Chapter 71: Acid–Base Disorders

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UPDATE SUMMARY

Update Summary

May 15, 2023

The following sections, tables, and figures were updated:

- Veverimer: Updated to describe the FDA denial of approval
- Figure 71-4: Clarified role of alternative therapies
- Hydrochloric acid: Clarified dose of hydrochloric acid equation
- Self-assessment questions: Clarified questions 4, 10, 11, 13, 14, and 15

CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 74, Acid-Base Disorders.

KEY CONCEPTS

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1. The lung plays a central role in acid–base homeostatic regulation through an increase or decrease in respiration to regulate the partial pressure of CO_2 in the blood (PCO_2); an increased respiratory rate (RR) eliminates more CO_2, reduces the PCO_2 in the blood, and results in a reduced carbonic acid concentration and increased pH; the opposite occurs with decreased respiration.

2. The kidney also plays a central role in the regulation of acid–base homeostasis through the excretion or reabsorption of filtered bicarbonate (HCO_3^-), the excretion of metabolic fixed acids, and the generation of new HCO_3^-.

3. Each acid–base disturbance has a compensatory response that attempts to correct the HCO_3^--to-$PaCO_2$ ratio toward normal and mitigate the change in pH. The respiratory compensatory response to metabolic disturbances is initiated rapidly, whereas the metabolic compensatory response to respiratory disturbances occurs more slowly.

4. Metabolic acidosis and metabolic alkalosis are generated by a primary change in the serum bicarbonate concentration. In metabolic acidosis, bicarbonate is lost or a nonvolatile acid is gained, whereas metabolic alkalosis is characterized by a gain in bicarbonate or a loss of nonvolatile acid.

5. Arterial blood gases (ABGs), along with serum electrolytes, physical findings, medical and medication history, and the clinical condition of the patient, are the primary tools to determine the cause of an acid–base disorder and to design and monitor a course of therapy.

6. Renal tubular acidosis (RTA) refers to a group of disorders characterized by impaired tubular renal acid handling despite normal or near-normal glomerular filtration rates. These patients often present with hyperchloremic metabolic acidosis.

7. Primary therapy of most acid–base disorders must include treatment or removal of the underlying cause, not just correction of the pH and electrolyte disturbances.

8. Potassium supplementation is always necessary for patients with chronic metabolic acidosis, as the bicarbonaturia resulting from alkali therapy increases renal potassium wasting.

9. Effective treatment of the underlying cause of some organic acidoses (eg, ketoacidosis) can result in bicarbonate regeneration within hours thus mitigating the need for alkali therapy.

10. A patient's response to volume replacement can be predicted by the urine chloride concentration and permits the differential diagnosis of metabolic alkalosis.

11. Loss of gastric acid from vomiting or nasogastric suctioning may lead to hypochloremia and hyperbicarbonatemia and may often lead to a metabolic alkalosis.

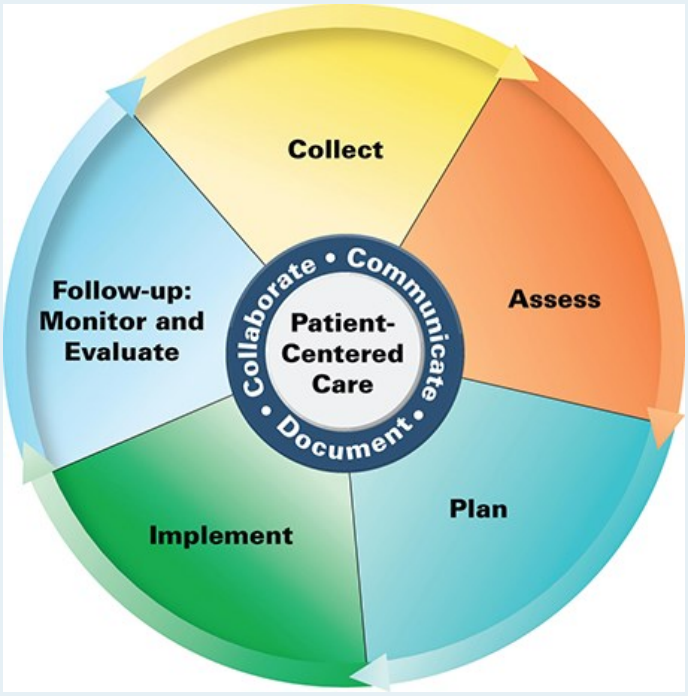
12. Aggressive loop diuretic therapy can produce a metabolic alkalosis, and the accompanying hypokalemia.

