Disorders of Acid-Base Balance

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Maintenance of acid-base homeostasis is a vital function of the living organism. Deviations of systemic acidity in either direction can impose adverse consequences and when severe can threaten life itself. Acid-base disorders frequently are encountered in the outpatient and especially in the inpatient setting. Effective management of acid-base disturbances, commonly a challenging task, rests with accurate diagnosis, sound understanding of the underlying pathophysiology and impact on organ function, and familiarity with treatment and attendant complications [1].

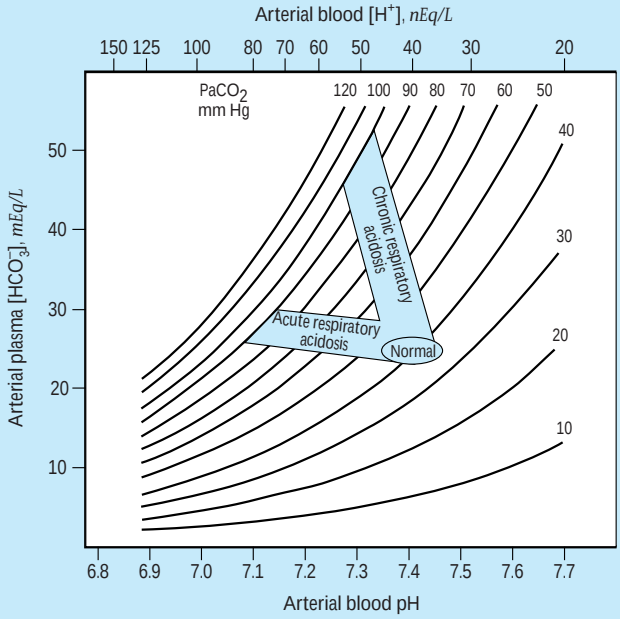
Clinical acid-base disorders are conventionally defined from the vantage point of their impact on the carbonic acid-bicarbonate buffer system. This approach is justified by the abundance of this buffer pair in body fluids; its physiologic preeminence; and the validity of the isohydric principle in the living organism, which specifies that all the other buffer systems are in equilibrium with the carbonic acid-bicarbonate buffer pair. Thus, as indicated by the Henderson equation, $[H^+] = 24 \times PaCO_2/[HCO_3^-]$ (the equilibrium relationship of the carbonic acid-bicarbonate system), the hydrogen ion concentration of blood ($[H^+]$, expressed in nEq/L) at any moment is a function of the prevailing ratio of the arterial carbon dioxide tension ($PaCO_2$, expressed in mm Hg) and the plasma bicarbonate concentration ($[HCO_3^-]$, expressed in mEq/L). As a corollary, changes in systemic acidity can occur only through changes in the values of its two determinants, $PaCO_2$ and the plasma bicarbonate concentration. Those acid-base disorders initiated by a change in $PaCO_2$ are referred to as respiratory disorders; those initiated by a change in plasma bicarbonate concentration are known as metabolic disorders. There are four cardinal acid-base disturbances: respiratory acidosis, respiratory alkalosis, metabolic acidosis, and metabolic alkalosis. Each can be encountered alone, as a simple disorder, or can be a part of a mixed-disorder, defined as the simultaneous presence of two or more simple

CHAPTER 6

acid-base disturbances. Mixed acid-base disorders are frequently observed in hospitalized patients, especially in the critically ill.

The clinical aspects of the four cardinal acid-base disorders are depicted. For each disorder the following are illustrated: the underlying pathophysiology, secondary adjustments in acid-base equilibrium in response to the initiating disturbance, clinical manifestations, causes, and therapeutic principles.

Respiratory Acidosis



Steady-state relationships in respiratory acidosis: average increase per mm Hg rise in $PaCO_2$

	$[HCO_3^-]$ mEq/L	$[H^+]$ nEq/L
Acute adaptation	0.1	0.75
Chronic adaptation	0.3	0.3

FIGURE 6-1

Quantitative aspects of adaptation to respiratory acidosis. Respiratory acidosis, or primary hypercapnia, is the acid-base disturbance initiated by an increase in arterial carbon dioxide tension ($PaCO_2$) and entails acidification of body fluids. Hypercapnia elicits adaptive increments in plasma bicarbonate concentration that should be viewed as an integral part of respiratory acidosis. An immediate increment in plasma bicarbonate occurs in response to hypercapnia. This acute adaptation is complete within 5 to 10 minutes from the onset of hypercapnia and originates exclusively from acidic titration of the nonbicarbonate buffers of the body (hemoglobin, intracellular proteins and phosphates, and to a lesser extent plasma proteins). When hypercapnia is sustained, renal adjustments markedly amplify the secondary increase in plasma bicarbonate, further ameliorating the resulting acidemia. This chronic adaptation requires 3 to 5 days for completion and reflects generation of new bicarbonate by the kidneys as a result of upregulation of renal acidification [2]. Average increases in plasma bicarbonate and hydrogen ion concentrations per mm Hg increase in $PaCO_2$ after completion of the acute or chronic adaptation to respiratory acidosis are shown. Empiric observations on these adaptations have been used for construction of 95% confidence intervals for graded degrees of acute or chronic respiratory acidosis represented by the areas in color in the acid-base template. The black ellipse near the center of the figure indicates the normal range for the acid-base parameters [3]. Note that for the same level of $PaCO_2$, the degree of acidemia is considerably lower in chronic respiratory acidosis than it is in acute respiratory acidosis. Assuming a steady state is present, values falling within the areas in color are consistent with but not diagnostic of the corresponding simple disorders. Acid-base values falling outside the areas in color denote the presence of a mixed acid-base disturbance [4].

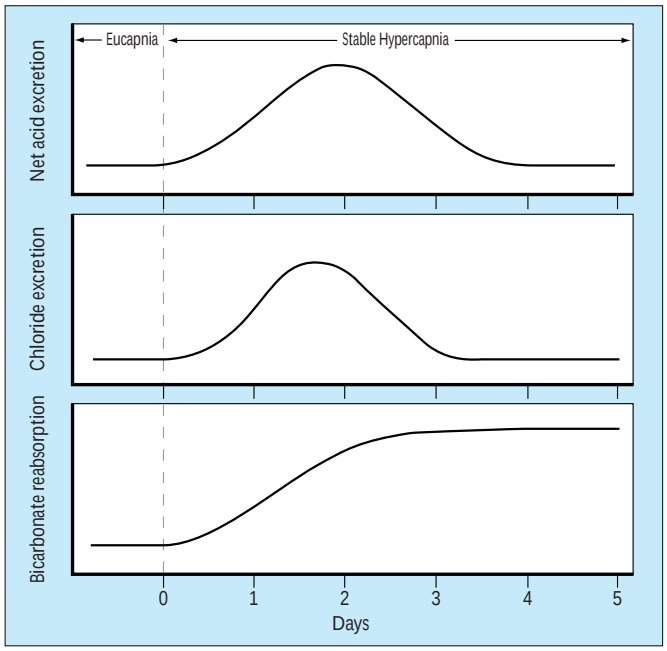


FIGURE 6-2

Renal acidification response to chronic hypercapnia. Sustained hypercapnia entails a persistent increase in the secretory rate of the renal tubule for hydrogen ions (H^+) and a persistent decrease in the reabsorption rate of chloride ions (Cl^-). Consequently, net acid excretion (largely in the form of ammonium) transiently exceeds endogenous acid production, leading to generation of new bicarbonate ions (HCO_3^-) for the body fluids. Conservation of these new bicarbonate ions is ensured by the gradual augmentation in the rate of renal bicarbonate reabsorption, itself a reflection of the hypercapnia-induced increase in the hydrogen ion secretory rate. A new steady state emerges when two things occur: the augmented filtered load of bicarbonate is precisely balanced by the accelerated rate of bicarbonate reabsorption and net acid excretion returns to the level required to offset daily endogenous acid production. The transient increase in net acid excretion is accompanied by a transient increase in chloride excretion. Thus, the resultant ammonium chloride (NH_4Cl) loss generates the hypochloremic hyperbicarbonatemia characteristic of chronic respiratory acidosis. Hypochloremia is sustained by the persistently depressed chloride reabsorption rate. The specific cellular mechanisms mediating the renal acidification response to chronic hypercapnia are under active investigation. Available evidence supports a parallel increase in the rates of the luminal sodium ion–hydrogen ion (Na^+-H^+) exchanger and the basolateral Na^+-$3HCO_3^-$ cotransporter in the proximal tubule. However, the nature of these adaptations remains unknown [5]. The quantity of the H^+-adenosine triphosphatase (ATPase) pumps does not change in either cortex or medulla. However, hypercapnia induces exocytotic insertion of H^+-ATPase–containing subapical vesicles to the luminal membrane of proximal tubule cells as well as type A intercalated cells of the cortical and medullary collecting ducts. New H^+-ATPase pumps thereby are recruited to the luminal membrane for augmented acidification [6,7]. Furthermore, chronic hypercapnia increases the steady-state abundance of mRNA coding for the basolateral $Cl—HCO_3^-$ exchanger (band 3 protein) of type A intercalated cells in rat renal cortex and medulla, likely indicating increased band 3 protein levels and therefore augmented basolateral anion exchanger activity [8].

SIGNS AND SYMPTOMS OF RESPIRATORY ACIDOSIS

Central Nervous System	Respiratory System	Cardiovascular System
Mild to moderate hypercapnia	Breathlessness	Mild to moderate hypercapnia
Cerebral vasodilation	Central and peripheral cyanosis (especially when breathing room air)	Warm and flushed skin
Increased intracranial pressure	Pulmonary hypertension	Bounding pulse
Headache		Well maintained cardiac output and blood pressure
Confusion		Diaphoresis
Combativeness		Severe hypercapnia
Hallucinations		Cor pulmonale
Transient psychosis		Decreased cardiac output
Myoclonic jerks		Systemic hypotension
Flapping tremor		Cardiac arrhythmias
Severe hypercapnia		Prerenal azotemia
Manifestations of pseudotumor cerebri		Peripheral edema
Stupor		
Coma		
Constricted pupils		
Depressed tendon reflexes		
Extensor plantar response		
Seizures		
Papilledema		

FIGURE 6-3

Signs and symptoms of respiratory acidosis. The effects of respiratory acidosis on the central nervous system are collectively known as hypercapnic encephalopathy. Factors responsible for its development include the magnitude and time course of the hypercapnia, severity of the acidemia, and degree of attendant hypoxemia. Progressive narcosis and coma may occur in patients receiving uncontrolled oxygen therapy in whom levels of arterial carbon dioxide tension ($PaCO_2$) may reach or exceed 100 mm Hg. The hemodynamic consequences of carbon dioxide retention reflect several mechanisms, including direct impairment of myocardial contractility, systemic vasodilation caused by direct relaxation of vascular smooth muscle, sympathetic stimulation, and acidosis-induced blunting of receptor responsiveness to catecholamines. The net effect is dilation of systemic vessels, including the cerebral circulation; whereas vasoconstriction might develop in the pulmonary and renal circulations. Salt and water retention commonly occur in chronic hypercapnia, especially in the presence of cor pulmonale. Mechanisms at play include hypercapnia-induced stimulation of the renin-angiotensin-aldosterone axis and the sympathetic nervous system, elevated levels of cortisol and antidiuretic hormone, and increased renal vascular resistance. Of course, coexisting heart failure amplifies most of these mechanisms [1,2].

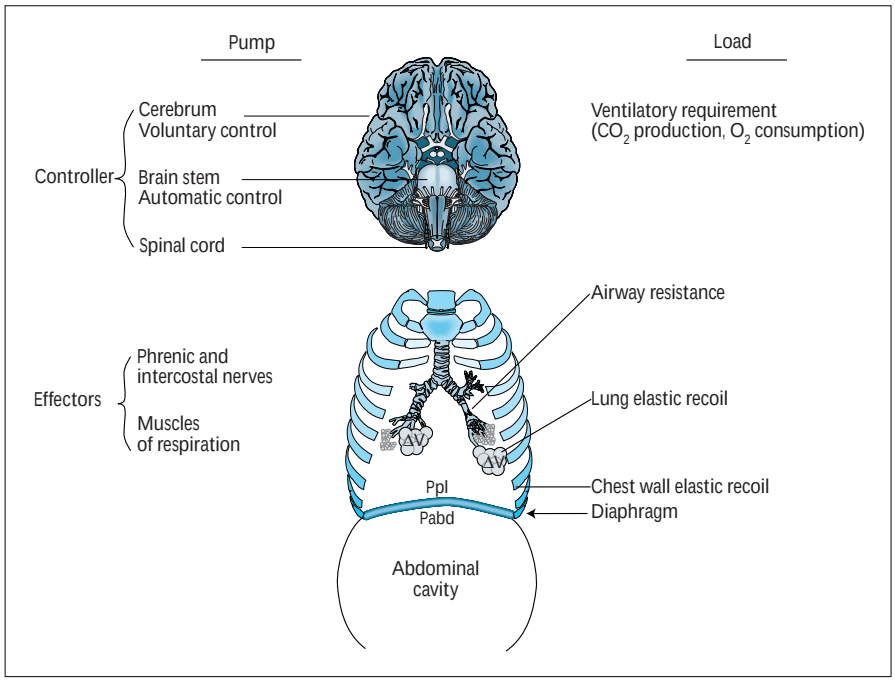


FIGURE 6-4

Main components of the ventilatory system. The ventilatory system is responsible for maintaining the arterial carbon dioxide tension ($PaCO_2$) within normal limits by adjusting minute ventilation ($\dot{V}$) to match the rate of carbon dioxide production. The main elements of ventilation are the respiratory pump, which generates a pressure gradient responsible for air flow, and the loads that oppose such action. The machinery of the respiratory pump includes the cerebrum, brain stem, spinal cord, phrenic and intercostal nerves, and the muscles of respiration. Inspiratory muscle contraction lowers pleural pressure (Ppl) thereby inflating the lungs (ΔV). The diaphragm, the most important inspiratory muscle, moves downward as a piston at the floor of the thorax, raising abdominal pressure (Pabd). The inspiratory decrease in Ppl by the respiratory pump must be sufficient to counterbalance the opposing effect of the combined loads, including the airway flow resistance, and the elastic recoil of the lungs and chest wall. The ventilatory requirement influences the load by altering the frequency and depth of the ventilatory cycle. The strength of the respiratory pump is evaluated by the pressure generated (ΔP = Ppl - Pabd).

