CHAPTER 122 Acid-Base Disorders

Jamie L. Collings

The human body must be maintained in a precise acid-base balance to maintain healthy cellular function. This balance is controlled by the lungs, kidneys, and serum buffers, interacting and responding to physiologic changes. Physiologic insults such as vomiting, diarrhea, respiratory failure, kidney dysfunction, diabetes, toxic ingestions, among others can result in life-threatening acid-base crises. Identifying and optimally treating the underlying condition is often achieved only through the diagnostic insights gained from acid-base measurements and calculations. This chapter presents essential acid-base physiology, beginning with an overview of the principles of acid-base function. This is followed by a discussion of primary respiratory acidosis and alkalosis and then metabolic causes of acidosis and alkalosis. Finally, mixed acid-base disorders are analyzed. Clinical implications are included along with the mathematical knowledge that the emergency physician requires to expertly manage these complex and potentially life-threatening conditions.

PRINCIPLES OF DISEASE

The kidneys, lungs, and physiologic buffers normally maintain the serum pH within a narrow spectrum, between 7.36 and 7.44. Each of these three systems dynamically responds to small changes in acid-base balance. Such precise physiologic control is required for normal cellular function. Consequently, disorders of kidneys, lungs, and physiologic buffers result in acid-base abnormalities.

Blood pH is determined by the ratio of the serum bicarbonate concentration and $Paco_2$ (partial pressure of CO_2 in arterial blood). Primary metabolic acid-base disorders and the secondary metabolic compensation for primary respiratory disturbances alter the serum bicarbonate concentration [HCO_3^-]. Primary respiratory acid-base disorders and the secondary respiratory compensation for primary metabolic disturbances alter the $Paco_2$.

The Henderson-Hasselbalch equation relates the concentrations of the acid-base pair to the pH. As the pH changes, so does the concentration. Because the equation produces a logarithmic result, subtle changes in the serum pH can cause large and often significant alterations in the concentration of the acid-base pair. Clinically, this equation dictates how drugs disperse, enzymes react, and medications bind at a given serum pH. In humans, hydrogen ion concentration [H^+] is extremely low (approximately 4×10^{-12} mEq/L) and strictly regulated. Normally, blood is slightly alkalemic relative to water (pH 7.0). Blood pH must be maintained within relatively narrow limits because protein and enzyme systems function properly only within a narrow pH spectrum. A pH outside the range of 6.8 to 7.8 is generally associated with serious disease processes and the potential for considerable morbidity or mortality.

Acidemia is defined as a serum pH of less than 7.36. Conversely, *alkalemia* is defined as a pH of greater than 7.44. *Acidosis* is defined as a pathologic process that lowers the [HCO_3^-] (metabolic acidosis) or raises the $Paco_2$ (respiratory acidosis); *alkalosis* is defined as a pathologic process that raises the [HCO_3^-] (metabolic alkalosis) or lowers the $Paco_2$ (respiratory alkalosis). A simple acid-base disorder is a single acid-base disturbance with its accompanying compensatory response. Mixed acid-base disorders are the result of two or more primary disturbances.

Physiologic Buffers

Physiologic buffers, defined as a weak acid and its salt, oppose marked changes in pH after the addition of an organic acid or a base, as follows:

$$H^+ + \text{buffer}^-Na^+ \rightleftarrows \text{buffer}^-H^+ + Na^+$$

The human body uses three important physiologic buffers to minimize surges in pH: (1) the bicarbonate/carbonic acid system (primarily located in red blood cells), (2) intracellular protein buffers, and (3) phosphate buffers located within bone. Patients with malnutrition or chronic disease, and thus low albumin and bone density, and anemic patients have an ineffective buffering capability.

Bicarbonate/Carbonic Acid Buffer System

The bicarbonate/carbonic acid buffer system is unique among physiologic buffering systems. The system is open-ended; continuous removal of organic acid is made possible by the exhalation of carbon dioxide (CO_2). In equilibrium, the equation is as follows:

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

Bicarbonate is present in large quantities and can be controlled by the lungs and kidneys; thus, it serves as the major contributor to the maintenance of acid-base balance. Clinically, its importance is in the transient buffering of serum and interstitial fluid.

Intracellular Protein Buffers

Many protein buffers in blood are effective in maintaining acid-base homeostasis. Plasma proteins, particularly albumin and hemoglobin, can buffer large amounts of H^+, preventing significant changes in the pH. If hemoglobin did not exist, venous blood would be 800 times more acidic than arterial blood, circulating at a pH of 4.5 instead of the normal venous pH of 7.37.

Bone as Buffer

Bone contains a large reservoir of bicarbonate and phosphate and can buffer a significant acute acid load. Bone is probably involved in providing some buffering (mostly ionic exchange) in most acute acid-base disorders, but there is very little research in this area. In terms of duration, only two types of metabolic acidosis are long-lasting enough to be associated with the loss of bone mineral (through release of calcium carbonate): renal tubular acidosis and uremic acidosis. In uremic acidosis, loss of bone crystal is multifactorial (changes in vitamin D metabolism, phosphate metabolism and secondary hyperparathyroidism) and acidosis is only a minor factor.

Pulmonary Compensation

The second compensatory system for pH changes involves a relationship between the peripheral chemoreceptors, located in the carotid bodies, and central chemoreceptors, located in the medulla oblongata. Both these receptors influence respiratory drive and can initiate changes in minute ventilation. A drop in pH stimulates the respiratory center, resulting in increased minute ventilation. This in turn lowers the $Paco_2$, driving the pH toward the normal range. Conversely, an increase in pH decreases ventilatory effort, which increases $Paco_2$ and lowers the pH back toward normal. A diabetic patient in ketoacidosis hyperventilates to compensate for the organic acidemia and would be expected to have a low $Paco_2$. This compensatory response is the expected reaction to a fall in serum pH. In general, compensatory processes return the pH toward normal over a period of 4 to 12 hours, but do not fully normalize it. Respiratory alkalosis is the only primary acid-base disorder in which the pH does often normalize with time.

Renal Compensation

The kidneys play little role in the acute compensation of acid-base disorders because they do not immediately respond to changes in pH. More than 6 to 12 hours of sustained acidosis results in active excretion of H^+ (predominantly in the form of ammonium, NH_4^+, with retention of bicarbonate, HCO_3^-). Conversely, more than 6 hours of alkalemia stimulates renal excretion of bicarbonate with retention of H^+ in the form of organic acids, resulting in near-normalization of pH.

In metabolic acidosis, there is either an excess production or an infusion of H^+ (e.g., lactic acid production, ketoacid production) or an excessive loss of anion (HCO_3^-) and accompanying sodium and potassium cations (Na^+, K^+; e.g., diarrhea). In general, the kidneys attempt to preserve Na^+ by exchanging it for excreted H^+ or K^+. The quantity of potassium excreted depends on the level of acidosis and the serum K^+ level. In the presence of an H^+ load, hydrogen ions move from the extracellular fluid (ECF) into the intracellular fluid. For this to occur, K^+ moves outside the cell into the ECF to maintain electroneutrality. In cases of severe acidosis, significant overall depletion of total body K^+ stores can occur despite serum hyperkalemia. Clinically, this is the rationale for initiating intravenous administration of K^+ in the patient with diabetic ketoacidosis (DKA) and good renal function, despite an often elevated serum K^+ level.

