorus level is high, hypoparathyroid disease must be suspected and the patient treated accordingly. If the serum phosphorus is normal or low, then primary bone disease (hungry bone) must be considered. It is imperative that magnesium levels be checked because replenishment of calcium cannot be accomplished in a patient who is hypomagnesemic.

Hypercalcemia

The clinical manifestations of hypercalcemia usually are seen when the total serum calcium is greater than 12 mg/dL. Common presenting symptoms include weakness, fatigue, nausea, vomiting, constipation, polyuria, polydipsia, lethargy, and confusion. Psychiatric disturbances and coma can be seen in severe cases of hypercalcemia. Electrocardiogram changes include prolongation of PR and QRS intervals with a shortening of the QT interval. Complete heart block and cardiac arrest can occur in profound hypercalcemia. Additional laboratory

abnormalities can include elevations in serum amylase and creatinine levels. The phosphorus level is critical in establishing the cause of hypercalcemia. A phosphorus level below 3.5 mg/dL suggests hyperparathyroidism,

whereas an elevated phosphorus level suggests an underlying malignancy.

TABLE 10.9 Causes of Hypocalcemia

Deficiency or absence of PTH
Vitamin D deficiency—decreased intestinal absorption
Septic shock—suppression of PTH products
Renal failure—decreased 1:25 dihydroxycholecalciferol
Hypomagnesemia—decreased PTH release and decreased organ response to calcium
Hyperphosphatemia

Hypercalcemia, unlike many other electrolyte disturbances, is rarely iatrogenically induced. There are several causes of hypercalcemia. The majority of hospitalized patients with hypercalcemia have an underlying malignancy, whereas the most common etiology of hypercalcemia in the ambulatory setting is hyperparathyroidism. Additional causes of hypercalcemia include thiazide diuretics, lithium, vitamin D intoxication, hyperthyroidism, and sarcoidosis. In the setting of gynecology, hypercalcemia is most often seen with malignancy. In patients with cancer, hypercalcemia results from increased bone resorption and decreased renal excretion. Metastasis to the bony skeleton causes an increase in osteoclastic activity that increases bone resorption. Some gynecologic tumors, however, may cause hypercalcemia by production of a substance similar to PTH, causing bone resorption without evidence of bony metastasis.

Volume expansion is crucial in the treatment of acute hypercalcemia. Replacement with normal saline solution decreases calcium reabsorption in the proximal renal tubule, thus improving renal function. Initial IV fluid therapy should be aggressive, with rates of 250 to 500 mL/h, as most patients are volume contracted. Addition of loop diuretics such as furosemide may aid in increasing urinary calcium excretion, but caution must be used because these drugs may result in volume contraction and hypokalemia. After initial volume is restored, 3 to 6 L/d of normal saline solution should be given. Close monitoring of daily patient weights, intake and output, and frequent monitoring of serum electrolytes is necessary in patients with hypercalcemia.

Bisphosphonates are commonly used for the treatment of hypercalcemia. This class of drugs inhibits osteoclast precursors and induces osteoclast cytotoxicity, thereby decreasing serum calcium levels. Etidronate disodium (Didronel) is given at a dose of 7.5 mg/kg IV over 2 hours daily for 3 to 7 days. Alternatively, pamidronate (Aredia) is given as a single dose of 60 to 90 mg IV over 4 to 24 hours. Peak onset of action with these medications is usually seen in 48 to *96* hours and may last 2 to 3 weeks. The single dose of 90 mg IV of pamidronate is recommended for severe cases of hypercalcemia because of its effectiveness.

Zoledronic acid (Zometa) is a new-generation, nitrogencontaining bisphosphonate that has been shown to be superior to pamidronate at inhibiting the induction of hypercalcemia of malignancy. Zometa can be given over 5 minutes in a 4-mg dose for the initial treatment of hypercalcemia and an 8-mg dose for relapsed or refractory hypercalcemia. The duration of response with zoledronic acid is approximately 32 days with a 4-mg dose and 43 days with an 8-mg dose compared with 18 days with a 90-mg dose of pamidronate.