DETERMINANTS AND CAUSES OF CARBON DIOXIDE RETENTION

Respiratory Pump

- Depressed Central Drive
  - Acute
    - General anesthesia
    - Sedative overdose
    - Head trauma
    - Cerebrovascular accident
    - Central sleep apnea
    - Cerebral edema
    - Brain tumor
    - Encephalitis
    - Brainstem lesion
  - Chronic
    - Sedative overdose
    - Methadone or heroin addiction
    - Sleep disordered breathing
    - Brain tumor
    - Bulbar poliomyelitis
    - Hypothyroidism
- Abnormal Neuromuscular Transmission
  - Acute
    - High spinal cord injury
    - Guillain-Barré syndrome
    - Status epilepticus
    - Botulism
    - Tetanus
    - Crisis in myasthenia gravis
    - Hypokalemic myopathy
    - Familial periodic paralysis
    - Drugs or toxic agents *eg*, curare, succinylcholine, aminoglycosides, organophosphorus
  - Chronic
    - Poliomyelitis
    - Multiple sclerosis
    - Muscular dystrophy
    - Amyotrophic lateral sclerosis
    - Diaphragmatic paralysis
    - Myopathic disease *eg*, polymyositis
- Muscle Dysfunction
  - Acute
    - Fatigue
    - Hyperkalemia
    - Hypokalemia
    - Hypoperfusion state
    - Hypoxemia
    - Malnutrition
  - Chronic
    - Myopathic disease *eg*, polymyositis

Load

- Increased Ventilatory Demand
  - High carbohydrate diet
  - Sorbent-regenerative hemodialysis
  - Pulmonary thromboembolism
  - Fat, air pulmonary embolism
  - Sepsis
  - Hypovolemia
- Augmented Airway Flow Resistance
  - Acute
    - Upper airway obstruction
      - Coma-induced hypopharyngeal obstruction
      - Aspiration of foreign body or vomitus
      - Laryngospasm
      - Angioedema
      - Obstructive sleep apnea
      - Inadequate laryngeal intubation
      - Laryngeal obstruction after intubation
    - Lower airway obstruction
      - Generalized bronchospasm
      - Airway edema and secretions
      - Severe episode of spasmodic asthma
      - Bronchiolitis of infants and adults
  - Chronic
    - Upper airway obstruction
      - Tonsillar and peritonsillar hypertrophy
      - Paralysis of vocal cords
      - Tumor of the cords or larynx
      - Airway stenosis after prolonged intubation
      - Thymoma, aortic aneurysm
    - Lower airway obstruction
      - Airway scarring
      - Chronic obstructive lung disease *eg*, bronchitis, bronchiolitis, bronchiectasis, emphysema
- Lung Stiffness
  - Acute
    - Severe bilateral pneumonia or bronchopneumonia
    - Acute respiratory distress syndrome
    - Severe pulmonary edema
    - Atelectasis
  - Chronic
    - Severe chronic pneumonitis
    - Diffuse infiltrative disease *eg*, alveolar proteinosis
    - Interstitial fibrosis
- Chest Wall Stiffness
  - Acute
    - Rib fractures with flail chest
    - Pneumothorax
    - Hemothorax
    - Abdominal distention
    - Ascites
    - Peritoneal dialysis
  - Chronic
    - Kyphoscoliosis, spinal arthritis
    - Obesity
    - Fibrothorax
    - Hydrothorax
    - Chest wall tumor

FIGURE 6-5

Determinants and causes of carbon dioxide retention. When the respiratory pump is unable to balance the opposing load, respiratory acidosis develops. Decreases in respiratory pump strength, increases in load, or a combination of the two, can result in carbon dioxide retention. Respiratory pump failure can occur because of depressed central drive, abnormal neuromuscular transmission, or respiratory muscle dysfunction. A higher load can be caused by increased ventilatory demand, augmented airway flow resistance, and stiffness of the lungs or chest wall. In most cases, causes of the various determinants of carbon dioxide retention, and thus respiratory acidosis, are categorized into acute and chronic subgroups, taking into consideration their usual mode of onset and duration [2].

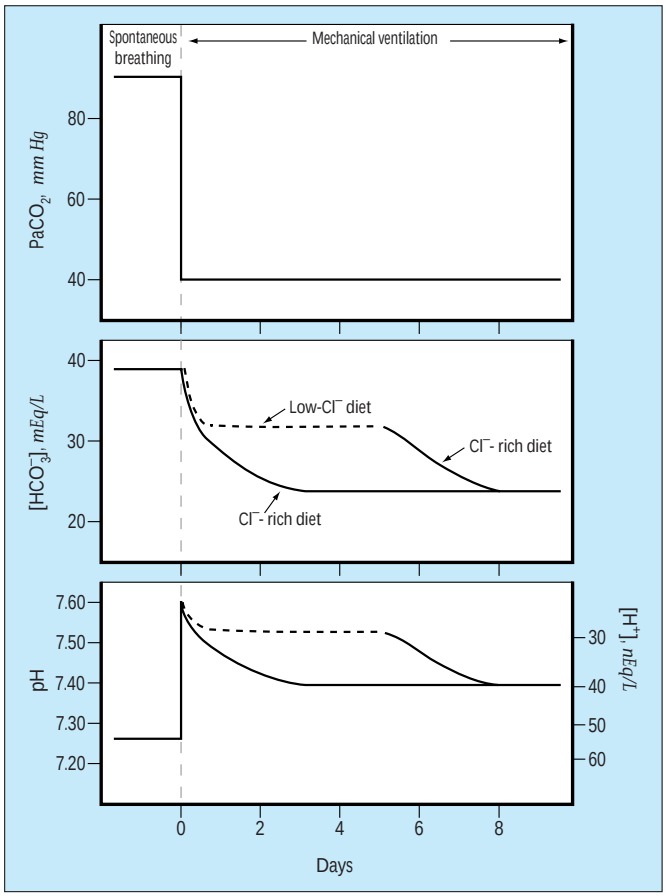


FIGURE 6-6

Posthypercapnic metabolic alkalosis. Development of posthypercapnic metabolic alkalosis is shown after abrupt normalization of the arterial carbon dioxide tension ($PaCO_2$) by way of mechanical ventilation in a 70-year-old man with respiratory decompensation who has chronic obstructive pulmonary disease and chronic hypercapnia. The acute decrease in plasma bicarbonate concentration ($[HCO_3^-]$) over the first few minutes after the decrease in $PaCO_2$ originates from alkaline titration of the nonbicarbonate buffers of the body. When a diet rich in chloride (Cl^-) is provided, the excess bicarbonate is excreted by the kidneys over the next 2 to 3 days, and acid-base equilibrium is normalized. In contrast, a low-chloride diet sustains the hyperbicarbonatemia and perpetuates the posthypercapnic metabolic alkalosis. Abrupt correction of severe hypercapnia by way of mechanical ventilation generally is not recommended. Rather, gradual return toward the patient's baseline $PaCO_2$ level should be pursued [1,2]. $[H^+]$—hydrogen ion concentration.

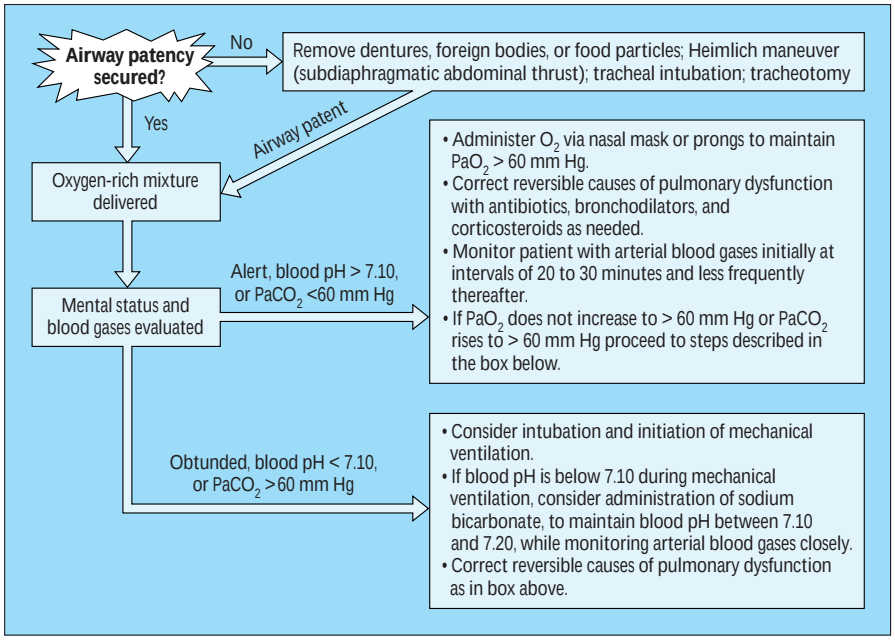


FIGURE 6-7

Acute respiratory acidosis management. Securing airway patency and delivering an oxygen-rich mixture are critical initial steps in management. Subsequent measures must be directed at identifying and correcting the underlying cause, whenever possible [1,9]. $PaCO_2$—arterial carbon dioxide tension.

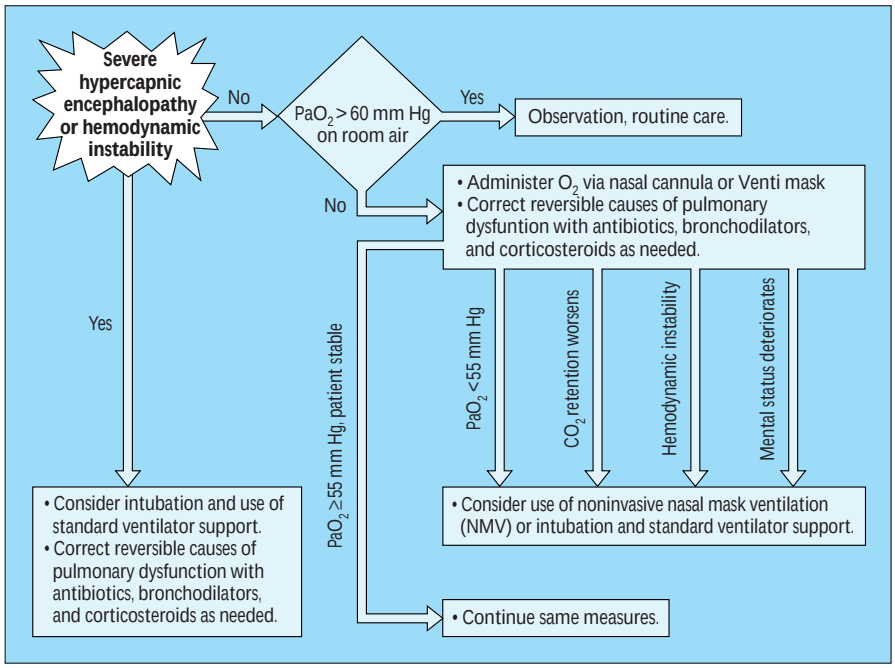
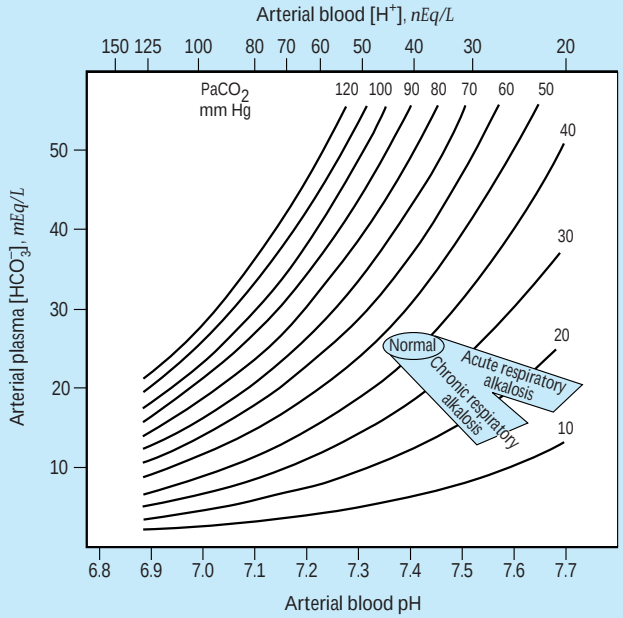


FIGURE 6-8

Chronic respiratory acidosis management. Therapeutic measures are guided by the presence or absence of severe hypercapnic encephalopathy or hemodynamic instability. An aggressive approach that favors the early use of ventilator assistance is most appropriate for patients with acute respiratory acidosis. In contrast, a more conservative approach is advisable in patients with chronic hypercapnia because of the great difficulty often encountered in weaning these patients from ventilators. As a rule, the lowest possible inspired fraction of oxygen that achieves adequate oxygenation (PaO_2 on the order of 60 mm Hg) is used. Contrary to acute respiratory acidosis, the underlying cause of chronic respiratory acidosis only rarely can be resolved [1,9].

Respiratory Alkalosis



Steady-state relationships in respiratory alkalosis: average decrease per mm Hg fall in $PaCO_2$

	$[HCO_3^-]$ mEq/L	$[H^+]$ nEq/L
Acute adaptation	0.2	0.75
Chronic adaptation	0.4	0.4

FIGURE 6-9

Adaptation to respiratory alkalosis. Respiratory alkalosis, or primary hypocapnia, is the acid-base disturbance initiated by a decrease in arterial carbon dioxide tension ($PaCO_2$) and entails alkalinization of body fluids. Hypocapnia elicits adaptive decrements in plasma bicarbonate concentration that should be viewed as an integral part of respiratory alkalosis. An immediate decrement in plasma bicarbonate occurs in response to hypocapnia. This acute adaptation is complete within 5 to 10 minutes from the onset of hypocapnia and is accounted for principally by alkaline titration of the nonbicarbonate buffers of the body. To a lesser extent, this acute adaptation reflects increased production of organic acids, notably lactic acid. When hypocapnia is sustained, renal adjustments cause an additional decrease in plasma bicarbonate, further ameliorating the resulting alkalemia. This chronic adaptation requires 2 to 3 days for completion and reflects retention of hydrogen ions by the kidneys as a result of downregulation of renal acidification [2,10]. Shown are the average decreases in plasma bicarbonate and hydrogen ion concentrations per mm Hg decrease in $PaCO_2$after completion of the acute or chronic adaptation to respiratory alkalosis. Empiric observations on these adaptations have been used for constructing 95% confidence intervals for graded degrees of acute or chronic respiratory alkalosis, which are represented by the areas in color in the acid-base template. The black ellipse near the center of the figure indicates the normal range for the acid-base parameters. Note that for the same level of $PaCO_2$, the degree of alkalemia is considerably lower in chronic than it is in acute respiratory alkalosis. Assuming that a steady state is present, values falling within the areas in color are consistent with but not diagnostic of the corresponding simple disorders. Acid-base values falling outside the areas in color denote the presence of a mixed acid-base disturbance [4].