In metabolic alkalosis, there is a shift of H^+ extracellularly, accompanied by an electroneutral shift of serum Na^+ and K^+ intracellularly. Renal excretion of K^+ also occurs in an attempt to preserve H^+. If the alkalosis continues, the renal compensation may be unable to keep pace, especially if hypokalemia ensues. With excessive total body depletion of K^+ (usually as the result of nasogastric suction or some other inciting event), the kidney paradoxically begins to excrete H^+ in an attempt to retain K^+; thus, an aciduria can coexist with a serum alkalosis. This paradoxical aciduria is a clinical clue to the magnitude of hypokalemia and explains why renal compensation is unable to correct for alkalosis until K^+ levels are restored.

Conditions that change serum K^+ also alter serum pH. Excessive diuresis, occurring without potassium supplementation, generate a mild alkalemia, as H^+ is shifted intracellularly to support the extracellular osmotic movement of K^+. Conversely, excessive administration of potassium can cause H^+ to shift extracellularly, which may produce a mild acidosis.

DIAGNOSTIC STRATEGIES

A stepwise clinical approach to acid-base disorders starts with a well-conducted history and physical examination. Particular attention should be paid to the patient's past medical history, current medications, chance of toxic ingestion, occurrence of vomiting or diarrhea, level of consciousness on admission, respiratory rate, skin turgor, and urine output.

Evaluation progresses with analysis of serum electrolytes and pH, and calculation of any anion gap, and calculation of the delta gap. These calculations assist in determining the type of acidosis or alkalosis present and whether it is part of a mixed condition. The anion gap (AG) can be calculated as follows:

$$AG = Na^+ - (Cl^- + HCO_3^-)$$

Traditionally, a normal AG has been considered 12 ± 3 mEq/L. This number can vary from one laboratory to another (mostly based on whether potassium is included in the calculation) and the clinician should take this possibility into consideration. The "gap" provides an estimate of unmeasured anions in plasma, primarily albumin plus small amounts of sulfate, phosphate, and organic anions (e.g., citrate). If there are excess organic acids in the circulation, the organic acids dissociate and the resulting H^+ is titrated by HCO_3^-, which increases the AG. If the AG is increased, especially when it is more than 10 mEq/L above the upper limit of the reference range, the clinician should consider an excess in organic acids or acidic substances. With smaller gaps up to one third of patients will not have a metabolic acidosis. The concept of a "low" AG (<3 mEq/L) may be useful in the diagnosis of lithium toxicity, immunoglobulin G myelomas, and hypoalbuminemia of chronic disease.

Calculating the delta gap (ΔG = deviation of AG from normal – deviation of HCO_3^- from normal) may help resolve the possibility of a mixed acid-base disorder or further differentiate an elevated AG metabolic acidosis. Mathematically refined and with normal values substituted, the equation is as follows:

$$\Delta G = (\text{calculated AG} - 12) - (24 - \text{measured } HCO_3^-)$$

Values greater than +6 equate with metabolic alkalosis or respiratory acidosis. Values less than –6 imply a greater loss of HCO_3^-, suggesting a mixed disorder.

No significant differences were found for pH, $Paco_2$, or [HCO_3^-] when values obtained from intraosseous sites were compared with central venous specimens during steady and low-flow cardiac states.[1] Venous blood gas measurements, when compared with arterial specimens, accurately demonstrate the degree of acidemia in adult emergency department patients presenting with organic acidemia.[2] In infants, capillary tube blood gases are as reliable as formal arterial blood gases in determining hypercarbia or acidosis.[3]

It is also possible to utilize the acid-base calculations to predict the magnitude of shock and need for blood products. The base deficit or base excess can be a valuable indicator of shock and the efficacy of resuscitation. The base excess is a calculated figure that estimates the metabolic component of the acid-base balance. The base excess is defined as the amount of H^+ that would be required to return the pH of blood to 7.35 if the $Paco_2$ were adjusted to 40. A large base deficit (typically more than 6) indicates that even if the patient's respiratory problems were resolved, a significant metabolic acidosis is present. The clinician should keep in mind, however, that given the dynamic condition of pH balance, the base deficit and base excess numbers could be out of sync with the real-time condition of the patient. Therefore, circumspection is required when deciding what these numbers mean for treatment.

RESPIRATORY ACIDOSIS

Respiratory acidosis is defined as decreased pH that results from pulmonary CO_2 retention. In other words, hypoventilation leads to hypercapnia. CO_2 retention results in excess H_2CO_3 production, which leads to acidemia. In the acute state, the serum [HCO_3^-] is normal. The transition from acute to chronic respiratory acidosis is defined as the point at which renal compensation manifests as HCO_3^- retention (Fig. 122-1).[4]

Clinical Features

Respiratory acidosis is caused by any disorder that results in a decrease in minute ventilation and thus CO_2 retention. Common causes include pulmonary pathologic conditions, airway obstruction, and conditions that influence respiratory drive (Box 122-1). The clinical picture depends on the severity and chronicity of the process as well as on the underlying disease. Patients with acute respiratory acidosis may have CO_2 narcosis, characterized by symptoms and signs such as headache, asterixis, weakness, tremors, blurred vision, confusion, or somnolence. If prolonged, signs of intracranial pressure elevation with papilledema become manifest.

Physiologic Compensation

In acute respiratory acidosis, the only effective buffers are the intracellular proteins. The HCO_3^- formed by intracellular buffering diffuses out of the cell into the ECF, increasing about 1 mEq/L for every 10-mm Hg rise in the $Paco_2$. In acute situations, this HCO_3^- compensation is insignificant and has only minimal effect on the prevailing pH. Profound acidemia develops quickly if ventilation is not improved.

In chronic respiratory acidosis, such as chronic obstructive pulmonary disease, renal retention of HCO_3^- plays a significant role in acid buffering. The initial response occurs beyond the first 6 to 12 hours and takes several days to reach maximal contribution. Chloride (Cl^-) is excreted to maintain electrical neutrality and results in the characteristic hypochloremia of a chronic respiratory acidosis. Plasma [HCO_3^-] increases approx-

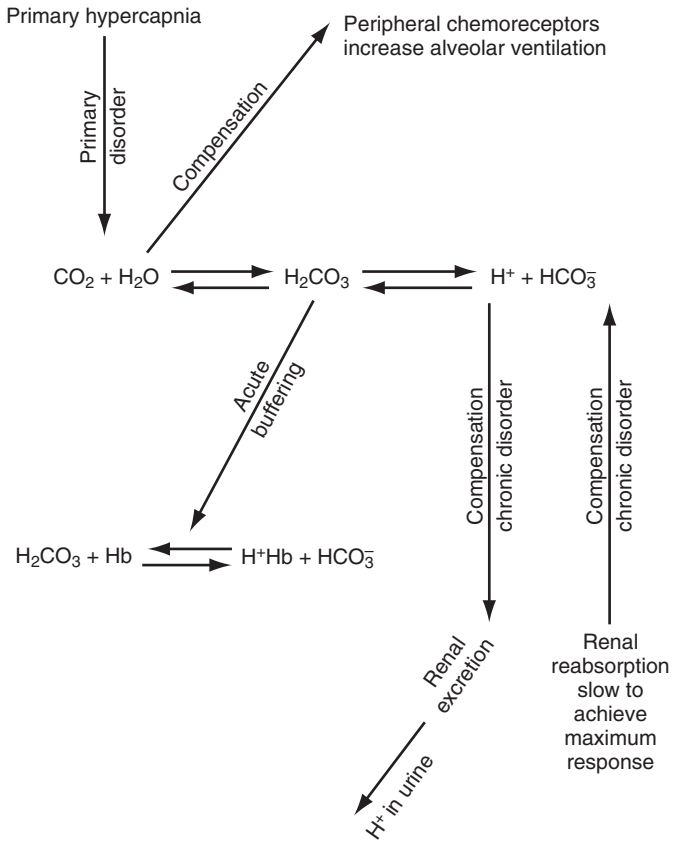

Figure 122-1. Respiratory acidosis and regulation.