Calcitonin increases renal excretion of calcium and inhibits osteoclastic activity. In patients with hypercalcemia, calcitonin can be given at a dose of 4 to 8 IU/kg intramuscularly or subcutaneously every 6 to 12 hours. Commercial calcitonin preparations are generally from salmon. It has a rapid onset of action, and serum calcium levels may decrease within several hours. Its effect usually subsides after several days but may be potentiated by concomitant glucocorticoid administration. Calcitonin has minimal side effects. Tachyphylaxis is seen with calcitonin, limiting its repeated usage and causing it to be less consistently effective compared with other available hypercalcemic treatments.

Glucocorticoids decrease the intestinal absorption of calcium, promote urinary excretion of calcium, and may lower calcium levels by a direct cytolytic effect on some tumor cells. Lowering of serum calcium levels with glucocorticoids may take 5 to 10 days. Dosages may vary from 20 to 100 mg of oral prednisone or its IV equivalent per day. Side effects limit the long-term use of glucocorticoids for hypercalcemia.

Another potent inhibitor of bone resorption is gallium nitrate. Its onset of action is usually seen in 1 to 2 days, with a peak at 5 to 10 days after administration. Gallium nitrate is administered in a dose of 100 to 200 mg/kg/d for 5 days in a continuous drip. It is important to maintain a saline diuresis of at least 2 L/d during this therapy. Side effects are relatively uncommon, but renal toxicity may be seen. Gallium nitrate in early studies was significantly more effective than was calcitonin with or without the addition of corticosteroids. Its obvious disadvantage over the biphosphonates is that it requires continuous IV infusion over 4 or 5 days.

Oral and IV phosphorus has been used successfully to treat hypercalcemia. It has fallen out of favor, however, because it causes decreased excretion of calcium from the kidneys. Intravenous phosphorus can also lead to soft tissue deposition of calcium compounds and renal failure. It was used in patients with serum phosphorus levels less than 3 mg/dL and normal renal function. For patients with extremely high calcium levels and severe symptoms (e.g., coma, arrhythmia), renal dialysis may be necessary for rapid correction of hypercalcemia.

Plicamycin (mithramycin) is an antibiotic that blocks bone resorption, thus lowering serum calcium. The recommended dose of plicamycin in the treatment of hypercalcemia is 25 mg/kg IV over 4 to 6 hours and may be repeated every 24 to 48 hours. Its onset of action is relatively quick, and peak action is usually noted in 2 to 3 days. Side effects can be severe and include nausea, vomiting, bleeding, thrombocytopenia, renal failure, and hepatotoxicity. These side effects are more common with repeated doses of plicamycin. Because of these side effects, plicamycin usually is reserved for hypercalcemia of malignancy or hypercalcemia refractory to other therapies.

Magnesium

Magnesium has several functions in the human body. Its primary role is in neuromuscular function, but it also serves as an enzyme cofactor in protein and carbohydrate metabolism. The majority (60%) of magnesium in the body is contained within the bone. Most of the remainder is found intracellularly, with only about 1% found in the ECF. Normal serum magnesium levels are between 1.2 and 2.2 mEq/L. Magnesium metabolism depends on potassium and calcium levels. The kidney serves as the organ primarily responsible for magnesium homeostasis. Magnesium is filtered at the glomerulus and reabsorbed in the ascending loop of Henle and to a lesser degree in the proximal and distal tubules.

Hypomagnesemia

Hypomagnesemia is more common than hypermagnesemia. Hypomagnesemia results from decreased gastrointestinal absorption with conditions such as chronic diarrhea, malabsorption syndromes, and nasogastric suction. Increased renal and gastrointestinal losses from osmotic diuresis, hypercalcemia, and medications such as cisplatin, diuretics, and aminoglycosides also can cause hypomagnesemia. Hypomagnesemia can result from decreased intake in malnutrition. For example, 10% to 15% of hospitalized patients and more than half of

patients in intensive care units exhibit low magnesium levels. Patients with heavy alcohol use may have hypomagnesemia.