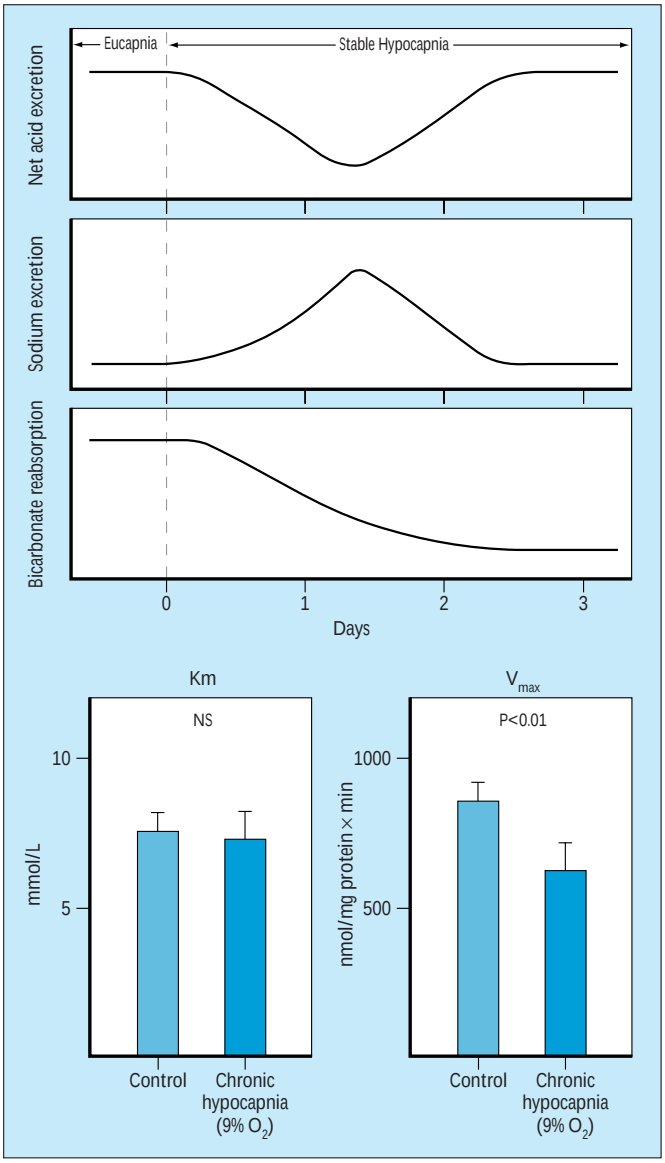


FIGURE 6-10

Renal acidification response to chronic hypocapnia. **A**, Sustained hypocapnia entails a persistent decrease in the renal tubular secretory rate of hydrogen ions and a persistent increase in the chloride reabsorption rate. As a result, transient suppression of net acid excretion occurs. This suppression is largely manifested by a decrease in ammonium excretion and, early on, by an increase in bicarbonate excretion. The transient discrepancy between net acid excretion and endogenous acid production, in turn, leads to positive hydrogen ion balance and a reduction in the bicarbonate stores of the body. Maintenance of the resulting hypobicarbonatemia is ensured by the gradual suppression in the rate of renal bicarbonate reabsorption. This suppression itself is a reflection of the hypocapnia-induced decrease in the hydrogen ion secretory rate. A new steady state emerges when two things occur: the reduced filtered load of bicarbonate is precisely balanced by the dampened rate of bicarbonate reabsorption and net acid excretion returns to the level required to offset daily endogenous acid production. The transient retention of acid during sustained hypocapnia is normally accompanied by a loss of sodium in the urine (and *not* by a retention of chloride as analogy with chronic respiratory acidosis would dictate). The resulting extracellular fluid loss is responsible for the hyperchloremia that typically accompanies chronic respiratory alkalosis. Hyperchloremia is sustained by the persistently enhanced chloride reabsorption rate. If dietary sodium is restricted, acid retention is achieved in the company of increased potassium excretion. The specific cellular mechanisms mediating the renal acidification response to chronic hypocapnia are under investigation. Available evidence indicates a parallel decrease in the rates of the luminal sodium ion–hydrogen ion (Na^+-H^+) exchanger and the basolateral sodium ion–3 bicarbonate ion (Na^+-$3HCO_3^-$) cotransporter in the proximal tubule. This parallel decrease reflects a decrease in the maximum velocity (V_{max}) of each transporter but no change in the substrate concentration at half-maximal velocity (K_m) for sodium (as shown in **B** for the Na^+-H^+ exchanger in rabbit renal cortical brush-border membrane vesicles) [11]. Moreover, hypocapnia induces endocytotic retrieval of H^+-adenosine triphosphatase (ATPase) pumps from the luminal membrane of the proximal tubule cells as well as type A intercalated cells of the cortical and medullary collecting ducts. It remains unknown whether chronic hypocapnia alters the quantity of the H^+-ATPase pumps as well as the kinetics or quantity of other acidification transporters in the renal cortex or medulla [6]. NS—not significant. (**B**, *From* Hilden and coworkers [11]; with permission.)

SIGNS AND SYMPTOMS OF RESPIRATORY ALKALOSIS

Central Nervous System	Cardiovascular System	Neuromuscular System
Cerebral vasoconstriction	Chest oppression	Numbness and paresthesias of the extremities
Reduction in intracranial pressure	Angina pectoris	Circumoral numbness
Light-headedness	Ischemic electrocardiographic changes	Laryngeal spasm
Confusion	Normal or decreased blood pressure	Manifestations of tetany
Increased deep tendon reflexes	Cardiac arrhythmias	Muscle cramps
Generalized seizures	Peripheral vasoconstriction	Carpopedal spasm
		Trousseau's sign
		Chvostek's sign

FIGURE 6-11

Signs and symptoms of respiratory alkalosis. The manifestations of primary hypocapnia frequently occur in the acute phase, but seldom are evident in chronic respiratory alkalosis. Several mechanisms mediate these clinical manifestations, including cerebral hypoperfusion, alkalemia, hypocalcemia, hypokalemia, and decreased release of oxygen to the tissues by hemoglobin. The cardiovascular effects of respiratory alkalosis are more prominent in patients undergoing mechanical ventilation and those with ischemic heart disease [2].

CAUSES OF RESPIRATORY ALKALOSIS

Hypoxemia or Tissue Hypoxia	Central Nervous System Stimulation	Drugs or Hormones	Stimulation of Chest Receptors	Miscellaneous
Decreased inspired oxygen tension	Voluntary	Nikethamide, ethamivan	Pneumonia	Pregnancy
High altitude	Pain	Doxapram	Asthma	Gram-positive septicemia
Bacterial or viral pneumonia	Anxiety syndrome-hyperventilation syndrome	Xanthines	Pneumothorax	Gram-negative septicemia
Aspiration of food, foreign object, or vomitus	Psychosis	Salicylates	Hemothorax	Hepatic failure
Laryngospasm	Fever	Catecholamines	Flail chest	Mechanical hyperventilation
Drowning	Subarachnoid hemorrhage	Angiotensin II	Acute respiratory distress syndrome	Heat exposure
Cyanotic heart disease	Cerebrovascular accident	Vasopressor agents	Cardiogenic and noncardiogenic pulmonary edema	Recovery from metabolic acidosis
Severe anemia	Meningoencephalitis	Progesterone	Pulmonary embolism	
Left shift deviation of oxyhemoglobin curve	Tumor	Medroxyprogesterone	Pulmonary fibrosis	
Hypotension	Trauma	Dinitrophenol		
Severe circulatory failure		Nicotine		
Pulmonary edema				

FIGURE 6-12

Respiratory alkalosis is the most frequent acid-base disorder encountered because it occurs in normal pregnancy and high-altitude residence. Pathologic causes of respiratory alkalosis include various hypoxemic conditions, pulmonary disorders, central nervous system diseases, pharmacologic or hormonal stimulation of ventilation, hepatic failure, sepsis, the anxiety-hyperventilation syndrome, and other entities. Most of these causes are associated with the abrupt occurrence of hypocapnia; however, in many instances, the process might be sufficiently prolonged to permit full chronic adaptation to occur. Consequently, no attempt has been made to separate these conditions into acute and chronic categories. Some of the major causes of respiratory alkalosis are benign, whereas others are life-threatening. Primary hypocapnia is particularly common among the critically ill, occurring either as the simple disorder or as a component of mixed disturbances. Its presence constitutes an ominous prognostic sign, with mortality increasing in direct proportion to the severity of the hypocapnia [2].

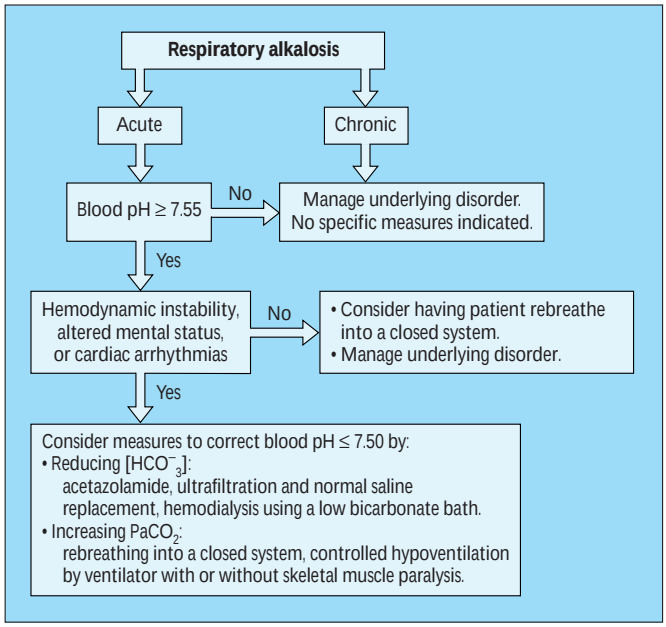


FIGURE 6-13

Respiratory alkalosis management. Because chronic respiratory alkalosis poses a low risk to health and produces few or no symptoms, measures for treating the acid-base disorder itself are not required. In contrast, severe alkalemia caused by acute primary hypocapnia requires corrective measures that depend on whether serious clinical manifestations are present. Such measures can be directed at reducing plasma bicarbonate concentration ($[HCO_3^-]$), increasing the arterial carbon dioxide tension ($PaCO_2$), or both. Even if the baseline plasma bicarbonate is moderately decreased, reducing it further can be particularly rewarding in this setting. In addition, this maneuver combines effectiveness with relatively little risk [1,2].

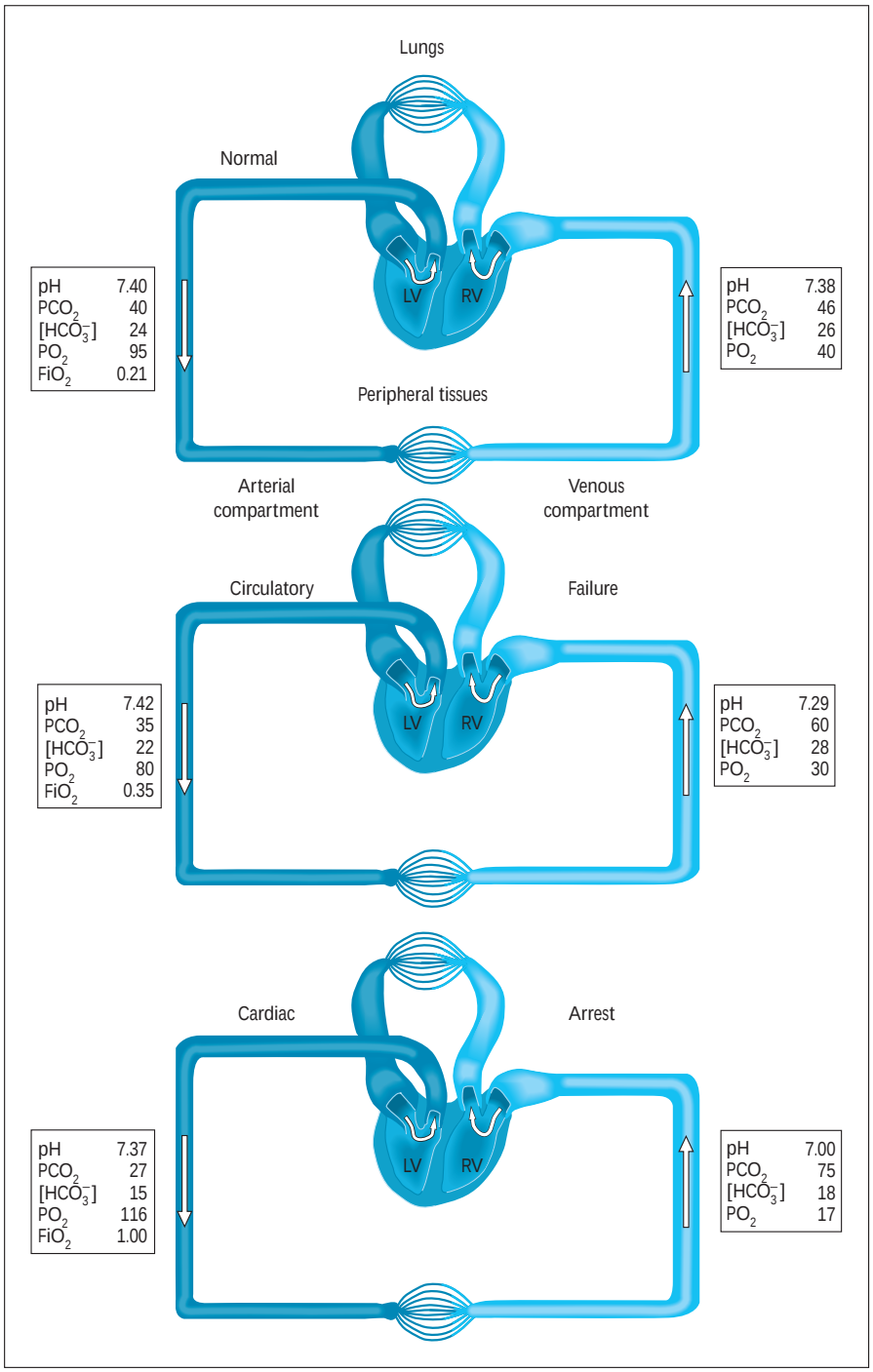


FIGURE 6-14

Pseudorespiratory alkalosis. This entity develops in patients with profound depression of cardiac function and pulmonary perfusion but relative preservation of alveolar ventilation. Patients include those with advanced circulatory failure and those undergoing cardiopulmonary resuscitation. The severely reduced pulmonary blood flow limits the amount of carbon dioxide delivered to the lungs for excretion, thereby increasing the venous carbon dioxide tension (PCO_2). In contrast, the increased ventilation-to-perfusion ratio causes a larger than normal removal of carbon dioxide per unit of blood traversing the pulmonary circulation, thereby giving rise to arterial hypocapnia [12,13]. Note a progressive widening of the arteriovenous difference in pH and PCO_2 in the two settings of cardiac dysfunction. The hypobicarbonatemia in the setting of cardiac arrest represents a complicating element of lactic acidosis. Despite the presence of arterial hypocapnia, pseudorespiratory alkalosis represents a special case of respiratory acidosis, as absolute carbon dioxide excretion is decreased and body carbon dioxide balance is positive. Furthermore, the extreme oxygen deprivation prevailing in the tissues might be completely disguised by the reasonably preserved arterial oxygen values. Appropriate monitoring of acid-base composition and oxygenation in patients with advanced cardiac dysfunction requires mixed (or central) venous blood sampling in addition to arterial blood sampling. Management of pseudorespiratory alkalosis must be directed at optimizing systemic hemodynamics [1,13].