BOX 122-1 CAUSES OF RESPIRATORY ACIDOSIS

Acute

- Airway disturbances
  - Obstruction (foreign body, bronchospasm, laryngospasm)
  - Aspiration
- Drug-induced CNS depression
  - Alcohol
  - GHB/GABA toxicity
  - Narcotics
  - IV sedation
- Hypoventilation of muscular or CNS origin
  - Myasthenia gravis
  - CNS injury
  - Guillain-Barré syndrome
- Pulmonary disease
  - Pneumonia
  - Edema
- Thoracic cage disorders
  - Pneumothorax
  - Flail chest

Chronic

- Lung disease
  - Chronic bronchitis
  - Chronic obstructive pulmonary disease
  - Interstitial fibrosis
- Neuromuscular disorders
  - Myasthenia gravis
  - Muscular dystrophy
- Obesity with decreased alveolar ventilation

CNS, central nervous system; GHB/GABA, γ-hydroxybutyrate/γ-aminobutyric acid; IV, intravenous.

imately 3.5 mEq/L for every 10-mm Hg increase in the $Paco_2$. This response provides excellent compensation and nearly normalizes the pH.

Management

Therapy of acute respiratory acidosis is directed toward correction of minute ventilation, thus returning the $Paco_2$ to normal. This may entail establishment of a definitive airway, initiation of artificial respiration, or treatment of an underlying toxic or neurologic condition.

Likewise, improving ventilation treats chronic respiratory acidosis. Bronchodilators, postural drainage, and antibiotics for infection are used to manage the underlying cause. In patients with chronic respiratory acidosis, sensitivity of the respiratory center progressively decreases with prolonged exposure to acidosis and hypercapnia, resulting in a ventilatory drive that depends on relative hypoxemia. Administration of oxygen to these patients reduces their hypoxic drive and minute ventilation, potentially creating CO_2 narcosis. Therefore, oxygen must be given with caution to patients with chronic respiratory acidosis. If the patient has severe hypoxemia, however, sufficient oxygen must be administered and the physician should be prepared to actively manage airway and ventilation. If assisted ventilation is required, the $Paco_2$ should be lowered slowly to avoid posthypercapnic metabolic alkalosis.

In patients with known coronary artery disease, research suggests that acute respiratory acidosis leads to direct vasodilation of coronary vasculature. This is believed to be an instinctive attempt to maintain myocardial blood flow.[5]

RESPIRATORY ALKALOSIS

Increased minute ventilation is the primary cause of respiratory alkalosis, characterized by decreased $Paco_2$ and increased pH. Patients with uncompensated acute respiratory alkalosis have normal plasma [HCO_3^-]. In chronic respiratory alkalosis, eventual renal compensation results in decreased plasma [HCO_3^-].

Etiology

Conditions that lead to respiratory alkalosis are central nervous system (CNS) diseases, hypoxemia, anxiety, hysteria, hypermetabolic states, toxic states, hepatic insufficiency, and assisted ventilation (Box 122-2).

BOX 122-2 CAUSES OF RESPIRATORY ALKALOSIS

- Hypoxia-mediated hyperventilation
  - High altitude
  - Severe anemia
  - Ventilation-perfusion inequality
- CNS-mediated hyperventilation
  - Voluntary, psychogenic
  - Cerebrovascular accident
  - Increased intracranial pressure, tumor
  - Trauma
- Pharmacologic
  - Salicylate, caffeine, or nicotine toxicity
  - Progesterone
  - Pressors, epinephrine
  - Thyroxine
- Septicemia
- Pulmonary
  - Pneumonia
  - Pulmonary embolism
  - Edema
  - Mechanical hyperventilation
  - Atelectasis
- Hepatic
  - Encephalopathy
- Hyponatremia

CNS, central nervous system.

Clinical Features

Symptoms vary according to the degree and chronicity of the alkalosis and the associated symptoms caused by the underlying disorder. The symptoms of alkalosis result from irritability of the central and peripheral nervous systems and from increased resistance in the cerebral vasculature. Symptoms include paresthesias of the lips and extremities, lightheadedness, dizziness, muscle cramps, and carpopedal spasms; symptoms are identical to those seen with hypocalcemia.

Physiologic Compensation

Acute Alkalosis

After the onset of respiratory alkalosis, H^+ is secreted from within the cell to the ECF. H^+ reduces the plasma [HCO_3^-], attempting to offset the acute alkalosis. During the acute state, the plasma [HCO_3^-] is lowered approximately 2 mEq/L for each 10-mm Hg decrease in the $Paco_2$.

Chronic Alkalosis

With persistently low $Paco_2$, renal H^+ secretion is decreased. Mild hypokalemia often occurs as K^+ shifts into the cells while H^+ enters the ECF. Renal secretion of HCO_3^- occurs, and Cl^- is retained to maintain electroneutrality. This creates the hypokalemia and hyperchloremia characteristic of a chronic respiratory alkalosis. During the first 7 to 9 days, compensation is insufficient to normalize the pH, and alkalemia prevails. Beyond 2 weeks, patients with a chronic respiratory alkalosis have a normal or near-normal pH, making this the only primary acid-base disorder in which the pH does often normalize.

Alkalemia of pregnancy (pH 7.46–7.50) is primarily respiratory in origin, occurs early, and is sustained throughout the gestation. A $Paco_2$ of 31 to 35 mm Hg is considered normal in the antepartum period. Therefore, a $Paco_2$ of 40 mm Hg in the pregnant woman represents hypercapnia. In these patients, renal compensation leads to an excretion of HCO_3^-, and a serum HCO_3^- level between 18 and 22 mEq/L in these women is normal.[6]

Management

Respiratory alkalosis itself is rarely life-threatening, and treatment should be directed toward the underlying cause. Treatment should be aimed at removing the stimulus, and when that is not possible, at treating the symptoms. For example, benzodiazepines and pain control may benefit the patient who is overbreathing the ventilator, the anxious patient, or the cocaine or methamphetamine toxic patient. In the patient with tetany or syncope caused by psychogenic hyperventilating, a rebreathing mask allows for CO_2 retention and acid-base normalization. This should be used cautiously and only when other serious conditions have been eliminated from the differential diagnosis.