Symptoms and signs of hypomagnesemia are usually nonspecific but may manifest by neuromuscular excitability. Hypomagnesemia is often seen in combination with hypokalemia, hypocalcemia, and metabolic alkalosis. Neurologic

abnormalities include weakness, dizziness, lethargy, confusion, tremors, fasciculations, and seizures. Typical ECG findings are prolonged PR and QT intervals; however, atrial and ventricular arrhythmias can result.

The treatment of hypomagnesemia involves the replacement of magnesium. Mild or chronic cases may be treated with oral magnesium supplements. Oral repletion is also preferred in asymptomatic patients. This is accomplished by giving 240 mg of elemental magnesium one to four times a day. Diarrhea is the most common side effect. For severe or acute cases, IV magnesium is indicated. Obstetricians and gynecologists are familiar with the 4-g magnesium load mixed with 50 mL of D_5W infused over 30 minutes. Deep tendon reflexes should be evaluated frequently because hyperreflexia suggests hypermagnesemia. Long-term oral therapy can be provided with magnesium oxide 300 mg/d. Patients should receive proper nutritional counseling and be warned to avoid alcohol. Any underlying medical disorder that may contribute to magnesium losses should be treated. Hydration status should be evaluated because overhydration can lead to mild forms of hypomagnesemia. Gastrointestinal tract losses and alcohol consumption also should be addressed in the evaluation of this disease process.

Hypermagnesemia

Hypermagnesemia is rare and usually iatrogenic. Causes of hypermagnesemia include therapy with magnesium-containing antacids or laxatives or secondary to administration of parenteral hyperalimentation. Often hypermagnesemia is seen in patients with some degree of renal insufficiency and in preeclamptic or preterm labor patients treated with IV magnesium.

Mild to moderate hypermagnesemia usually is asymptomatic, but patients with severe cases may present with several symptoms. Clinical manifestations are normally seen if magnesium levels are greater than 4 mEq/L. Signs and symptoms include nausea, vomiting, weakness, lethargy, and somnolence. A prolonged PR interval, widening of the QRS complex, and increased T-wave amplitude can be seen with levels greater than 5 mEq/L. Areflexia occurs at levels above 6 to 7 mEq/L. Respiratory arrest, bradycardia, and hypotension can be seen when levels are higher than 10 to 11 mEq/L. Finally, cardiac arrest can occur when serum magnesium is above 14 mEq/L.

Discontinuation of magnesium intake is the primary therapy for symptomatic hypermagnesemia. Patients with severe cases should be given 10% calcium gluconate, 10 to 20 mL IV over 10 minutes. The calcium therapy antagonizes the effects of magnesium and is cardioprotective. Supportive therapy and mechanical ventilation may be necessary in those with respiratory failure. Hemodialysis may be required in patients with hypermagnesemia and renal insufficiency.

Phosphorus

As with magnesium, the majority of phosphorus is contained in the bony skeleton and the intracellular space, and only 1% is found in the ECF. As a result, serum phosphate levels may not accurately reflect total body phosphate stores. A normal range for serum phosphorus is 3 to 4.5 mg/dL. Phosphorus serves as an important energy source by means of high-energy phosphates. It is a key component to protein and lipid structure and is a vital component for carbohydrate metabolism.

Hypophosphatemia

Causes of hypophosphatemia defined as a serum phosphate below 2.5 mg/dL include a redistribution of phosphate into the cells, a decrease in intestinal absorption, or an increase in renal excretion. Several causes of hypophosphatemia are listed in **Table 10.10**. Most patients with mild hypophosphatemia are asymptomatic. Moderate to severe hypophosphatemia causes neuromuscular abnormalities, including weakness, rhabdomyolysis, paresthesias, confusion, seizures, and coma. Erythrocyte, leukocyte, and platelet dysfunction also can be seen because of a depletion of cellular adenosine triphosphate and 2,3-diphosphoglycerate.