Metabolic Acidosis

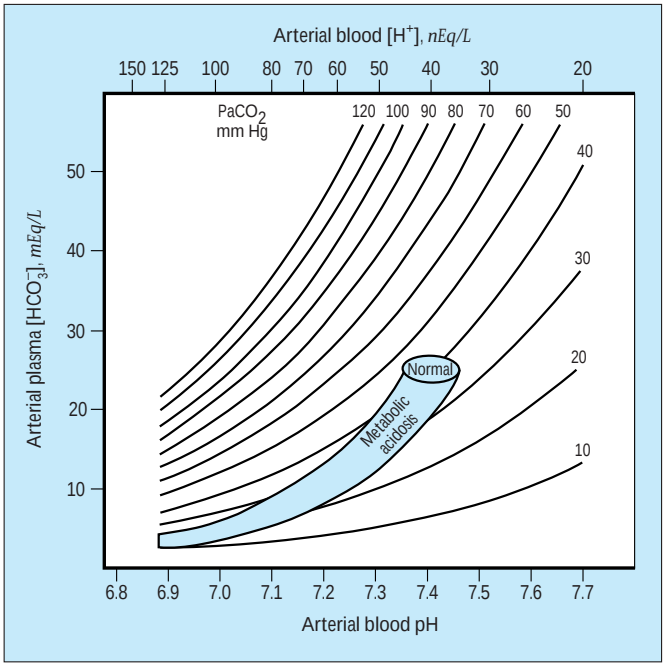


FIGURE 6-15

Ninety-five percent confidence intervals for metabolic acidosis. Metabolic acidosis is the acid-base disturbance initiated by a decrease in plasma bicarbonate concentration ($[HCO_3^-]$). The resultant acidemia stimulates alveolar ventilation and leads to the secondary hypocapnia characteristic of the disorder. Extensive observations in humans encompassing a wide range of stable metabolic acidosis indicate a roughly linear relationship between the steady-state decrease in plasma bicarbonate concentration and the associated decrement in arterial carbon dioxide tension ($PaCO_2$). The slope of the steady state $\Delta PaCO_2$ versus $\Delta[HCO_3^-]$ relationship has been estimated as approximately 1.2 mm Hg per mEq/L decrease in plasma bicarbonate concentration. Such empiric observations have been used for construction of 95% confidence intervals for graded degrees of metabolic acidosis, represented by the area in color in the acid-base template. The black ellipse near the center of the figure indicates the normal range for the acid-base parameters [3]. Assuming a steady state is present, values falling within the area in color are consistent with but not diagnostic of simple metabolic acidosis. Acid-base values falling outside the area in color denote the presence of a mixed acid-base disturbance [4]. $[H^+]$—hydrogen ion concentration.

SIGNS AND SYMPTOMS OF METABOLIC ACIDOSIS

Respiratory System	Cardiovascular System	Metabolism	Central Nervous System	Skeleton
Hyperventilation	Impairment of cardiac contractility, arteriolar dilation, venoconstriction, and centralization of blood volume	Increased metabolic demands	Impaired metabolism	Osteomalacia
Respiratory distress and dyspnea	Reductions in cardiac output, arterial blood pressure, and hepatic and renal blood flow	Insulin resistance	Inhibition of cell volume regulation	Fractures
Decreased strength of respiratory muscles and promotion of muscle fatigue	Sensitization to reentrant arrhythmias and reduction in threshold for ventricular fibrillation	Inhibition of anaerobic glycolysis	Progressive obtundation	
	Increased sympathetic discharge but attenuation of cardiovascular responsiveness to catecholamines	Reduction in adenosine triphosphate synthesis	Coma	
		Hyperkalemia		
		Increased protein degradation		

FIGURE 6-16

Signs and symptoms of metabolic acidosis. Among the various clinical manifestations, particularly pernicious are the effects of severe acidemia (blood pH < 7.20) on the cardiovascular system. Reductions in cardiac output, arterial blood pressure, and hepatic and renal blood flow can occur and life-threatening arrhythmias can develop. Chronic acidemia, as it occurs in untreated renal tubular acidosis and uremic acidosis, can cause calcium dissolution from the bone mineral and consequent skeletal abnormalities.

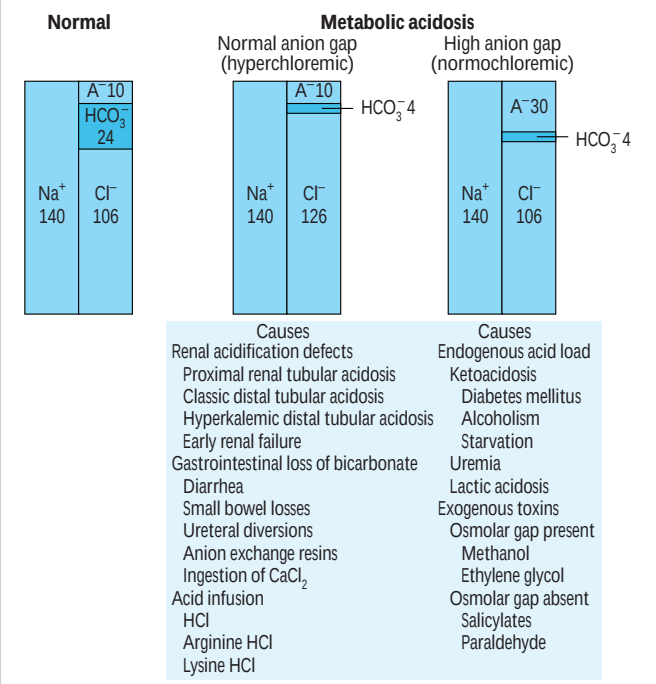


FIGURE 6-17

Causes of metabolic acidosis tabulated according to the prevailing pattern of plasma electrolyte composition. Assessment of the plasma unmeasured anion concentration (anion gap) is a very useful first step in approaching the differential diagnosis of unexplained metabolic acidosis. The plasma anion gap is calculated as the difference between the sodium concentration and the sum of chloride and bicarbonate concentrations. Under normal circumstances, the plasma anion gap is primarily composed of the net negative charges of plasma proteins, predominantly albumin, with a smaller contribution from many other organic and inorganic anions. The normal value of the plasma anion gap is 12 ± 4 (mean ± 2 SD) mEq/L, where SD is the standard deviation. However, recent introduction of ion-specific electrodes has shifted the normal anion gap to the range of about 6 ± 3 mEq/L. In one pattern of metabolic acidosis, the decrease in bicarbonate concentration is offset by an increase in the concentration of chloride, with the plasma anion gap remaining normal. In the other pattern, the decrease in bicarbonate is balanced by an increase in the concentration of unmeasured anions (*ie*, anions not measured routinely), with the plasma chloride concentration remaining normal.

Lactic acidosis

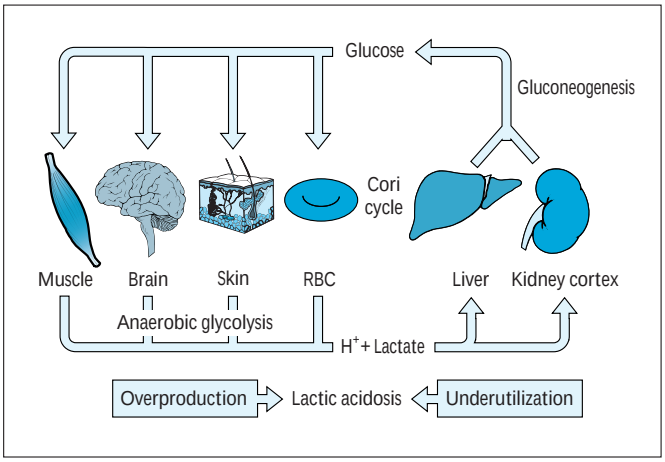


FIGURE 6-18

Lactate-producing and lactate-consuming tissues under basal conditions and pathogenesis of lactic acidosis. Although all tissues produce lactate during the course of glycolysis, those listed contribute substantial quantities of lactate to the extracellular fluid under normal aerobic conditions. In turn, lactate is extracted by the liver and to a lesser degree by the renal cortex and primarily is reconverted to glucose by way of gluconeogenesis (a smaller portion of lactate is oxidized to carbon dioxide and water). This cyclical relationship between glucose and lactate is known as the *Cori cycle*. The basal turnover rate of lactate in humans is enormous, on the order of 15 to 25 mEq/kg/d. Precise equivalence between lactate production and its use ensures the stability of plasma lactate concentration, normally ranging from 1 to 2 mEq/L. Hydrogen ions (H^+) released during lactate generation are quantitatively consumed during the use of lactate such that acid-base balance remains undisturbed. Accumulation of lactate in the circulation, and consequent lactic acidosis, is generated whenever the rate of production of lactate is higher than the rate of utilization. The pathogenesis of this imbalance reflects overproduction of lactate, underutilization, or both. Most cases of persistent lactic acidosis actually involve both overproduction and underutilization of lactate. During hypoxia, almost all tissues can release lactate into the circulation; indeed, even the liver can be converted from the premier consumer of lactate to a net producer [1,14].

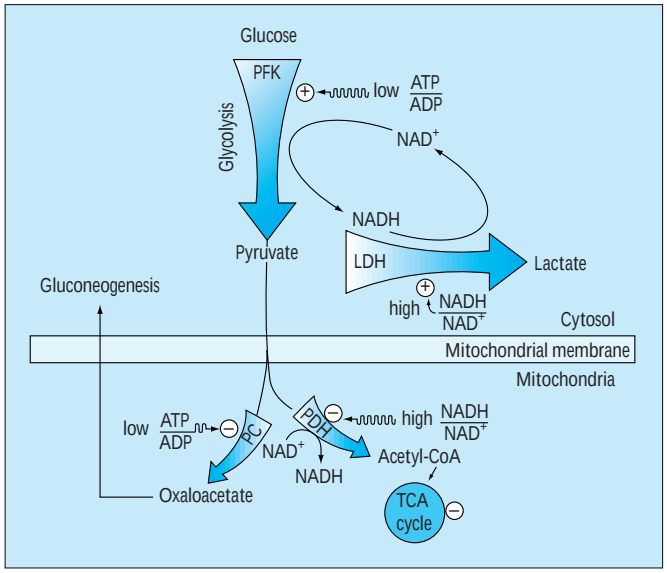


FIGURE 6-19

Hypoxia-induced lactic acidosis. Accumulation of lactate during hypoxia, by far the most common clinical setting of the disorder, originates from impaired mitochondrial oxidative function that reduces the availability of adenosine triphosphate (ATP) and NAD^+ (oxidized nicotinamide adenine dinucleotide) within the cytosol. In turn, these changes cause cytosolic accumulation of pyruvate as a consequence of both increased production and decreased utilization. Increased production of pyruvate occurs because the reduced cytosolic supply of ATP stimulates the activity of 6-phosphofructokinase (PFK), thereby accelerating glycolysis. Decreased utilization of pyruvate reflects the fact that both pathways of its consumption depend on mitochondrial oxidative reactions: oxidative decarboxylation to acetyl coenzyme A (acetyl-CoA), a reaction catalyzed by pyruvate dehydrogenase (PDH), requires a continuous supply of NAD^+; and carboxylation of pyruvate to oxaloacetate, a reaction catalyzed by pyruvate carboxylase (PC), requires ATP. The increased [NADH]/[NAD^+] ratio (NADH refers to the reduced form of the dinucleotide) shifts the equilibrium of the lactate dehydrogenase (LDH) reaction (that catalyzes the interconversion of pyruvate and lactate) to the right. In turn, this change coupled with the accumulation of pyruvate in the cytosol results in increased accumulation of lactate. Despite the prevailing mitochondrial dysfunction, continuation of glycolysis is assured by the cytosolic regeneration of NAD^+ during the conversion of pyruvate to lactate. Provision of NAD^+ is required for the oxidation of glyceraldehyde 3-phosphate, a key step in glycolysis. Thus, lactate accumulation can be viewed as the toll paid by the organism to maintain energy production during anaerobiosis (hypoxia) [14]. ADP—adenosine diphosphate; TCA cycle—tricarboxylic acid cycle.

CAUSES OF LACTIC ACIDOSIS

Type A: Impaired Tissue Oxygenation

- Shock
- Severe hypoxemia
- Generalized convulsions
- Vigorous exercise
- Exertional heat stroke
- Hypothermic shivering
- Massive pulmonary emboli
- Severe heart failure
- Profound anemia
- Mesenteric ischemia
- Carbon monoxide poisoning
- Cyanide poisoning

Type B: Preserved Tissue Oxygenation

Diseases and conditions
- Diabetes mellitus
- Hypoglycemia
- Renal failure
- Hepatic failure
- Severe infections
- Alkaloses
- Malignancies (lymphoma, leukemia, sarcoma)
- Thiamine deficiency
- Acquired immunodeficiency syndrome
- Pheochromocytoma
- Iron deficiency
- D-Lactic acidosis

Congenital enzymatic defects

Drugs and toxins
- Epinephrine, norepinephrine, vasoconstrictor agents
- Salicylates
- Ethanol
- Methanol
- Ethylene glycol
- Biguanides
- Acetaminophen
- Zidovudine
- Fructose, sorbitol, and xylitol
- Streptozotocin
- Isoniazid
- Nitroprusside
- Papaverine
- Nalidixic acid

FIGURE 6-20

Conventionally, two broad types of lactic acidosis are recognized. In type A, clinical evidence exists of impaired tissue oxygenation. In type B, no such evidence is apparent. Occasionally, the distinction between the two types may be less than obvious. Thus, inadequate tissue oxygenation can at times defy clinical detection, and tissue hypoxia can be a part of the pathogenesis of certain causes of type B lactic acidosis. Most cases of lactic acidosis are caused by tissue hypoxia arising from circulatory failure [14,15].

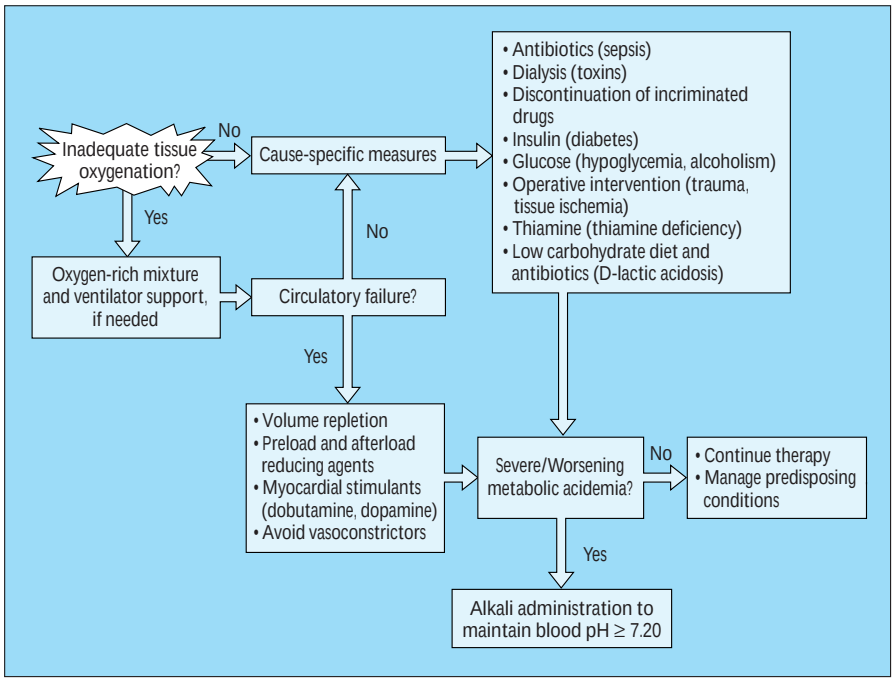


FIGURE 6-21

Lactic acidosis management. Management of lactic acidosis should focus primarily on securing adequate tissue oxygenation and on aggressively identifying and treating the underlying cause or predisposing condition. Monitoring of the patient's hemodynamics, oxygenation, and acid-base status should be used to guide therapy. In the presence of severe or worsening metabolic acidemia, these measures should be supplemented by judicious administration of sodium bicarbonate, given as an infusion rather than a bolus. Alkali administration should be regarded as a temporizing maneuver adjunctive to cause-specific measures. Given the ominous prognosis of lactic acidosis, clinicians should strive to prevent its development by maintaining adequate fluid balance, optimizing cardiorespiratory function, managing infection, and using drugs that predispose to the disorder cautiously. Preventing the development of lactic acidosis is all the more important in patients at special risk for developing it, such as those with diabetes mellitus or advanced cardiac, respiratory, renal, or hepatic disease [1,14–16].