METABOLIC ACIDOSIS

Metabolic acidosis is defined as acidemia created by a primary increase in [H^+] or a reduction in [HCO_3^-]. The acute state is compensated for by hyperventilation, resulting in reduction of $Paco_2$. Chronically, renal reabsorption of HCO_3^- takes place (Fig. 122-2).

Etiology

Metabolic acidosis can be caused by one of three mechanisms: (1) increased production of acids, (2) decreased renal excretion of acids, or (3) loss of alkali. The causes of metabolic acidosis can be clinically divided into those that create an elevation in AG (Box 122-3) and those that do not (Box 122-4). Dehydration from prolonged diarrhea is the most common cause of normal gap metabolic acidosis.

Elevated Anion Gap

Metabolic acidosis with an elevated AG implies either the addition of exogenous acids or the creation of endogenous acids that cannot be fully neutralized by buffers. The causes can be broadly broken into ketoacidosis, lactic acidosis (either physiologic or from toxins), renal failure, toxins that are metabolized to acids, and, rarely, rhabdomyolysis.

Carbon Monoxide and Cyanide Poisoning. Elevated serum levels of carbon monoxide and cyanide have increasingly been found together in patients exposed to smoke from fires. Victims of smoke inhalation found unconscious and with metabolic acidosis should be considered to have been exposed to both agents. Known as *cellular poisons*, both toxins interfere with cellular respiration at the cytochrome/electron transfer stage, resulting in anaerobic metabolism and the generation of organic acidemia.

Alcoholic Ketoacidosis. Alcoholic ketoacidosis (AKA) results from an abrupt termination of ethyl alcohol intake after a significant and usually lengthy exposure to it. AKA also has a component of malnutrition and dehydration. Clinically, AKA manifests similarly to DKA; however, hyperglycemia and glycosuria are traditionally absent. Patients may present with AGs in the range of 30 to 35 mEq/L and hypocapnia secondary to compensatory hyperventilation. They may also have double and triple acid-base disorders due to alcohol withdrawal (respiratory alkalosis) and vomiting (metabolic alkalosis), which results in a pH that may be alkalemic. The ratio of β-hydroxybutyrate to acetoacetate is at least twice as high in AKA (6–10:1) as it is in DKA (3–4:1).[7] This is important because there is a greater chance of missed diagnosis and inappropriate therapy in cases of AKA, since the β-hydroxybutyrate is not detected by the usual means and because during recovery, as β-hydroxybutyrate is converted to acetoacetate and acetone, a paradoxi-

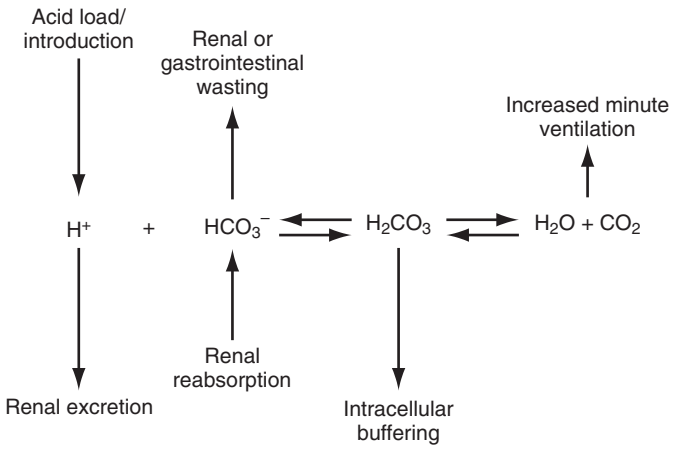

Figure 122-2. Metabolic acidosis and regulation.

BOX 122-3 CAUSES OF ANION GAP METABOLIC ACIDOSIS

Ketoacidosis
Diabetes
Alcohol intoxication/alcoholic ketoacidosis
Malnutrition/fasting

Lactic Acidosis (from physiologic processes)
Shock
Primary hypoxia due to lung disorders
Seizures

Lactic Acidosis (from exogenous toxins)
Carbon monoxide
Cyanide
Iron
Isoniazid
Toluene (initially high gap; subsequent excretion of metabolites normalizes gap)

Renal Failure

Toxins Metabolized to Acids
Alcohol
Methanol (formate)
Ethylene glycol (oxalate)
Paraldehyde (acetate, chloracetate)
Salicylates

Rhabdomyolysis (rare)

BOX 122-4 CAUSES OF NORMAL ANION GAP METABOLIC ACIDOSIS

GI HCO_3^- Loss
Colostomy
Diarrhea
Enteric fistulas
Ileostomy
Use of ion-exchange resins

Urologic Procedures
Ureterosigmoidostomy
Ureteroileal conduit

Renal HCO_3^- Loss
Tubulointerstitial renal disease
Renal tubular acidosis, types 1, 2, and 4
Hyperparathyroidism

Ingestions
Acetazolamide
Calcium chloride ($CaCl_2$)
Magnesium sulfate ($MgSO_4$)

Parenteral Infusion
Arginine
Lysine
Ammonium chloride (NH_4Cl)
Rapid sodium chloride infusion

Other
Hypoaldosteronism
Hyperkalemia
Toluene (late)

cal worsening of the ketoacidosis results. (The usual dipstick tests have 0% sensitivity for β-hydroxybutyrate, 100% for acetoacetate, and 5% for acetone.) The main treatment for AKA is hydration with 5% dextrose in normal saline (D_5NS). Carbohydrate and fluid replacement reverse the pathophysiologic derangements that lead to AKA by increasing serum insulin levels and suppressing the release of glucagon and other counter-regulatory hormones. Fluids alone do not correct AKA as quickly as fluids and carbohydrates together, and in general, insulin is contraindicated.

Toluene Inhalation. Traditionally used as a solvent, toluene has become an inhalational agent abused for its euphoric effect. Toluene produces AG acidosis that is further complicated by distal renal tubular damage. The end result is a mix of non-AG and AG metabolic acidosis due to the renal tubular acidosis and HCO_3^- loss. Treatment is supportive and is aimed at fluid and electrolyte replacement when needed.

Methanol, Ethylene Glycol, and Paraldehyde. The toxic effects of methanol (methyl or wood alcohol) ingestion result from the formation of its metabolite, formaldehyde, which is converted to formic acid, which causes metabolic acidosis. Ethylene glycol's toxic metabolites are oxalates, aldehydes, and lactic acid; oxalates result in significantly elevated AGs and increased mortality. Paraldehyde poisoning is rare; its use is now restricted to hospitalized patients and patients under close medical supervision. Ingestion leads to the creation of acetic and chloracetic acids. Treatment of methanol or ethylene glycol poisoning is aimed at preventing their metabolism into toxins with fomepizole or ethanol or elimination through hemodialysis.

Uremia. The acidosis in uremic patients results from a failure by the kidneys to excrete acids. H^+ elimination is a direct secretory function of the renal tubules. The ability to excrete NH_4^+, HSO_4^-, and HPO_4^{-2}, however, varies directly with the glomerular filtration rate (GFR). Any pathologic process affecting the GFR increases HSO_4^- and HPO_4^{-2}, resulting in an increased AG. In cases of pure uremia, the AG rarely exceeds 25 mEq/L. In the patient with chronic renal failure, increased AG metabolic acidosis is common. In cases of acute renal failure, however, hyperchloremic, non-AG metabolic acidosis is more common.