TABLE 10.10 Causes of Moderate to Severe Hypophosphatemia (<1.5 mg/dL)

Respiratory alkalosis
Malabsorption
Vitamin D deficiency
Hyperalimentation
Treatment of diabetic ketoacidosis
Hyperparathyroidism
Excessive alcohol use

Most patients with serum phosphate levels between 1 and 2.5 mg/dL usually are asymptomatic. Treatment is aimed at correcting the underlying cause. In cases of chronic hypophosphatemia, oral repletion can be instituted at a dose of 500 to 1,000 mg of elemental phosphorus two to three times per day, and the most common side effect is diarrhea. This can be given in the form of sodium/potassium phosphate tablets called Neutra-Phos or Neutra-Phos K (each contains 250 mg of elemental phosphorus). Parenteral administration of phosphorus is indicated when serum phosphorus levels are below 1 mg/dL. Infusion at a dose of 2.5 to 5 mg elemental phosphorus/kg given every 6 hours is recommended. When the serum levels are greater than 1.5 to 2 mg/dL, patients may be switched to oral supplements. Care must be taken to avoid hyperphosphatemia. Also, concomitant calcium supplementation often is needed to prevent hypocalcemia. Serum magnesium, calcium, and potassium levels should be monitored closely.

Hyperphosphatemia

Hyperphosphatemia is relatively rare and is seen either with an increased endogenous or exogenous phosphorus load or with a decrease in renal clearance of phosphorus. Renal failure is the most common cause of hyperphosphatemia. Elevated phosphorus levels also may be seen secondary to rhabdomyolysis, tumor lysis syndrome, hypoparathyroidism, and respiratory or metabolic acidosis. Clinical manifestations include numbness, tingling, muscle cramps, paresthesias, and tetany and are caused by hypocalcemia. Hyperphosphatemia causes hypocalcemia by decreasing calcium absorption from the gastrointestinal tract.

Addressing the underlying cause is the cornerstone of management for hyperphosphatemia. In acute cases, saline diuresis can be used in patients with normal renal function. Additionally, administration of glucose and insulin causes a shift in phosphorus from ECF to the intracellular space. Dialysis may be required if renal failure

is present. Oral phosphate binders such as calcium carbonate can be used in patients with chronic hyperphosphatemia.

ACID-BASE METABOLISM

Chemicals that are able to provide a hydrogen ion (H^+), such as HCl and H_2CO_2, are defined as acids. Bases are defined as chemicals with the ability to accept a H^+ and include OH^- and HCO_3^-. The acidity of a solution is governed by the concentration of hydrogen ions it contains. The pH of a system is defined as the negative logarithm of hydrogen ions within that system expressed in moles per liter. The normal pH of human ECF ranges from 7.35 to 7.45.

Buffer Systems

In order for optimal cellular function to occur within the body, the pH must remain in this range. Humans have the ability to absorb excess acids or alkali in circumstances of abnormal pH. The lungs correct for acid-base disorders in an acute setting until the kidneys can compensate. In acidotic states, patients will hyperventilate to decrease CO_2 levels in the blood. Conversely, in alkalotic states, patients will hypoventilate, driving up the level of CO_2 in the blood. Renal function will gradually compensate by retaining or releasing bicarbonate and hydrogen ions. The most important human buffer system is the bicarbonate system. It is the principal extracellular buffer. Organic phosphates and peptides are the other major intracellular buffers.

Table 10.11 shows the directional changes in acid-base parameters for the primary acid-base disorders. If the kidney detects a respiratory acidotic state, CO_2 and H_2O in renal tubule cells are converted by carbonic anhydrase to carbonic acid (H_2CO_3). This dissociates into H_2CO_3, which is secreted back into ECF, and H^+, which is exchanged for sodium from the renal tubule. This in effect causes excretion of the hydrogen ion into the urine, where it is buffered with ammonium and phosphate ions or acted on by carbonic anhydrase (in the tubule) to ultimately form CO_2 and H_2O. The CO_2 is absorbed back into the cell, where more bicarbonate can be generated to buffer ECF acidosis. If a patient has a respiratory alkalosis, available levels of CO_2 are low, causing a decrease in hydrogen excretion.