Diabetic ketoacidosis and nonketotic hyperglycemia

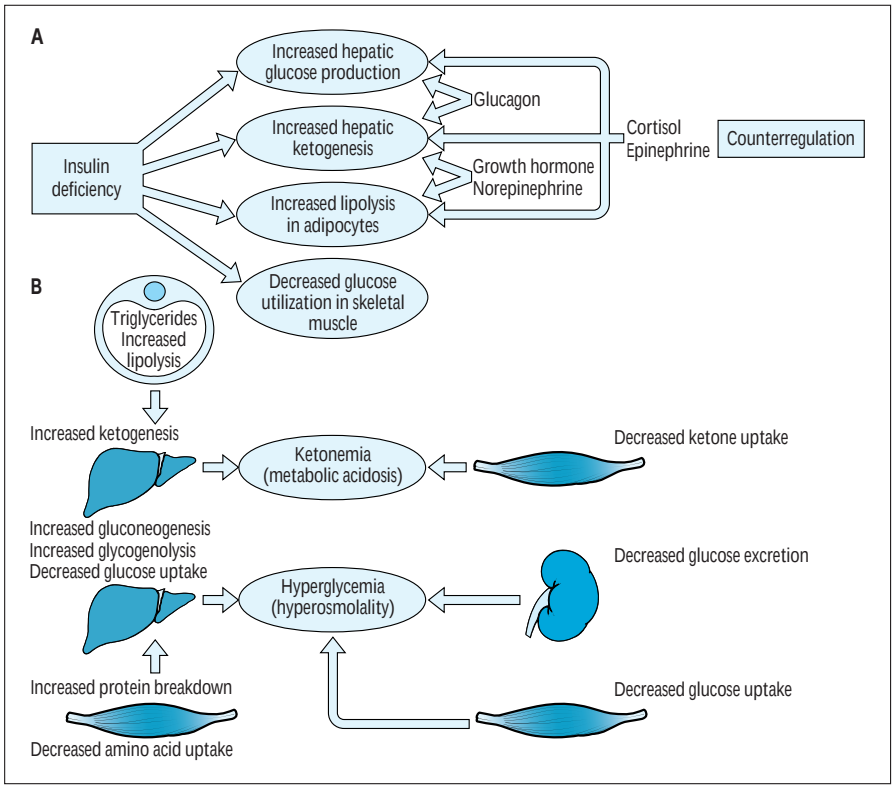
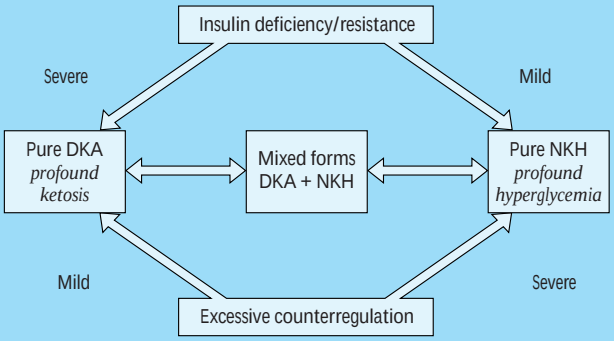


FIGURE 6-22

Role of insulin deficiency and the counterregulatory hormones, and their respective sites of action, in the pathogenesis of hyperglycemia and ketosis in diabetic ketoacidosis (DKA).**A**, Metabolic processes affected by insulin deficiency, on the one hand, and excess of glucagon, cortisol, epinephrine, norepinephrine, and growth hormone, on the other. **B**, The roles of the adipose tissue, liver, skeletal muscle, and kidney in the pathogenesis of hyperglycemia and ketonemia. Impairment of glucose oxidation in most tissues and excessive hepatic production of glucose are the main determinants of hyperglycemia. Excessive counterregulation and the prevailing hypertonicity, metabolic acidosis, and electrolyte imbalance superimpose a state of insulin resistance. Prerenal azotemia caused by volume depletion can contribute significantly to severe hyperglycemia. Increased hepatic production of ketones and their reduced utilization by peripheral tissues account for the ketonemia typically observed in DKA.



Feature	Pure DKA	Mixed forms	Pure NKH
Incidence	5–10 times higher	⟺	5–10 times lower
Mortality	5–10%	⟺	10–60%
Onset	Rapid (<2 days)	⟺	Slow (> 5 days)
Age of patient	Usually < 40 years	⟺	Usually > 40 years
Type I diabetes	Common	⟺	Rare
Type II diabetes	Rare	⟺	Common
First indication of diabetes	Often	⟺	Often
Volume depletion	Mild/moderate	⟺	Severe
Renal failure (most commonly of prerenal nature)	Mild, inconstant	⟺	Always present
Severe neurologic abnormalities	Rare	⟺	Frequent (coma in 25–50%)
Subsequent therapy with insulin	Always	⟺	Not always
Glucose	< 800 mg/dL	⟺	> 800 mg/dL
Ketone bodies	≥ 2 + in 1:1 dilution	⟺	<2+ in 1:1 dilution
Effective osmolality	< 340 mOsm/kg	⟺	> 340 mOsm/kg
pH	Decreased	⟺	Normal
$[HCO^-_3]$	Decreased	⟺	Normal
$[Na^+]$	Normal or low	⟺	Normal or high
$[K^+]$	Variable	⟺	Variable

FIGURE 6-23

Clinical features of diabetic ketoacidosis (DKA) and nonketotic hyperglycemia (NKH). DKA and NKH are the most important acute metabolic complications of patients with uncontrolled diabetes mellitus. These disorders share the same overall pathogenesis that includes insulin deficiency and resistance and excessive counterregulation; however, the importance of each of these endocrine abnormalities differs significantly in DKA and NKH. As depicted here, pure NKH is characterized by profound hyperglycemia, the result of mild insulin deficiency and severe counterregulation (*eg*, high glucagon levels). In contrast, pure DKA is characterized by profound ketosis that largely is due to severe insulin deficiency, with counterregulation being generally of lesser importance. These pure forms define a continuum that includes mixed forms incorporating clinical and biochemical features of both DKA and NKH. Dyspnea and Kussmaul's respiration result from the metabolic acidosis of DKA, which is generally absent in NKH. Sodium and water deficits and secondary renal dysfunction are more severe in NKH than in DKA. These deficits also play a pathogenetic role in the profound hypertonicity characteristic of NKH. The severe hyperglycemia of NKH, often coupled with hypernatremia, increases serum osmolality, thereby causing the characteristic functional abnormalities of the central nervous system. Depression of the sensorium, somnolence, obtundation, and coma, are prominent manifestations of NKH. The degree of obtundation correlates with the severity of serum hypertonicity [17].

MANAGEMENT OF DIABETIC KETOACIDOSIS AND NONKETOTIC HYPERGLYCEMIA

Insulin

1. Give initial IV bolus of 0.2 U/kg actual body weight.
2. Add 100 U of regular insulin to 1 L of normal saline (0.1 U/mL), and follow with continuous IV drip of 0.1 U/kg actual body weight per h until correction of ketosis.
3. Give double rate of infusion if the blood glucose level does not decrease in a 2-h interval (expected decrease is 40–80 mg/dL/h or 10% of the initial value.)
4. Give SQ dose (10–30 U) of regular insulin when ketosis is corrected and the blood glucose level decreases to 300 mg/dL, and continue with SQ insulin injection every 4 h on a sliding scale (*ie*, 5 U if below 150, 10 U if 150–200, 15 U if 200–250, and 20 U if 250–300 mg/dL).

Fluid Administration

Shock absent: Normal saline (0.9% NaCl) at 7 mL/kg/h for 4 h, and half this rate thereafter

Shock present: Normal saline and plasma expanders (*ie*,albumin, low molecular weight dextran) at maximal possible rate

Start a glucose-containing solution (*eg*, 5% dextrose in water) when blood glucose level decreases to 250 mg/dL.

Potassium repletion

Potassium chloride should be added to the third liter of IV infusion and subsequently if urinary output is at least 30–60 mL/h and plasma $[K^+]$ < 5 mEq/L.

Add K^+ to the initial 2 L of IV fluids if initial plasma $[K^+]$ < 4 mEq/L and adequate diuresis is secured.

Alkali

Half-normal saline (0.45% NaCl) plus 1–2 ampules (44-88 mEq) $NaHCO_3$ per liter when blood pH < 7.0 or total CO_2 < 5 mmol/L; in hyperchloremic acidosis, add $NaHCO_3$ when pH < 7.20; discontinue $NaHCO_3$ in IV infusion when total CO_2>8–10 mmol/L.

CO_2—carbon dioxide; IV—intravenous; K^+—potassium ion; NaCl—sodium chloride; $NaHCO_3$—sodium bicarbonate; SQ—subcutaneous.

FIGURE 6-24

Diabetic ketoacidosis (DKA) and nonketotic hyperglycemia (NKH) management. Administration of insulin is the cornerstone of management for both DKA and NKH. Replacement of the prevailing water, sodium, and potassium deficits is also required. Alkali are administered only under certain circumstances in DKA and virtually never in NKH, in which ketoacidosis is generally absent. Because the fluid deficit is generally severe in patients with NKH, many of whom have preexisting heart disease and are relatively old, safe fluid replacement may require monitoring of central venous pressure, pulmonary capillary wedge pressure, or both [1,17,18].

Renal tubular acidosis

FEATURES OF THE RENAL TUBULAR ACIDOSIS (RTA) SYNDROMES

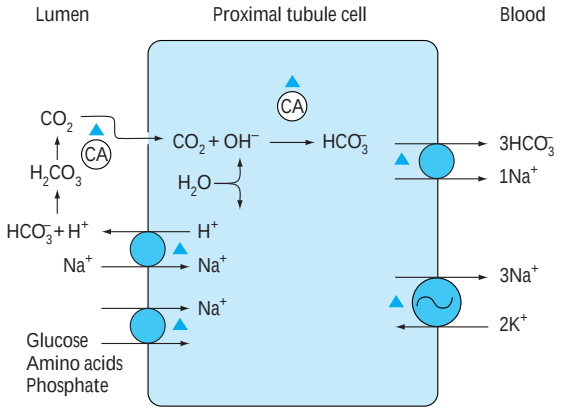
Feature	Proximal RTA	Classic Distal RTA	Hyperkalemic Distal RTA
Plasma bicarbonate ion concentration	14–18 mEq/L	Variable, may be < 10 mEq/L	15–20 mEq/L
Plasma chloride ion concentration	Increased	Increased	Increased
Plasma potassium ion concentration	Mildly decreased	Mildly to severely decreased	Mildly to severely increased
Plasma anion gap	Normal	Normal	Normal
Glomerular filtration rate	Normal or slightly decreased	Normal or slightly decreased	Normal to moderately decreased
Urine pH during acidosis	≤5.5	>6.0	≤5.5
Urine pH after acid loading	≤5.5	>6.0	≤5.5
U-B PCO_2 in alkaline urine	Normal	Decreased	Decreased
Fractional excretion of HCO_3^- at normal $[HCO_3^-]_p$	>15%	<5%	<5%
Tm HCO_3^-	Decreased	Normal	Normal
Nephrolithiasis	Absent	Present	Absent
Nephrocalcinosis	Absent	Present	Absent
Osteomalacia	Present	Present	Absent
Fanconi's syndrome*	Usually present	Absent	Absent
Alkali therapy	High dose	Low dose	Low dose

Tm HCO_3^-—maximum reabsorption of bicarbonate; U-B PCO_2—difference between partial pressure of carbon dioxide values in urine and arterial blood.

*This syndrome signifies generalized proximal tubule dysfunction and is characterized by impaired reabsorption of glucose, amino acids, phosphate, and urate.

FIGURE 6-25

Renal tubular acidosis (RTA) defines a group of disorders in which tubular hydrogen ion secretion is impaired out of proportion to any reduction in the glomerular filtration rate. These disorders are characterized by normal anion gap (hyperchloremic) metabolic acidosis. The defects responsible for impaired acidification give rise to three distinct syndromes known as proximal RTA (type 2), classic distal RTA (type 1), and hyperkalemic distal RTA (type 4).



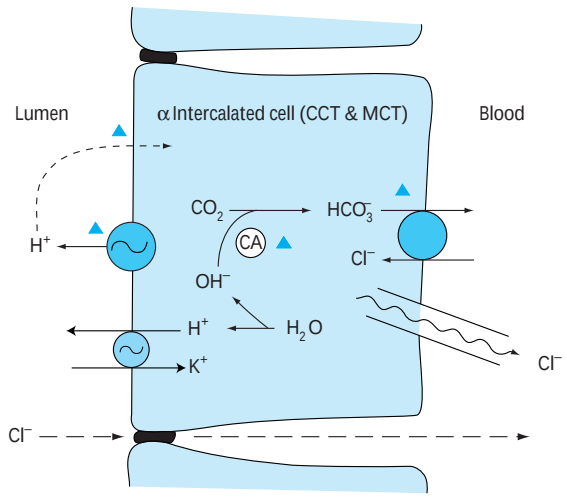
A

FIGURE 6-26

A and **B**, Potential defects and causes of proximal renal tubular acidosis (RTA) (type 2). Excluding the case of carbonic anhydrase inhibitors, the nature of the acidification defect responsible for bicarbonate (HCO_3) wastage remains unknown. It might represent defects in the luminal sodium ion– hydrogen ion (Na^+-H^+) exchanger, basolateral Na^+-$3HCO_3^-$ cotransporter, or carbonic anhydrase activity. Most patients with proximal RTA have additional defects in proximal tubule function (Fanconi's syndrome); this generalized proximal tubule dysfunction might reflect a defect in the basolateral Na^+-K^+ adenosine triphosphatase. K^+—potassium ion; CA—carbonic anhydrase. Causes of proximal renal tubular acidosis (RTA) (type 2). An idiopathic form and cystinosis are the most common causes of proximal RTA in children. In adults, multiple myeloma and carbonic anhydrase inhibitors (*eg*, acetazolamide) are the major causes. Ifosfamide is an increasingly common cause of the disorder in both age groups.