In pyelonephritis or obstructive uropathy, the acidosis is not related to an increased AG because tubular function is affected more than GFR. Increased AG metabolic acidosis in the patient with elevated serum blood urea nitrogen and creatinine levels suggests renocortical disease.

Diabetic Ketoacidosis. DKA manifests clinically as a triad: hyperglycemia (usually >200 mg/dL), ketonemia (>1:2 dilutions), and acidemia (pH < 7.3). DKA can be caused by any condition that reduces insulin availability or activity or that increases glucagon. DKA occurs most often in type 1 diabetic patients with little or no endogenous insulin; however, its occurrence in patients with type 2 diabetes, particularly obese African Americans, is not as rare as once thought. DKA in these patients results from increased lipolysis, and the breakdown of free fatty acids leads to production of ketoacids. Precipitating events usually include infections, surgery, and emotional or physical stressors. Treatment is aimed at fluid replacement over the first 24 to 48 hours, insulin replacement, and potassium replacement.

Isoniazid and Iron Toxicity. Isoniazid is a common, important, but potentially lethal medication used for the treatment of tuberculosis. Clinicians must be aware that ingestions of greater than 40 to 60 mg/kg pose a danger of not only recurrent seizures but also life-threatening metabolic acidosis (as a result of the lactate-producing seizure activity). Treatment involves pyridoxine administration to control seizures and hemodialysis to reduce both intravascular drug concentration and acidemia.

Elevated AG metabolic acidosis from iron ingestion is a direct result of mitochondrial poisoning and uncoupled oxidative phosphorylation. Metabolic acidosis is typically appreciated in phase I of toxicity, usually within 6 hours of ingestion. It becomes quite apparent in phase III, signaling impending hepatic failure and shock. Effective treatment depends on early recognition and administration of deferoxamine.

Lactic Acidosis. There are two forms of lactic acid, the levorotary, or "L," form and the dextrorotary, or "D," form. The L form is most common and is the traditional form measured when obtaining serum lactate levels. A product of anaerobic metabolism, lactic acidosis develops when an imbalance exists between lactic acid production and subsequent conversion by the liver and kidney. Thus, lactic acidosis is a marker of hypoperfusion and ongoing shock, as hypoperfusion, hypoxemia, hypermetabolic states, or some combination of these results in an increase in serum lactate.

The D form has recently gained attention because of an increasing number of patients with small-bowel resection or gastric bypass surgery.[8] D-Lactic acidosis is characterized by episodes of encephalopathy and acidemia. Development of short-gut syndrome requires ingestion of a large carbohydrate load, carbohydrate malabsorption with increased delivery of carbohydrates to the large bowel, prominent lactobacilli, diminished colonic motility, and impaired D-lactic acid metabolism.

Nucleoside analogue reverse transcriptase inhibitors (e.g., zidovudine and stavudine) for human immunodeficiency virus have also been shown to induce lactic acidosis. The syndrome that results from the mitochondrial toxicity of these agents can manifest with severe lactic acidosis, hepatic steatosis, and a high rate of mortality.[9]

Initial measurement of metabolic acidosis (serum lactate levels), compared with the traditional carboxyhemoglobin levels, might better indicate the severity of carboxyhemoglobin toxicity and better predict hyperbaric treatment requirements.[10]

Metformin, currently considered the initial drug of choice for overweight patients with type 2 diabetes mellitus, is a biguanide derivative that is pharmacologically related to phenformin hydrochloride, which was withdrawn from the U.S. market in 1976 (owing to a high incidence of lactic acidosis). Studies support the clinical experience of metformin-induced lactic acidosis as well.[11] Metformin is believed to induce lactic acidosis, especially in the patient with renal insufficiency, by reducing pyruvate dehydrogenase activity and enhancing anaerobic metabolism. A serum creatinine concentration greater than 1.5 mg/dL, congestive heart failure requiring medications, acute or chronic metabolic acidosis, or exposure to iodinated contrast agents within 48 hours are considered absolute contraindications to the drug.

Salicylates. Salicylates' first toxic effect on acid-base balance results from direct stimulation of the respiratory center, increasing minute ventilation and inducing hypocapnia. This is known as the first phase and may last as long as 12 hours. In the early presentation of salicylate toxicity, respiratory alkalosis is often the only acid-base disturbance appreciated. Salicylates can also cause metabolic acidosis by uncoupling oxidative phosphorylation and inhibiting the dehydrogenase enzymes of the Krebs cycle. The second phase of salicylate poisoning is marked by paradoxical aciduria in the presence of continued respiratory alkalosis. This phase may begin within hours and may last 12 to24 hours. The third phase is marked by dehydration, hypokalemia, and progressive metabolic acidosis. This phase may begin within 4 to 6 hours in infants or more than 24 hours later in adolescents and adults. Treatment

is supportive, and gastrointestinal decontamination with charcoal may be indicated. Fluid and electrolyte replacement will likely be necessary, and both urinary and serum alkalinization may be of benefit in enhancing elimination and minimizing toxicity.

Normal Anion Gap Metabolic Acidosis

Metabolic acidosis with a normal AG is caused by either an excessive loss of HCO_3^- or an inability to excrete H^+ (see Box 122-4). Any condition that causes excessive loss of intestinal fluid distal to the stomach can cause a normal AG metabolic acidosis. Normal AG metabolic acidosis is primarily a HCO_3^--wasting condition and in 95% of cases results from diarrhea. Other possible, although less common, causes include tube drainage and skin fistulae, with loss of HCO_3^--rich intestinal, biliary, or pancreatic fluids. Ureterosigmoidostomy (surgical insertion of ureters into the sigmoid colon) produces a hyperchloremic acidosis because of loss of HCO_3^- in exchange for the reabsorption of Cl^-.

Patients with renal failure develop an inability to excrete their dietary H^+ load; the severity is proportional to the degree of reduction in the GFR. Patients with renal tubular acidosis type 1 are unable to secrete H^+ at the distal tubule, whereas impairment of HCO_3^- reabsorption at the proximal tubule is the defect in renal tubular acidosis type 2. Calculation of the urinary anion gap (UAG = $[Na^+ + K^+] - Cl^-$) may be helpful; a negative urinary AG suggests GI loss of HCO_3^-, whereas a positive urinary AG suggests altered urinary acidification, indicating a renal tubule abnormality.

Other causes of normal AG metabolic acidosis include hyperparathyroidism, medications such as carbonic anhydrase inhibitors (e.g., acetazolamide [Diamox], mafenide acetate [Sulfamylon]), spironolactone and cholestyramine, chloride-containing acids ingestion (e.g., NH_4Cl, arginine HCl, lycine), renal tubular acidosis, sulfur, $CaCl_2$ and $MgCl_2$ ingestions, and hyperalimentation with excess arginine, lysine, or Cl^-.