Primary Acid-Base Disorders

Metabolic Acidosis

Metabolic acidosis begins as a reduction in plasma HCO3 and a rise in H^+. In response to these changes, alveolar ventilation is increased, resulting in a decrease in $PaCO_2$ and restoration of H^+ toward normal. Metabolic acidosis can be divided into normal anion gap and increased anion gap acidosis. **Table 10.12** shows the major causes of metabolic acidosis.

Increased Anion Gap

Renal failure, either acute or chronic, can result in an increased anion gap metabolic acidosis resulting from the kidneys' inability to excrete inorganic acids, such as phosphate and sulfate. Organic acid accumulation also results in an increased anion gap metabolic acidosis. In the case of lactic acidosis, cellular respiration is disturbed. This occurs as a result of anaerobic glycolysis in muscle, red blood cells, and other tissues. Conditions such as shock, hypoxemia, and septicemia can produce lactic acidosis by causing inadequate oxygen delivery to tissues. Conditions such as diabetic ketoacidosis, alcoholic ketoacidosis, and starvation cause an accelerated rate of organic acid production by lipolysis and ketogenesis. Ingestion of substances such as

salicylates, methanol, ethylene glycol, and paraldehyde can result in an increased anion gap metabolic acidosis.

Normal Anion Gap

Normal anion gap metabolic acidosis occurs with abnormal increases in net bicarbonate losses. This can occur when the kidney fails to reabsorb bicarbonate in proximal renal tubular acidosis. The administration of carbonic anhydrase inhibitors can also cause normal anion gap metabolic acidosis. Excessive diarrhea or small bowel/pancreatic drainage can cause bicarbonate losses from the gastrointestinal tract. Hyperchloremic acidosis occurs when the kidney fails to regenerate bicarbonate in conditions such as distal renal tubular acidosis and hyporeninemic hypoaldosteronism. Administration of acid salts can result in chloremic acidosis.

MANAGEMENT

The treatment for metabolic acidosis depends on the severity of acidosis and the underlying cause. A clinical manifestation of metabolic acidosis is hyperventilation. In the surgical patient, metabolic acidosis is commonly due to hypoxia secondary to inadequate tissue perfusion and subsequent accumulation of lactic acid. Volume resuscitation, including blood transfusion, will correct many of these cases of metabolic acidosis. Volume resuscitation and insulin are recommended to correct diabetic ketoacidosis. Patients with this form of metabolic acidosis will often require 4 to 5 L of intravenous fluid on diagnosis. Regular insulin can be given with a loading dose of 15 to 20 IU, followed by a continuous insulin infusion at 5 to 10 IU/h. In cases of renal tubular acidosis, bicarbonate therapy, thiazide diuretics, and a low-salt diet are used for correction.

In cases of acute, severe acidosis (pH <7.1, bicarbonate <10), patients will become dyspneic with depressed cardiac function and mental status changes. It may be necessary to administer intravenous bicarbonate to these patients. In general, the serum bicarbonate concentration should not be acutely raised to levels greater than 15 to 18 mEq/L. Too-rapid correction requires infusion of large amounts of sodium bicarbonate, which can cause overexpansion of the ECF and CHF. Finally,

rapidly restoring the plasma bicarbonate level to normal may produce alkalosis because of persistence of a low $PaCO_2$. That is, if plasma bicarbonate is rapidly restored to normal or above in the treatment of metabolic acidosis, alveolar ventilation frequently persists at elevated levels for an additional 24 to 48 hours. Thus, the low PCO_2 with normal plasma bicarbonate level can result in severe alkalosis, which, in turn, can cause cardiac arrhythmias, tetany, and seizures.