B. CAUSES OF PROXIMAL RENAL TUBULAR ACIDOSIS

- Selective defect (isolated bicarbonate wasting)
  - Primary (no obvious associated disease)
    - Genetically transmitted
    - Transient (infants)
  - Due to altered carbonic anhydrase activity
    - Acetazolamide
    - Sulfanilamide
    - Mafenide acetate
    - Genetically transmitted
    - Idiopathic
    - Osteopetrosis with carbonic anhydrase II deficiency
    - York-Yendt syndrome
- Generalized defect (associated with multiple dysfunctions of the proximal tubule)
  - Primary (no obvious associated disease)
    - Sporadic
    - Genetically transmitted
  - Genetically transmitted systemic disease
    - Tyrosinemia
    - Wilson's disease
    - Lowe syndrome
    - Hereditary fructose intolerance (during administration of fructose)
    - Cystinosis
    - Pyruvate carboxylate deficiency
    - Metachromatic leukodystrophy
    - Methylmalonic acidemia
- Conditions associated with chronic hypocalcemia and secondary hyperparathyroidism
  - Vitamin D deficiency or resistance
  - Vitamin D dependence
- Dysproteinemic states
  - Multiple myeloma
  - Monoclonal gammopathy
- Drug- or toxin-induced
  - Outdated tetracycline
  - 3-Methylchromone
  - Streptozotocin
  - Lead
  - Mercury
  - Arginine
  - Valproic acid
  - Gentamicin
  - Ifosfamide
- Tubulointerstitial diseases
  - Renal transplantation
  - Sjögren's syndrome
  - Medullary cystic disease
- Other renal diseases
  - Nephrotic syndrome
  - Amyloidosis
- Miscellaneous
  - Paroxysmal nocturnal hemoglobinuria
  - Hyperparathyroidism



▲ Indicates possible cellular mechanisms responsible for Type 1 distal RTA

A

B. CAUSES OF CLASSIC DISTAL RENAL TUBULAR ACIDOSIS

Primary (no obvious associated disease)
- Sporadic
- Genetically transmitted

Autoimmune disorders
- Hypergammaglobulinemia
- Hyperglobulinemic purpura
- Cryoglobulinemia
- Familial
- Sjögren's syndrome
- Thyroiditis
- Pulmonary fibrosis
- Chronic active hepatitis
- Primary biliary cirrhosis
- Systemic lupus erythematosus
- Vasculitis

Genetically transmitted systemic disease
- Ehlers-Danlos syndrome
- Hereditary elliptocytosis
- Sickle cell anemia
- Marfan syndrome
- Carbonic anhydrase I deficiency or alteration
- Osteopetrosis with carbonic anhydrase II deficiency
- Medullary cystic disease
- Neuroaxonal dystrophy

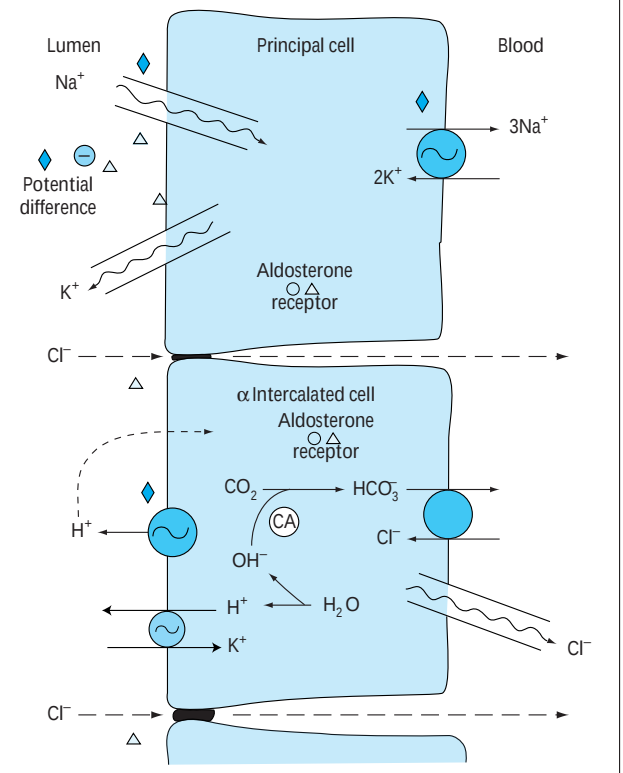
Disorders associated with nephrocalcinosis
- Primary or familial hyperparathyroidism
- Vitamin D intoxication
- Milk-alkali syndrome
- Hyperthyroidism
- Idiopathic hypercalciuria
  - Genetically transmitted
  - Sporadic
- Hereditary fructose intolerance (after chronic fructose ingestion)
- Medullary sponge kidney
- Fabry's disease
- Wilson's disease

Drug- or toxin-induced
- Amphotericin B
- Toluene
- Analgesics
- Lithium
- Cyclamate
- Balkan nephropathy

Tubulointerstitial diseases
- Chronic pyelonephritis
- Obstructive uropathy
- Renal transplantation
- Leprosy
- Hyperoxaluria

FIGURE 6-27

A and **B**, Potential defects and causes of classic distal renal tubular acidosis (RTA) (type 1). Potential cellular defects underlying classic distal RTA include a faulty luminal hydrogen ion–adenosine triphosphatase (H^+ pump failure or secretory defect), an abnormality in the basolateral bicarbonate ion–chloride ion exchanger, inadequacy of carbonic anhydrase activity, or an increase in the luminal membrane permeability for hydrogen ions (backleak of protons or permeability defect). Most of the causes of classic distal RTA likely reflect a secretory defect, whereas amphotericin B is the only established cause of a permeability defect. The hereditary form is the most common cause of this disorder in children. Major causes in adults include autoimmune disorders (*eg*, Sjögren's syndrome) and hypercalciuria [19]. CA—carbonic anhydrase.



B. CAUSES OF HYPERKALEMIC DISTAL RENAL TUBULAR ACIDOSIS

- Deficiency of aldosterone
  - Associated with glucocorticoid deficiency
    - Addison's disease
    - Bilateral adrenalectomy
    - Enzymatic defects
      - 21-Hydroxylase deficiency
      - 3-β-ol-Dehydrogenase deficiency
      - Desmolase deficiency
    - Acquired immunodeficiency syndrome
  - Isolated aldosterone deficiency
    - Genetically transmitted
      - Corticosterone methyl oxidase deficiency
    - Transient (infants)
    - Sporadic
    - Heparin
    - Deficient renin secretion
      - Diabetic nephropathy
      - Tubulointerstitial renal disease
      - Nonsteroidal antiinflammatory drugs
      - β-adrenergic blockers
      - Acquired immunodeficiency syndrome
      - Renal transplantation
  - Angiotensin I-converting enzyme inhibition
    - Endogenous
    - Captopril and related drugs
  - Angiotensin AT, receptor blockers
- Resistance to aldosterone action
  - Pseudohypoaldosteronism type I (with salt wasting)
    - Childhood forms with obstructive uropathy
    - Adult forms with renal insufficiency
  - Spironolactone
  - Pseudohypoaldosteronism type II (without salt wasting)
  - Combined aldosterone deficiency and resistance
    - Deficient renin secretion
    - Cyclosporine nephrotoxicity
    - Uncertain renin status
  - Voltage-mediated defects
    - Obstructive uropathy
    - Sickle cell anemia
    - Lithium
    - Triamterene
    - Amiloride
    - Trimethoprim, pentamidine
  - Renal transplantation

FIGURE 6-28

A and **B**, Potential defects and causes of hyperkalemic distal renal tubular acidosis (RTA) (type 4). This syndrome represents the most common type of RTA encountered in adults. The characteristic hyperchloremic metabolic acidosis in the company of hyperkalemia emerges as a consequence of generalized dysfunction of the collecting tubule, including diminished sodium reabsorption and impaired hydrogen ion and potassium secretion. The resultant hyperkalemia causes impaired ammonium excretion that is an important contribution to the generation of the metabolic acidosis. The causes of this syndrome are broadly classified into disorders resulting in aldosterone deficiency and those that impose resistance to the action of aldosterone. Aldosterone deficiency can arise from hyporeninemia, impaired conversion of angiotensin I to angiotensin II, or abnormal aldosterone synthesis. Aldosterone resistance can reflect the following: blockade of the mineralocorticoid receptor; destruction of the target cells in the collecting tubule (*tubulointerstitial nephropathies*); interference with the sodium channel of the principal cell, thereby decreasing the lumen-negative potential difference and thus the secretion of potassium and hydrogen ions (voltage-mediated defect); inhibition of the basolateral sodium ion, potassium ion–adenosine triphosphatase; and enhanced chloride ion permeability in the collecting tubule, with consequent shunting of the transepithelial potential difference. Some disorders cause combined aldosterone deficiency and resistance [20].

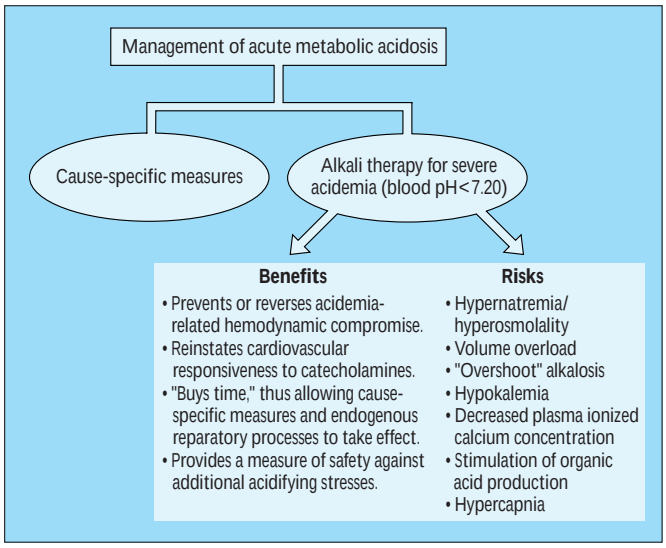


FIGURE 6-29

Treatment of acute metabolic acidosis. Whenever possible, cause-specific measures should be at the center of treatment of metabolic acidosis. In the presence of severe acidemia, such measures should be supplemented by judicious administration of sodium bicarbonate. The goal of alkali therapy is to return the blood pH to a safer level of about 7.20. Anticipated benefits and potential risks of alkali therapy are depicted here [1].

Metabolic Alkalosis

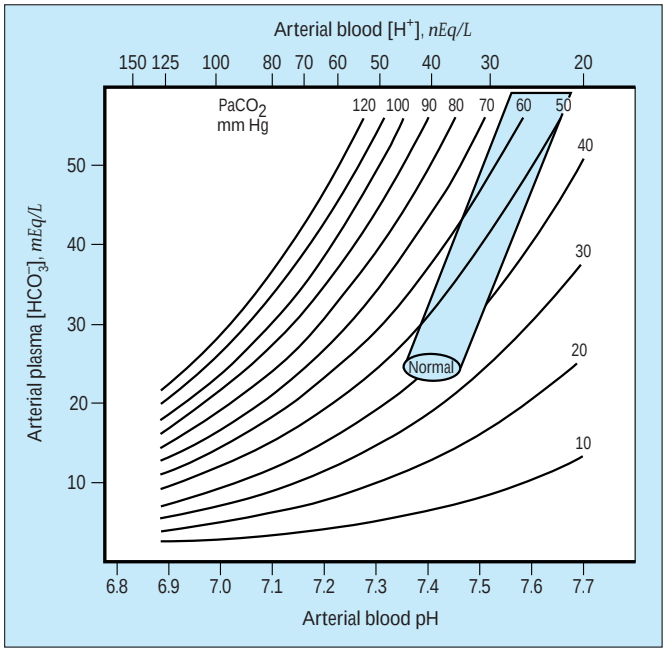


FIGURE 6-30

Ninety-five percent confidence intervals for metabolic alkalosis. Metabolic alkalosis is the acid-base disturbance initiated by an increase in plasma bicarbonate concentration ($[HCO_3^-]$). The resultant alkalemia dampens alveolar ventilation and leads to the secondary hypercapnia characteristic of the disorder. Available observations in humans suggest a roughly linear relationship between the steady-state increase in bicarbonate concentration and the associated increment in the arterial carbon dioxide tension ($PaCO_2$). Although data are limited, the slope of the steady-state $\Delta PaCO_2$ versus $\Delta[HCO_3^-]$ relationship has been estimated as about a 0.7 mm Hg per mEq/L increase in plasma bicarbonate concentration. The value of this slope is virtually identical to that in dogs that has been derived from rigorously controlled observations [21]. Empiric observations in humans have been used for construction of 95% confidence intervals for graded degrees of metabolic alkalosis represented by the area in color in the acid-base template. The black ellipse near the center of the figure indicates the normal range for the acid-base parameters [3]. Assuming a steady state is present, values falling within the area in color are consistent with but not diagnostic of simple metabolic alkalosis. Acid-base values falling outside the area in color denote the presence of a mixed acid-base disturbance [4]. $[H^+]$—hydrogen ion concentration.

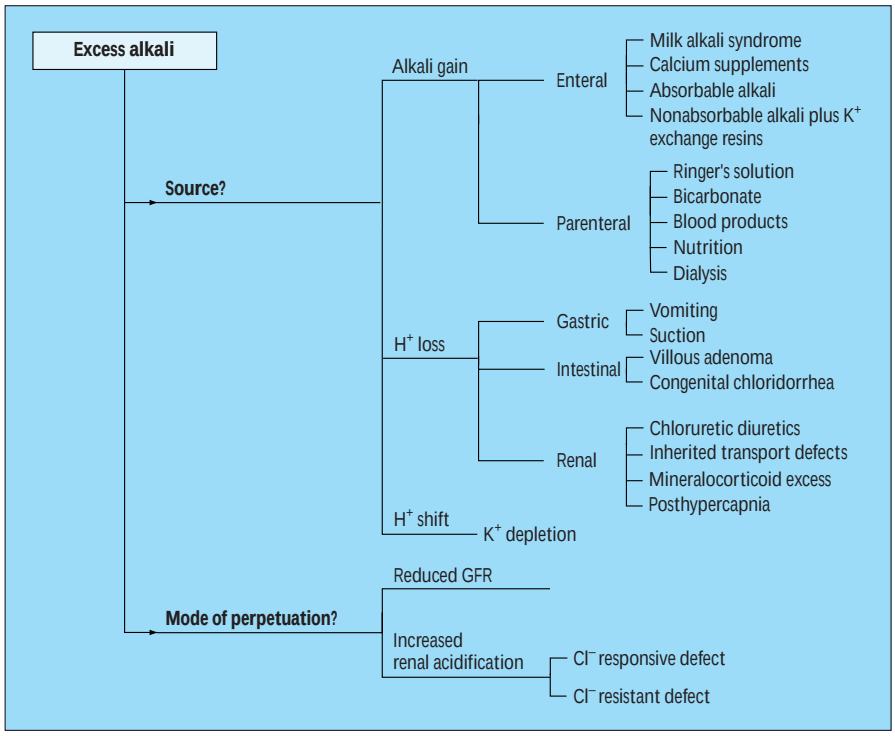


FIGURE 6-31

Pathogenesis of metabolic alkalosis. Two crucial questions must be answered when evaluating the pathogenesis of a case of metabolic alkalosis. 1) What is the source of the excess alkali? Answering this question addresses the primary event responsible for *generating* the hyperbicarbonatemia. 2) What factors perpetuate the hyperbicarbonatemia? Answering this question addresses the pathophysiologic events that *maintain* the metabolic alkalosis.