Physiologic Compensation

The body responds to acidemia by utilizing four buffering systems: (1) extracellular bicarbonate/carbonic acid (HCO_3^-/H_2CO_3) system, (2) intracellular blood protein system, and (3) renal and (4) respiratory compensation systems (see Fig. 122-2).

The first two processes minimize the initial $[H^+]$, while the kidneys eliminate excessive H^+ in the urine, reabsorb HCO_3^-, and restore acid-base homeostasis. The CNS responds to increased $[H^+]$, through direct stimulation of the chemoreceptors in the medulla oblongata, by stimulating the respiratory center. This results in an increase in alveolar ventilation, producing a compensatory elimination of $Paco_2$ and elimination of excess H^+. It may take 12 to 24 hours to achieve a maximal respiratory response to a sustained metabolic acidosis. When the arterial pH is 7.1 or less, the minute ventilation can reach 30 L/min, and at this level of pH, Kussmaul's respiration and its prominent hyperventilation can be seen.

In response to metabolic acidosis, H^+ is excreted by the kidney while HCO_3^- is reabsorbed. The rate-limiting reaction (the synthesis of H_2CO_3 from CO_2 and H_2O) is catalyzed by carbonic anhydrase. Therefore, inhibitors of this enzyme can create a metabolic acidosis by preventing the renal excretion of H^+. The excretion of H^+ requires buffering with HPO_4^- or NH_3, with NH_4^+ playing the largest role. This buffering is called *titratable acidity*. The kidney responds to an increased H^+ load by the augmentation of cellular NH_3 production and consequently NH_4^+ excretion.

In summary, H^+ is acutely buffered by extracellular and intracellular mechanisms. However, these mechanisms are not potent enough to correct acidosis sufficiently. Acidemia stimulates the CNS ventilatory center, and the $Paco_2$ is reduced secondary to Kussmaul's respiration. With continued and chronic acidemia, the kidneys secrete H^+ (as NH_4^+ and $H_2PO_4^-$) and reabsorb HCO_3^- in an attempt to neutralize the acidosis.

Management

In treating patients with metabolic acidosis, primary efforts should be directed at restoring their homeostatic mechanisms. The clinician must treat the patient, using laboratory markers only as a guide. Individual therapies are directed toward the particular cause of the acidosis.

Active correction of the pH depends on the severity of the acid-base imbalance, the cause, the patient's compensatory capabilities, and the potential harm caused by therapy. Most patients with metabolic acidosis do not require aggressive attempts at pH manipulation. For many, the causality is easily discernible, and treatment involves stabilization of homeostatic mechanisms. For example, metabolic acidosis (average pH 7.1) after a seizure resolves within approximately 15 minutes, and the bicarbonate normalizes within 45 to 60 minutes. Rather than administration of sodium bicarbonate ($NaHCO_3$), immediate treatment would involve termination of the seizure activity, maintenance of the airway, and provision for acid-base normalization by ventilatory loss of CO_2.

Therapy with $NaHCO_3$ has some inherent complications, and rapid $NaHCO_3$ replacement can result in paradoxical CNS intracellular acidosis, impaired oxygen delivery, hypokalemia, hypocalcemia, "overshoot" alkalosis, hypernatremia, volume overload, and hyperosmolality. Bicarbonate penetration into the CNS across the blood-brain barrier is very slow; consequently, intravenous HCO_3^- therapy alkalinizes the plasma much faster than the CNS. As the serum pH increases, the peripheral chemoreceptors decrease minute ventilation, raising $Paco_2$ in an attempt to normalize the serum pH. CO_2, which rapidly diffuses across the blood-brain barrier, rises intracerebrally, and the CNS becomes more acidemic despite alkalinization of the plasma. This inverse reaction is referred to as *paradoxical CNS acidosis*. Much discussion surrounds this phenomenon and intravenous HCO_3^- use. Buffer therapy during out-of-hospital cardiac arrest had little to no benefit in one study, regardless of the arterial pH.[12] The only prospective, randomized, controlled study was done on hypovolemic rats and failed to demonstrate any difference between the HCO_3^- and control groups.[13] Furthermore, alkali therapy can lead to ECF volume overload (especially in patients with congestive heart failure) and hypokalemia, which may lead to respiratory muscle weakness and inability to hyperventilate if it is severe. Administration of loop diuretics may prevent or treat this complication, but if adequate diuresis cannot be established, emergent dialysis may be necessary.

Because $NaHCO_3$ imparts a significant sodium load on the patient, several low-sodium buffers have been developed. Unfortunately, none has proven to be clinically more efficacious than $NaHCO_3$.[14]

Because of the inherent complications associated with HCO_3^- replacement, the rule of thumb is to consider treatment in patients who have pH less than 7.1 with $NaHCO_3$ 1 mEq/kg unless the condition of acidemia is expected to be self-limited. For example, many experts do not recommend administration of HCO_3^- in patients with DKA and pHs as low

as 6.9. Another formula available to assist in determining the adequate dose is the following:

$$NaHCO_3(mEq) = 25 - (\text{measured } HCO_3^-) \times (\text{weight [kg]}/2)$$

Half should be replaced initially, and further $NaHCO_3$ therapy should be determined by patient response and laboratory parameters. Patients with normal AG metabolic acidosis have a greater loss of HCO_3^- than those with an increased AG, and therefore the clinician may have a lower threshold for replacement (i.e., treat serum HCO_3^- less than 8 mEq/L and correct to 12–15 mEq/L versus AG acidosis where it should be corrected to 10 mEq/L).

METABOLIC ALKALOSIS

Metabolic alkalosis is produced by conditions that increase HCO_3^- or reduce H^+. This usually requires either the loss of H^+ or the retention of HCO_3^-. The diagnosis requires knowledge of the $Paco_2$, because elevation of the plasma HCO_3^- may be secondary to renal compensation of a chronic respiratory acidosis.

Etiology

Metabolic alkalosis is usually caused by an increase in HCO_3^- reabsorption secondary to volume, potassium, or Cl^- loss (Box 122-5). Loss of H^+ and Cl^- from protracted vomiting and nasogastric suctioning can also lead to HCO_3^- retention. Renal impairment of HCO_3^- excretion, especially in the setting of alkali therapy, can lead to a significant metabolic alkalosis.

An ECF volume reduction can increase the plasma HCO_3^- concentration when combined salt and water losses occur, typically in patients using diuretics. This state forces a contraction of the ECF around a constant plasma HCO_3^-, creating a relative excess in HCO_3^- concentration; this is known as *contraction alkalosis*.

Metabolic alkalosis can be caused by hypokalemia as H^+ is shifted intracellularly in exchange for the osmotic movement of K^+ extracellularly. There is also an increase in renal H^+ secretion and HCO_3^- reabsorption. The net effect is ECF alkalosis with paradoxical intracellular acidosis, which is easily reversed with K^+ therapy.

Primary hyperaldosteronism, hyper-reninism, licorice ingestion, Cushing's syndrome, and congenital adrenal hyperplasia are associated with mineralocorticoid excess. This leads to an increased Na^+ reabsorption in the distal tubule with its accompanying H^+ and K^+ secretion to maintain electroneutrality.