TABLE 10.11 Primary Disorders of Acid-Base Regulation

ACID-BASE DISTURBANCE	PRIMARY (INITIATING) EVENT	SECONDARY (COMPENSATORY) EVENT	RESULTANT CHANGE IN BLOOD H^+ AND PH
Metabolic acidosis	↓ HCO_3^-	↓ PCO_2^-	H^+ ↑, pH ↓
Metabolic alkalosis	↑ HCO_3^-	↑ PCO_2 (minimal and only with severe increase in HCO_3^-)	H^+ ↓, pH ↑
Respiratory acidosis			

Acute (24 h)	↑ $PaCO_2$	Negligible ↑ HCO_3^-	H^+ ↑, pH ↓
Chronic (3-7 days or longer)	↑ $PaCO_2$	Important ↑ HCO_3^-	
Respiratory alkalosis	↓ $PaCO_2$	↓ HCO_3^-	H^+ ↓, pH ↑

TABLE 10.12 Major Causes of Metabolic Acidosis

Increased anion gap
Accumulation of acids
Alcoholic ketoacidosis
Diabetic ketoacidosis
Lactic acidosis
Starvation
Salicylate ingestion
Methanol ingestion
Ethylene glycol ingestion
Paraldehyde ingestion
Reduced excretion of acids
Renal failure
Normal anion gap
Excessive bicarbonate loss
Diarrhea
Ureterosigmoidostomy
Proximal renal tubular acidosis
Small bowel or pancreatic drainage
Carbonic anhydrase inhibitors
Excessive acid production
Ammonium chloride
Arginine HCl
Lysine HCl
Hyperalimentation-containing acids

Decreased renal bicarbonate production
Distal renal tubular acidosis Hyporeninemic hypoaldosteronism

METABOLIC ALKALOSIS

Metabolic alkalosis occurs when extracellular bicarbonate concentration is increased and renal excretion of this excess bicarbonate is decreased. This cascade may begin with the loss of a hydrogen ion. The major causes of metabolic alkalosis are listed in **Table 10.13**.

One of the most common causes of metabolic alkalosis is vomiting or gastric suction. Volume contraction ensues, and bicarbonate is saved in the kidney. Profound potassium depletion can also increase renal reabsorption of bicarbonate and cause a metabolic alkalosis. Diuretics cause a metabolic alkalosis by inducing a sodium chloride excretion without bicarbonate, excretion of potassium, and secondary aldosteronism.

Gastric acid secretion normally has no net effect on acidbase regulation. If the gastric HCl is lost from the body and is not replaced, metabolic alkalosis will ensue (**Fig. 10.3**).

Mineralocorticoid excess in conditions such as hyperaldosteronism, Bartter syndrome, Liddle syndrome, and Cushing syndrome can cause metabolic alkalosis. The mechanism for alkalosis in these conditions is an increase in bicarbonate via the kidneys. Hypercalcemia can result in an increase in proximal tubular reabsorption of bicarbonate leading to metabolic alkalosis. Massive alkali administration in the form of massive blood and/or platelet transfusion or $NaHCO_3$ ingestion can lead to metabolic alkalosis.

TABLE 10.13 Major Causes of Metabolic Alkalosis

Extracellular volume depletion
Mineralocorticoid excess
Increased renal acid excretion
Massive alkali administration

Management

Metabolic alkalosis can have serious consequences, such as tetany, major motor seizures, production of hypokalemia and cardiac arrhythmias (particularly in patients receiving digitalis), suppression of alveolar ventilation, and decrease in cerebral blood flow. Furthermore, the presence of metabolic alkalosis often is a sign that the patient is significantly volume contracted. For these reasons, it is important to treat metabolic alkalosis and its underlying causes. Effective treatment consists of replacing sodium, potassium, and chloride deficits as they occur, as discussed. Rarely, it is necessary to treat metabolic alkalosis with IV infusion of hydrochloric acid, ammonium chloride, arginine hydrochloride, or a carbonic anhydrase inhibitor (acetazolamide). This form of treatment is necessary in patients who cannot undergo the sodium bicarbonate diuresis necessary to correct the

metabolic alkalosis. This inability usually is the result of severely impaired renal or cardiac function.

Respiratory Acidosis

Inadequate alveolar ventilation leads to respiratory acidosis. Acutely, this can occur with depression of the medullary respiratory center by sedating drugs or narcotics, by impaired respiratory excursion of the thorax by paralysis or trauma, and by airway obstruction. Chronic respiratory acidosis can be seen in conditions such as emphysema, severe kyphoscoliosis, and extreme obesity with Pickwickian syndrome.