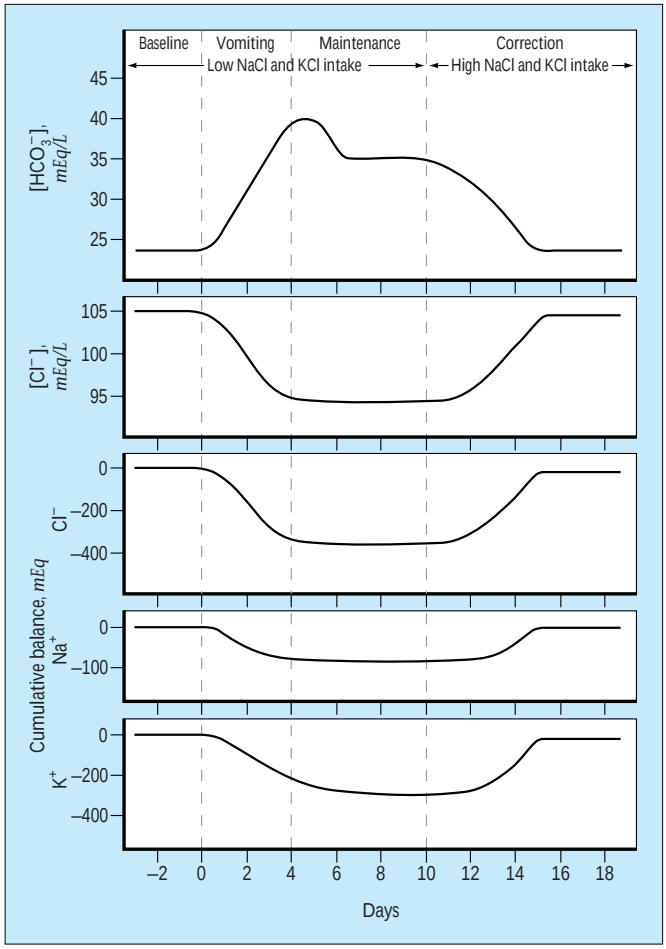


FIGURE 6-32

Changes in plasma anionic pattern and body electrolyte balance during development, maintenance, and correction of metabolic alkalosis induced by vomiting. Loss of hydrochloric acid from the stomach as a result of vomiting (or gastric drainage) generates the hypochloremic hyperbicarbonatemia characteristic of this disorder. During the generation phase, renal sodium and potassium excretion increases, yielding the deficits depicted here. Renal potassium losses continue in the early days of the maintenance phase. Subsequently, and as long as the low-chloride diet is continued, a new steady state is achieved in which plasma bicarbonate concentration ($[HCO_3^-]$) stabilizes at an elevated level, and renal excretion of electrolytes matches intake. Addition of sodium chloride (NaCl) and potassium chloride (KCl) in the correction phase repairs the electrolyte deficits incurred and normalizes the plasma bicarbonate and chloride concentration ($[Cl^-]$) levels [22,23].

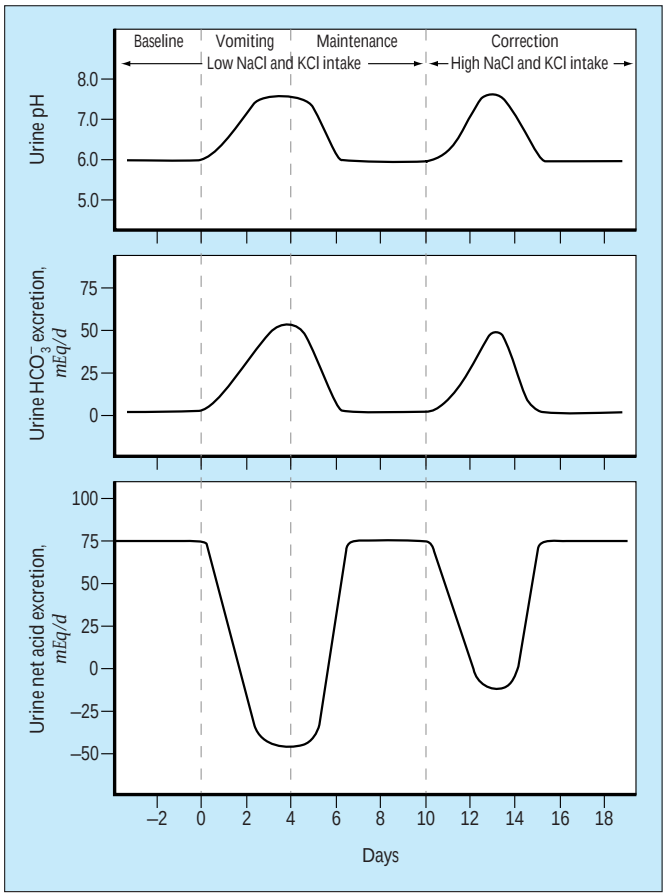


FIGURE 6-33

Changes in urine acid-base composition during development, maintenance, and correction of vomiting-induced metabolic alkalosis. During acid removal from the stomach as well as early in the phase after vomiting (maintenance), an alkaline urine is excreted as acid excretion is suppressed, and bicarbonate excretion (in the company of sodium and, especially potassium; *see* Fig. 6-32) is increased, with the net acid excretion being negative (net alkali excretion). This acid-base profile moderates the steady-state level of the resulting alkalosis. In the steady state (late maintenance phase), as all filtered bicarbonate is reclaimed the pH of urine becomes acidic, and the net acid excretion returns to baseline. Provision of sodium chloride (NaCl) and potassium chloride (KCl) in the correction phase alkalinizes the urine and suppresses the net acid excretion, as bicarbonaturia in the company of exogenous cations (sodium and potassium) supervenes [22,23]. HCO_3^-—bicarbonate ion.

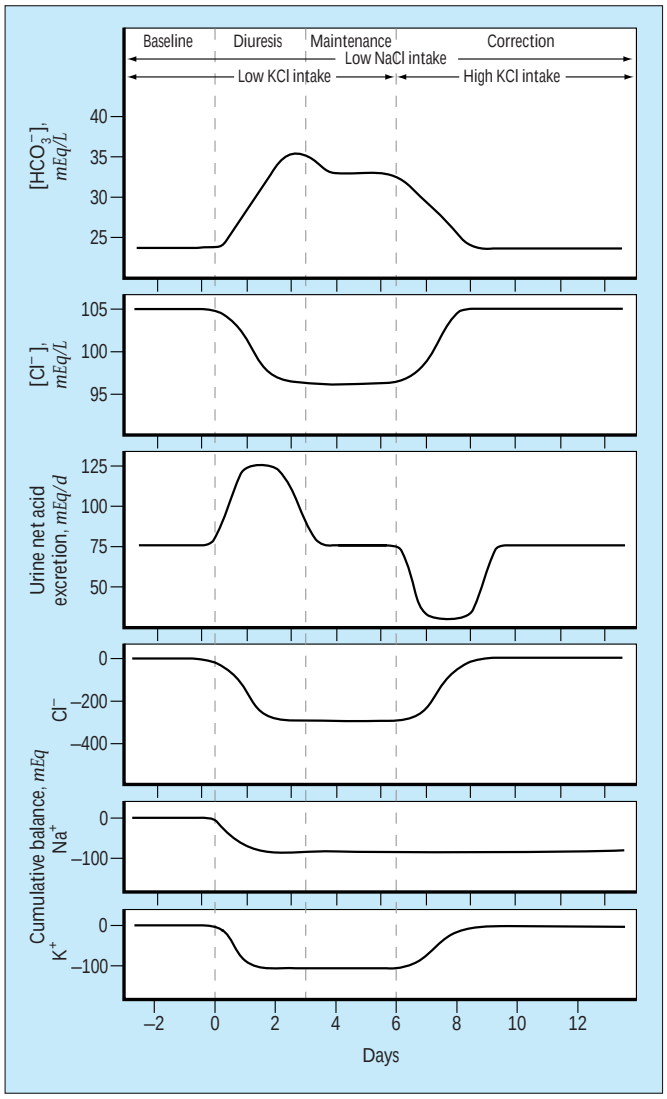


FIGURE 6-34

Changes in plasma anionic pattern, net acid excretion, and body electrolyte balance during development, maintenance, and correction of diuretic-induced metabolic alkalosis. Administration of a loop diuretic, such as furosemide, increases urine net acid excretion (largely in the form of ammonium) as well as the renal losses of chloride (Cl^-), sodium (Na^+), and potassium (K^+). The resulting hyperbicarbonatemia reflects both loss of excess ammonium chloride in the urine and an element of contraction (consequent to diuretic-induced sodium chloride [NaCl] losses) that limits the space of distribution of bicarbonate. During the phase after diuresis (maintenance), and as long as the low-chloride diet is continued, a new steady state is attained in which the plasma bicarbonate concentration ($[HCO_3^-]$) remains elevated, urine net acid excretion returns to baseline, and renal excretion of electrolytes matches intake. Addition of potassium chloride (KCl) in the correction phase repairs the chloride and potassium deficits, suppresses net acid excretion, and normalizes the plasma bicarbonate and chloride concentration ($[Cl^-]$) levels [23,24]. If extracellular fluid volume has become subnormal folllowing diuresis, administration of NaCl is also required for repair of the metabolic alkalosis.

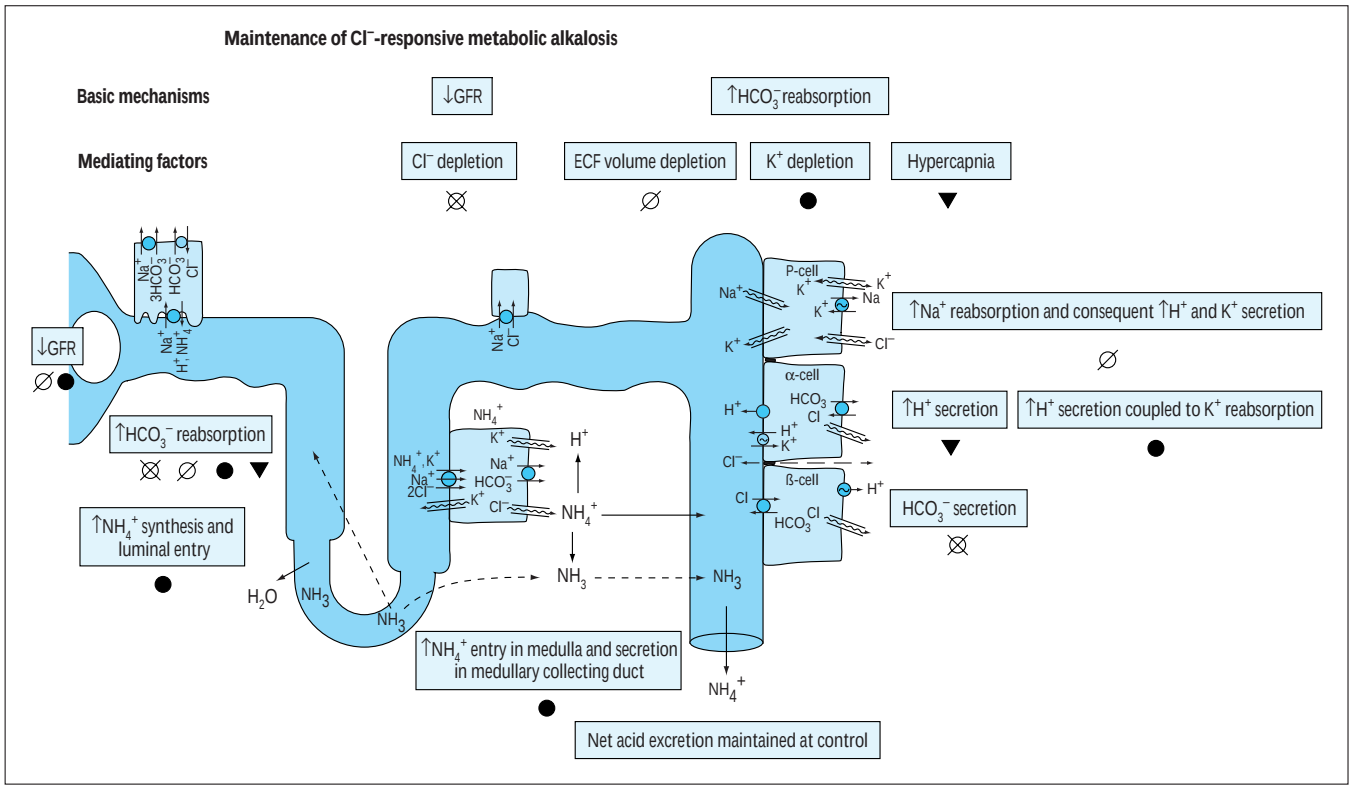


FIGURE 6-35

Maintenance of chloride-responsive metabolic alkalosis. Increased renal bicarbonate reabsorption frequently coupled with a reduced glomerular filtration rate are the basic mechanisms that maintain chloride-responsive metabolic alkalosis. These mechanisms have been ascribed to three mediating factors: chloride depletion itself, extracellular fluid (ECF) volume depletion, and potassium depletion. Assigning particular roles to each of these factors is a vexing task. Notwithstanding, here depicted is our current understanding of the participation of each of these factors in the nephronal processes that maintain chloride-responsive metabolic alkalosis [22–24]. In addition to these factors, the secondary hypercapnia of metabolic alkalosis contributes importantly to the maintenance of the prevailing hyperbicarbonatemia [25].

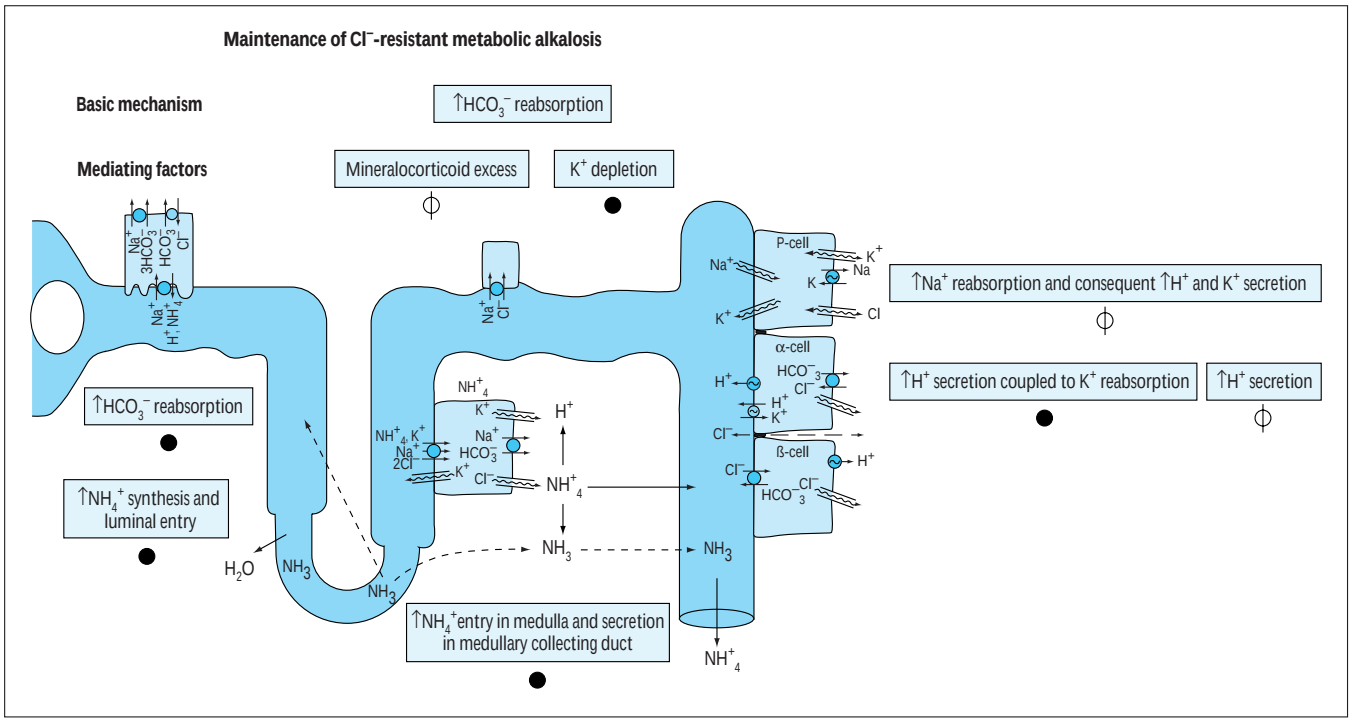


FIGURE 6-36

Maintenance of chloride-resistant metabolic alkalosis. Increased renal bicarbonate reabsorption is the sole basic mechanism that maintains chloride-resistant metabolic alkalosis. As its name implies, factors independent of chloride intake mediate the heightened bicarbonate reabsorption and include mineralocorticoid excess and potassium depletion. The participation of these factors in the nephronal processes that maintain chloride-resistant metabolic alkalosis is depicted [22–24, 26].