BOX 122-5 CAUSES OF METABOLIC ALKALOSIS

Volume-Contracted (Saline-Responsive)
Vomiting/gastric suction
Diuretics
Ion-deficient baby formula
Colonic adenomas
Postrespiratory acidosis

Normal Volume/Volume-Expanded (Saline-Resistant)
Hyperaldosteronism (primary, secondary, or exogenous mineralic corticoids, e.g., licorice, tobacco)
Cushing's syndrome
Severe potassium depletion
Adenocarcinoma
Bartter's syndrome
Ectopic adrenocorticotropic hormone

Unclassified
Milk-alkali syndrome
Carbenicillin therapy
Metabolism of organic acid anion (bicarbonate, lactate, citrate)
Massive transfusion with citrate anticoagulant or plasmanate (acetate) if renal impairment
Nonparathyroid hypercalcemia

Physiologic Compensation

Although somewhat less predictable, acute compensation of metabolic alkalosis involves the respiratory center, and chronic compensation involves the renal system. During acute compensation, chemoreceptors controlling ventilation respond to an increased pH by inducing hypoventilation, thus increasing $Paco_2$ and forming H^+, which lowers the pH back to normal. A $Paco_2$ of greater than 55 mm Hg is unlikely to be caused by simple respiratory compensation of metabolic alkalosis, and this value should alert the clinician to a ventilation disorder complicating the picture. Chronic compensation for metabolic acidosis results from the kidneys excreting excess HCO_3^- in the urine. In patients with renal failure, impairment in renal HCO_3^- excretion results in sustained metabolic alkalosis.

Management

Clinicians can easily treat the simple loss of H^+ from protracted vomiting or nasogastric suction. For more complicated causes, however, management can be directed by measurement of the urinary Cl^-, which helps classify metabolic alkalosis into saline-responsive or saline-resistant.

Saline-Responsive Alkalosis

Patients with saline-responsive alkalosis have a urinary Cl^- level less than 10 mEq/L. Treatment is directed toward correcting the urinary excretion of HCO_3^-. Administration of NaCl and KCl suppresses both renal acid excretion and renal HCO_3^- excretion. Administration of NaCl and KCl should be considered for patients with mild to moderate saline-responsive alkalosis. In patients who are severely volume-depleted, consultation for admission and administration of intravenous mineral acids (e.g., arginine monohydrochloride) may be necessary. In edematous states for which saline therapy may be contraindicated, acetazolamide increases the excretion of $NaHCO_3$, treating both the alkalosis and the edema. In renal failure patients, severe metabolic alkalosis should be treated with dialysis.

Saline-Resistant Alkalosis

Patients with saline-resistant alkalosis have a urinary Cl^- level greater than 10 mEq/L. In mineralocorticoid excess, hypokalemia and increased secretion of aldosterone lead to excessive renal excretion of H^+ and a reabsorption of HCO_3^-. Treatment can be successful with K^+ replacement by reversing the intracellular shift of H^+. This reduction of cellular H^+ also enhances HCO_3^- excretion. Additional therapy can be directed toward reducing mineralocorticoid activity (e.g., administering spironolactone, an aldosterone antagonist).

MIXED ACID-BASE DISORDERS

Double and triple primary acid-base disturbances are common. Traditionally, mixed disorders have been difficult to evaluate in the emergency department. However, recent literature pro-

vides some guidelines for ascertaining the mixed disorder and its causes. Clues to the presence of a mixed acid-base disturbance can either be historical (e.g., polydrug ingestion) or clinical, with varied chemistry and arterial blood gas findings that differ from those anticipated. We can use a six-step approach to analyzing acid-base disturbances as outline below and in Figure 122-3.

Step 1 involves measuring the pH. It is necessary to first assess whether the patient has an acidemia (pH < 7.36) or alkalemia (pH > 7.44). The human body almost never fully compensates for any primary acid-base disturbance except for chronic respiratory alkalosis.

Step 2: Is the primary disturbance respiratory or metabolic?

Step 3 requires the clinician to calculate the AG. Box 122-3 lists possible causes of an AG greater than 15 mEq/L, and Box 122-4 lists possible causes for a case in which the AG is normal but the patient has a metabolic acidosis.

Step 4 involves calculating the delta gap (ΔG = deviation of AG from normal – deviation of HCO_3^- from normal) to help resolve the possibility of a mixed acid-base disorder or further differentiate an elevated AG metabolic acidosis.

Values for the ΔG are all gaussian, and therefore the mean value should be near zero.[15] An expected normal range for the ΔG would be 0 ± 6. A positive ΔG (+6 or greater) is almost always caused by high AG acidosis and a primary metabolic alkalosis. DKA or AKA with severe vomiting, lactic acidosis in the setting of chronic diuretic use, and renal disease with vomiting are clinical examples.

A negative ΔG (–6 or less), on the other hand, can be of varied clinical representation. Most often there is either a mixed high AG and normal AG acidosis, or a high AG acidosis with chronic respiratory alkalosis and a compensating hyperchloremic acidosis. Clinically, these patients often have severe underlying metabolic disease with ongoing toxic ingestion (e.g., profound hypermagnesemia, hyponatremia, or hypercalcemia in patients with lithium toxicity) or chronic lung disease, acute lactic acidosis, and furosemide use. Other relationships in these disorders can also assist in rapid interpretation of mixed acid-base disturbances (Box 122-6).

Step 5 asks whether the respiratory disturbance (if there is one) is acute or chronic. If acute, for each change in P_{CO_2} of 10 mm Hg, the pH changes by 0.08 in the opposite direction. If chronic, for each change in P_{CO_2} of 10, the pH changes by 0.03 in the opposite direction.

Step 6 involves determining if the respiratory system has compensated fully when the primary disturbance is a metabolic acidosis. Using Winter's formula (P_{CO_2} = 1.5 ($HCO3^-$) + 8 ± 2), you can calculate the degree of compensation.

Mixed acid-base disturbances typically result from compensation failure, excessive compensation, or more than one disease process. Examples of compensation failures resulting in metabolic acidosis and respiratory acidosis include: cardiac arrest patients, chronic obstructive pulmonary disease patients with respiratory failure and hypoxemia, and hypoventilation and acidosis-causing toxins. Metabolic alkalosis and respiratory alkalosis may result from compensation failure in patients who are pregnant with hyperemesis and in patients with postoperative pain and vomiting. Patients with salicylate overdose, pulmonary edema, sepsis, and hepatic failure may exhibit excessive compensation and a combined metabolic acidosis and respiratory alkalosis that results in a near normal pH. Superimposed metabolic acidosis and alkalosis may also be present in patients with excessive compensation due to vomiting in association with DKA or AKA. In the alcoholic patient with AKA you may find a triple acid-base disturbance as a result of vomiting (metabolic alkalosis), withdrawal (respiratory alkalosis), and the AKA (metabolic acidosis). A thorough history and physical examination can be especially important in prompting the clinician to consider a complicated acid-base disturbance.

BOX 122-6 RELATIONSHIPS IN ACID-BASE DISTURBANCES

Respiratory Acidosis

Acute

HCO_3^- increases 1 mEq/L (range, 0.25–1.75) for every 10-mm Hg increase in P_{CO_2}.

pH drops 0.08 for every 10-mEq/L rise in HCO_3^-.