Management

The treatment for respiratory acidosis is to increase alveolar ventilation (by endotracheal intubation, mechanical ventilation, or bronchodilation). Within minutes, severe respiratory acidosis can be reversed with adequate ventilation. In patients with chronic respiratory acidosis, severe posthypercapnic alkalosis develops if the $PaCO_2$ is rapidly restored to normal and the patient is unable to initiate and sustain a bicarbonate diuresis. This inability usually results from sodium chloride or potassium chloride deficits. If sodium chloride or potassium chloride is provided to correct volume contraction and intracellular potassium deficits, a bicarbonate diuresis ensues, and correction of metabolic alkalosis is achieved.

Respiratory Alkalosis

Respiratory alkalosis occurs when hyperventilation decreases PCO_2, resulting in an increase in pH. Hyperventilation may be secondary to conditions such as pulmonary embolism and CHF, which can cause hypoxia. Fever, sepsis, salicylate toxicity, and hepatic failure all can increase alveolar ventilation and cause respiratory alkalosis. This condition can also be iatrogenically induced by mechanical ventilation. Chronic hyperventilation can be seen in pregnancy, exposure to high altitudes, and underlying pulmonary disease.

Management

The symptoms of acute respiratory alkalosis (e.g., paresthesia, lightheadedness, tetany) can be rapidly controlled by raising $PaCO_2$ to normal (e.g., by rebreathing into a paper bag). If the patient is being supported on a ventilator, the dead space can be increased, or tidal volume and respiratory rate can be decreased

while oxygenation is maintained. Definite treatment consists of removing the cause of hyperventilation. Respiratory alkalosis also can cause tetany and seizures and predispose to cardiac arrhythmias (by causing an intracellular shift of potassium), particularly in patients receiving digitalis. If the patient is septic, aggressive measures should be taken to alleviate this. She should be treated with appropriate antibiotics and adequate volume replacement. Surgery may be necessary if the patient has an abscess.