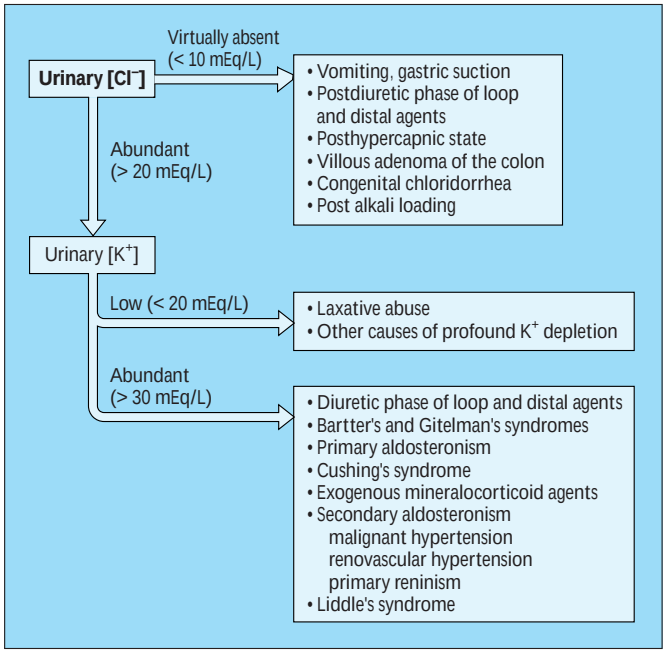


FIGURE 6-37

Urinary composition in the diagnostic evaluation of metabolic alkalosis. Assessing the urinary composition can be an important aid in the diagnostic evaluation of metabolic alkalosis. Measurement of urinary chloride ion concentration ($[Cl^-]$) can help distinguish between chloride-responsive and chloride-resistant metabolic alkalosis. The virtual absence of chloride (urine $[Cl^-] < 10$ mEq/L) indicates significant chloride depletion. Note, however, that this test loses its diagnostic significance if performed within several hours of administration of chloruretic diuretics, because these agents promote urinary chloride excretion. Measurement of urinary potassium ion concentration ($[K^+]$) provides further diagnostic differentiation. With the exception of the diuretic phase of chloruretic agents, abundance of both urinary chloride and potassium signifies a state of mineralocorticoid excess [22].

SIGNS AND SYMPTOMS OF METABOLIC ALKALOSIS

Central Nervous System	Cardiovascular System	Respiratory System	Neuromuscular System	Metabolic Effects	Renal (Associated Potassium Depletion)
Headache	Supraventricular and ventricular arrhythmias	Hypoventilation with attendant hypercapnia and hypoxemia	Chvostek's sign	Increased organic acid and ammonia production	Polyuria
Lethargy	Potentiation of digitalis toxicity		Trousseau's sign	Hypokalemia	Polydipsia
Stupor	Positive inotropic ventricular effect		Weakness (severity depends on degree of potassium depletion)	Hypocalcemia	Urinary concentration defect
Delirium				Hypomagnesemia	Cortical and medullary renal cysts
Tetany				Hypophosphatemia	
Seizures					
Potentiation of hepatic encephalopathy					

FIGURE 6-38

Signs and symptoms of metabolic alkalosis. Mild to moderate metabolic alkalosis usually is accompanied by few if any symptoms, unless potassium depletion is substantial. In contrast, severe metabolic alkalosis ($[HCO_3^-] > 40$ mEq/L) is usually a symptomatic disorder. Alkalemia, hypokalemia, hypoxemia, hypercapnia, and decreased plasma ionized calcium concentration all contribute to these clinical manifestations. The arrhythmogenic potential of alkalemia is more pronounced in patients with underlying heart disease and is heightened by the almost constant presence of hypokalemia, especially in those patients taking digitalis. Even mild alkalemia can frustrate efforts to wean patients from mechanical ventilation [23,24].

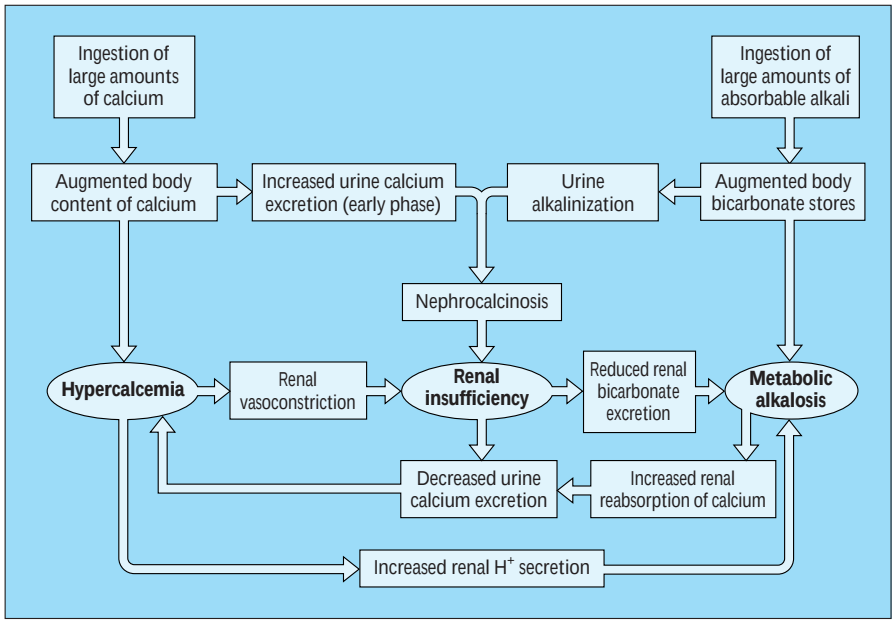


FIGURE 6-39

Pathophysiology of the milk-alkali syndrome. The milk-alkali syndrome comprises the triad of hypercalcemia, renal insufficiency, and metabolic alkalosis and is caused by the ingestion of large amounts of calcium and absorbable alkali. Although large amounts of milk and absorbable alkali were the culprits in the classic form of the syndrome, its modern version is usually the result of large doses of calcium carbonate alone. Because of recent emphasis on prevention and treatment of osteoporosis with calcium carbonate and the availability of this preparation over the counter, milk-alkali syndrome is currently the third leading cause of hypercalcemia after primary hyperparathyroidism and malignancy. Another common presentation of the syndrome originates from the current use of calcium carbonate in preference to aluminum as a phosphate binder in patients with chronic renal insufficiency. The critical element in the pathogenesis of the syndrome is the development of hypercalcemia that, in turn, results in renal dysfunction. Generation and maintenance of metabolic alkalosis reflect the combined effects of the large bicarbonate load, renal insufficiency, and hypercalcemia. Metabolic alkalosis contributes to the maintenance of hypercalcemia by increasing tubular calcium reabsorption. Superimposition of an element of volume contraction caused by vomiting, diuretics, or hypercalcemia-induced natriuresis can worsen each one of the three main components of the syndrome. Discontinuation of calcium carbonate coupled with a diet high in sodium chloride or the use of normal saline and furosemide therapy (depending on the severity of the syndrome) results in rapid resolution of hypercalcemia and metabolic alkalosis. Although renal function also improves, in a considerable fraction of patients with the chronic form of the syndrome serum creatinine fails to return to baseline as a result of irreversible structural changes in the kidneys [27].

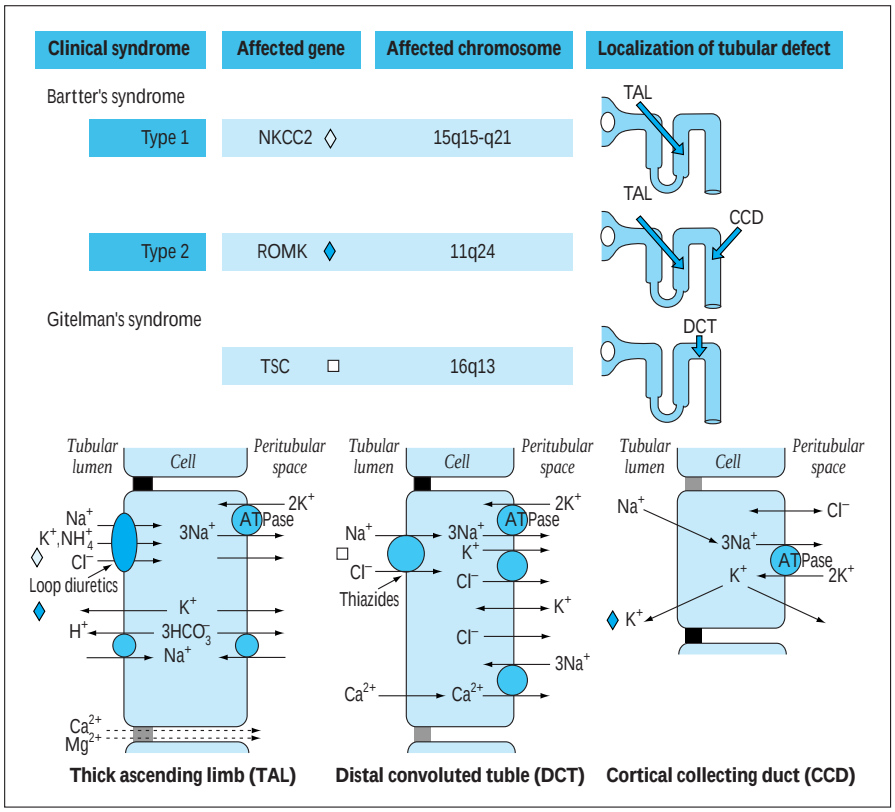


FIGURE 6-40

Clinical features and molecular basis of tubular defects of Bartter's and Gitelman's syndromes. These rare disorders are characterized by chloride-resistant metabolic alkalosis, renal potassium wasting and hypokalemia, hyperreninemia and hyperplasia of the juxtaglomerular apparatus, hyperaldosteronism, and normotension. Regarding differentiating features, Bartter's syndrome presents early in life, frequently in association with growth and mental retardation. In this syndrome, urinary concentrating ability is usually decreased, polyuria and polydipsia are present, the serum magnesium level is normal, and hypercalciuria and nephrocalcinosis are present. In contrast, Gitelman's syndrome is a milder disease presenting later in life. Patients often are asymptomatic, or they might have intermittent muscle spasms, cramps, or tetany. Urinary concentrating ability is maintained; hypocalciuria, renal magnesium wasting, and hypomagnesemia are almost constant features. On the basis of certain of these clinical features, it had been hypothesized that the primary tubular defects in Bartter's and Gitelman's syndromes reflect impairment in sodium reabsorption in the thick ascending limb (TAL) of the loop of Henle and the distal tubule, respectively. This hypothesis has been validated by recent genetic studies [28-31]. As illustrated here, Bartter's syndrome now has been shown to be caused by loss-of-function mutations in the loop diuretic–sensitive sodium-potassium-2chloride cotransporter (NKCC2) of the TAL (type 1 Bartter's syndrome) [28] or the apical potassium channel ROMK of the TAL (where it recycles reabsorbed potassium into the lumen for continued operation of the NKCC2 cotransporter) and the cortical collecting duct (where it mediates secretion of potassium by the principal cell) (type 2 Bartter's syndrome) [29,30]. On the other hand, Gitelman's syndrome is caused by mutations in the thiazide-sensitive Na-Cl cotransporter (TSC) of the distal tubule [31]. Note that the distal tubule is the major site of active calcium reabsorption. Stimulation of calcium reabsorption at this site is responsible for the hypocalciuric effect of thiazide diuretics.

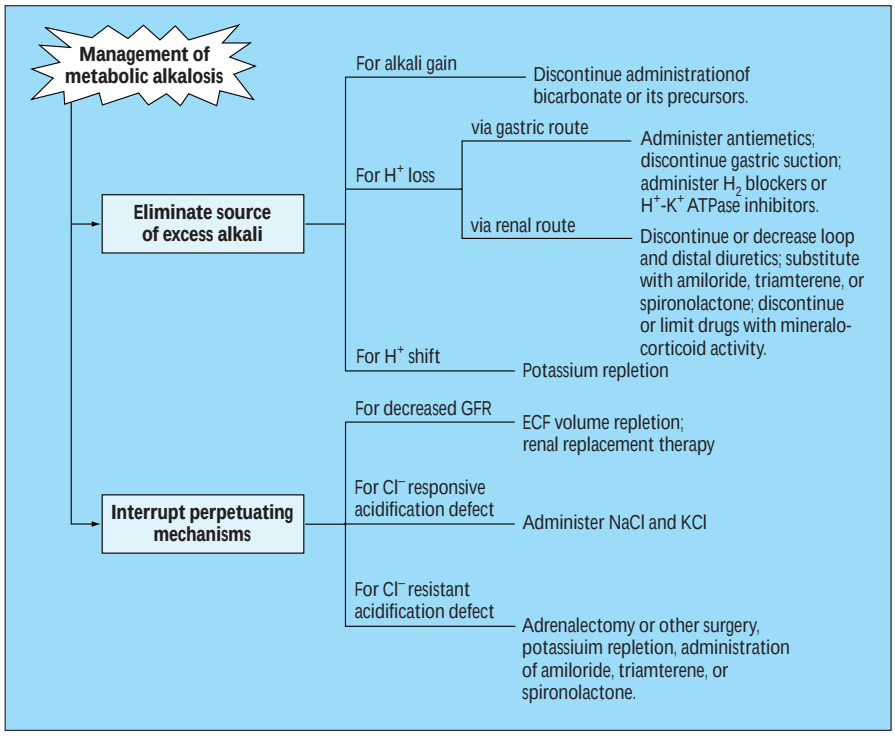


FIGURE 6-41

Metabolic alkalosis management. Effective management of metabolic alkalosis requires sound understanding of the underlying pathophysiology. Therapeutic efforts should focus on eliminating or moderating the processes that generate the alkali excess and on interrupting the mechanisms that perpetuate the hyperbicarbonatemia. Rarely, when the pace of correction of metabolic alkalosis must be accelerated, acetazolamide or an infusion of hydrochloric acid can be used. Treatment of severe metabolic alkalosis can be particularly challenging in patients with advanced cardiac or renal dysfunction. In such patients, hemodialysis or continuous hemofiltration might be required [1].

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