Chronic (>5 days of hypercapnia)

HCO_3^- increases 4 mEq/L for every 10-mm Hg increase in P_{CO_2} (±4).

Limit of compensation: bicarbonate will rarely exceed 38–45 mEq/L.

Metabolic Acidosis

Note: It may take 12–24 hours for maximal respiratory response to develop.

$P_{aCO_2} = (1.5 \times HCO_3) + 8 \pm 2$.

P_{aCO_2} is equivalent to last two digits of pH (e.g., if P_{CO_2} is 20, pH should be 7.20).

$\Delta P_{CO_2} - 1\ [1.3 \times (\Delta HCO_3^-)]$

For pure AG acidosis, the rise in anion gap should be equal to the fall in $[HCO_3^-]$ (i.e., ΔG should equal 0).

For pure non-AG (hyperchloremic) acidosis, the fall in HCO_3^- should be equal to the rise in $[Cl^-]$ (i.e., $\Delta HCO_3^- = -\Delta Cl^-$).

Limit of compensation: P_{aCO_2} will not fall below 10–15 mm Hg.

Respiratory Alkalosis

Acute

HCO_3^- drops 1 to 3.5 mEq/L for every 10-mm Hg drop in P_{CO_2}.

Limit of compensation: bicarbonate is rarely below 18 mEq/L.

Chronic (renal compensation starts within 6 hours and is usually at a steady state by 1½–2 days)

HCO_3^- drops 2–5 mEq/L for every 10-mm Hg drop in P_{CO_2}.

Limit of compensation: bicarbonate is rarely below 12–14 mEq/L.

Metabolic Alkalosis

$P_{CO_2} = 0.9\ (HCO_3^-) + 9$.

P_{CO_2} increases 0.6 mm Hg for each 1-mEq/L increase in HCO_3^-.

Limit of compensation: P_{CO_2} rarely exceeds 55 mm Hg but has been reported as high as 75.

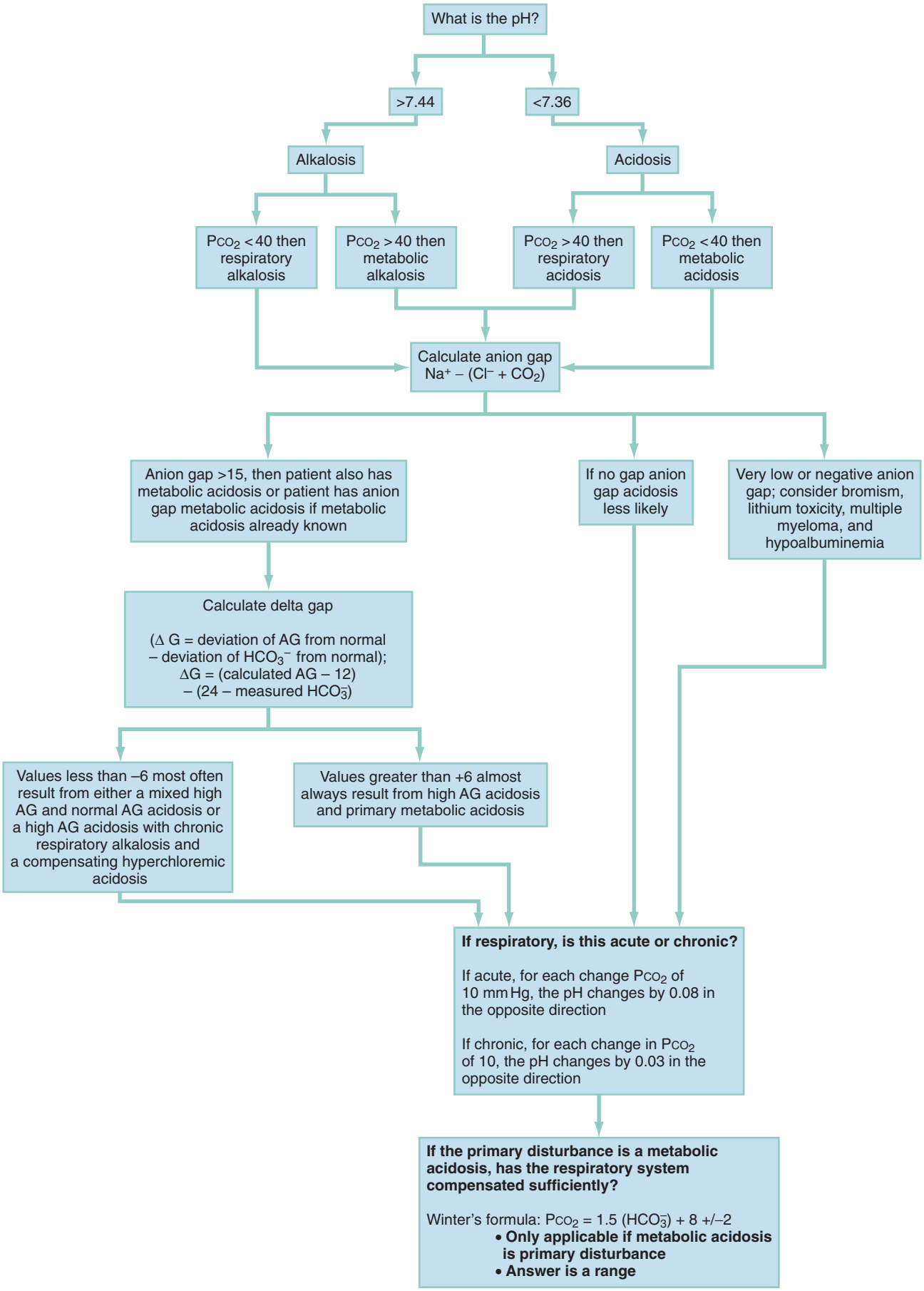

Figure 122-3. Algorithm for acid-base calculation.

KEY CONCEPTS

- Changes in serum pH are dealt with by three compensatory systems: (1) the physiologic buffers, (2) the lungs, and (3) the kidneys.
- HCO_3^- is present in large quantities and can be controlled by the lungs and kidneys, making it the major contributor to the maintenance of acid-base balance and the primary system to handle the acute load of organic acidemia.
- Respiratory acidosis is defined as decreased pH that results from pulmonary CO_2 retention. This CO_2 retention leads to excess H_2CO_3 production and acidemia.
- Increased minute ventilation is the primary cause of respiratory alkalosis, characterized by decreased $Paco_2$ and increased pH.
- Metabolic acidosis can be caused by one of three mechanisms: (1) increased production of acids, (2) decreased renal excretion of acids, or (3) loss of alkali. The causes of metabolic acidosis can be divided into those that create an elevation in the AG and those that do not.
- Metabolic alkalosis is usually caused by an increase in HCO_3^- reabsorption secondary to volume, potassium, or Cl^- loss.
- Contraction alkalosis can result from extracellular volume reduction, with a consequent increase in the plasma HCO_3^- concentration, when combined salt and water losses occur. This typically occurs in patients using diuretics.
- Determination of a mixed acid-base disorder requires knowledge of the pH, calculation of the AG, and calculation of the ΔG.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.