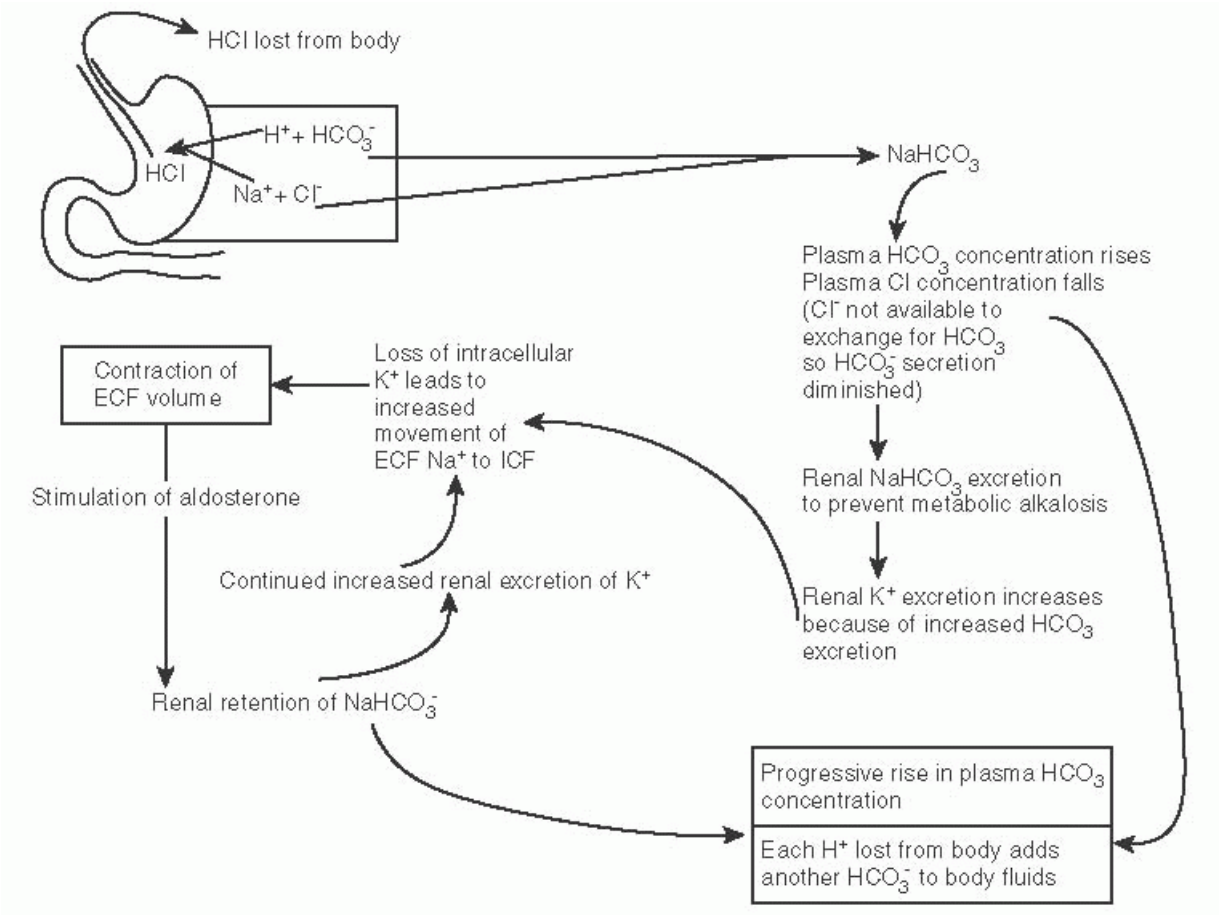

FIGURE 10.3 Pathogenesis of metabolic alkalosis from loss of gastric hydrochloric acid.

Mixed acid-base disturbances can commonly be seen in severely ill patients. Anion gap measurements and careful evaluation of compensatory changes in the pH, $HCO_3^{\square}$, and PCO_2 are necessary in the workup and management of these patients. The treatment of mixed acid-base disturbances is aimed at the underlying disease process.

BEST SURGICAL PRACTICES

- An accurate assessment of the effective IVV usually can be made based on a careful clinical assessment of the patient.
- Maintenance fluids in a hospitalized patient should be calculated by taking the body surface area and multiplying by 1,000 to come up with the daily fluid requirement in mL.
- The syndrome of inappropriate antidiuresis has been associated with malignant tumors, CNS disorders, infections, the postoperative state, hypopituitarism, and myxedema, as well as with many drugs. Infusion of oxytocin to induce uterine contraction also can cause hyponatremia because of the antidiuretic effects of oxytocin.
- Symptoms of hyponatremia include increased tendon reflexes, lethargy, mental confusion, and muscle twitching, which are followed by convulsions, coma, and possibly death if levels fall below 115 mEq/L.
- The initial step in correcting either hyponatremia or hypernatremia is an accurate assessment of the patient's volume status.
- Furosemide should not be used to correct hypernatremia or decreased urine output in a patient with decreased IVV.
- Intravenous replacement of potassium should never run at a rate of greater than 10 mEq/h. The oral route of

potassium replacement should be used whenever possible.

- In severe life-threatening hyperkalemia (ECG showing sine waves and broad QRS complexes), patients should first receive 10 mL of calcium gluconate IV for cardioprotective purposes. These patients should receive an amp of D50, 10 U of regular insulin, and 50 mEq of sodium bicarbonate. Subsequently, these patients should then receive 20 to 50 g of Kayexalate every 2 to 4 hours and infusions of glucose and insulin.
- Magnesium metabolism is closely related to potassium and calcium levels. In cases of hyponatremia or hypocalcemia, magnesium and potassium must be checked and corrected accordingly.
- If the patient has significant comorbidities, then transfusion may be considered to achieve a higher hemoglobin level, especially prior to surgery.
- For any acid-base disturbance, it is important to elucidate the underlying cause for both the diagnosis and the treatment to be effective and successful.

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