13. Management of metabolic alkalosis due to excessive renal acid excretion usually consists of treatment of the underlying cause of mineralocorticoid excess. In patients in whom the mineralocorticoid excess cannot be corrected, chronic pharmacologic therapy may be required.

14. In most cases of acute respiratory acidosis, such as following cardiopulmonary arrest, sodium bicarbonate therapy is not indicated and can be detrimental. Blood gas analysis and the clinical status of the patient should guide therapy.

PATIENT CARE PROCESS

Patient Care Process for Acid–Base Disorders



Collect

- Patient characteristics (eg, age, sex, pregnant)
- Patient medical history (eg, prior acid–base disorder, chronic lung or kidney disease, diabetes mellitus)
- Current medications, including intravenous (IV) fluids (see Tables 71-5, 71-6, 71-7, 71-11, 71-12, 71-13, and 71-14)
- Social history (alcohol use, potential for toxic ingestion)
- Objective data

  Blood pressure (BP), heart rate (HR), RR, height, weight, oxygen saturation

  Labs including arterial blood gases (ABG), serum electrolytes (including serum CO_2), serum creatinine (SCr), serum osmolality, serum lactate, blood glucose, urine chloride

  Current fraction of inspired oxygen (FiO_2)

Assess

- [HCO_3^-] on ABG and electrolyte panel to verify accuracy
- Serum anion gap (SAG)
- Presence of acidemia (pH less than 7.35) or alkalemia (pH greater than 7.45) (see Figure 71-3 and Table 71-4)
- Presence of respiratory disturbance (alteration in $PaCO_2$) or metabolic disturbance (alteration in HCO_3^-)
- Compensatory response (Table 71-8)

- Change in [Cl^-] with change in [Na^+]
- Presence of elevated SAG metabolic acidosis (Tables 71-6 and 71-7)
    - Presence of elevated serum osmolar gap and/or serum lactate
- Presence of metabolic alkalosis (Table 71-11)
    - Presence of urine chloride less than 10 mEq/L (mmol/L) or greater than 20 mEq/L (mmol/L)
- Presence of respiratory acid–base disorder (see Tables 71-12, 71-13, 71-14)

Plan*

- Identification and removal (when possible) of potential cause(s) for the acid–base disorder
- Fluid, electrolyte, or medication therapy (see Tables 71-9 and 71-10, and Figure 71-4)
    - Monitoring parameters may include a repeat RR, oxygen saturation, ABG, and serum electrolytes; repeat SCr, serum osmolality, serum lactate, blood glucose, and/or urine chloride
- Referrals to other providers when appropriate (eg, nephrologist, pulmonologist)

Implement*

- Patient education (eg, purpose of treatment, dietary and lifestyle modification, medication-specific information, medication administration instructions) when the acid–base disorder is chronic
- Schedule follow-up when appropriate

Follow-up: Monitor and Evaluate

- Resolution of acid–base disorder symptoms
- Presence of adverse medication reactions (if acid–base disorder treated with medication)
- Patient adherence to treatment plan using multiple sources of information

****Collaborate with patient, caregivers, and other healthcare professionals.***

BEYOND THE BOOK

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Watch the video entitled “Acid–Base Balance & Blood Gas Interpretation” in the 2019 National Council Licensure Examination (NCLEX) Review [available at https://youtu.be/kh62SRovgrI]. This 10-minute video provides a brief overview of acid–base balance, disturbances, compensation, and interpretation. This video is useful to enhance student understanding regarding the assessment of acid–base disorders in the patient care process.

INTRODUCTION

Acid–base disorders are common and often serious disturbances that can result in significant morbidity and mortality. This chapter reviews the mechanisms responsible for the maintenance of acid–base balance and the laboratory analyses that aid clinicians in their assessment of acid–base

disorders. The pathophysiology of the four primary acid–base disturbances is presented, evidence-based therapeutic options are reviewed, and management guidelines to optimize the outcome of patients with one of these disorders are presented. Given that medications are a frequent cause of acid–base abnormalities and that acid–base abnormalities are often preventable, clinicians must anticipate medication-related problems to avoid or minimize the clinical consequences of acid–base disorders, and when necessary, design appropriate treatment regimens.

ACID–BASE CHEMISTRY

An acid (in this equation, hydrochloric acid) is a substance that can *donate* protons (hydrogen ion [H^+]):

$$\text{(Acid)HCl} \rightarrow \text{H}^+ + \text{Chlorideion (Cl}^-\text{)}$$(Acid)HCl⟶H++Chlorideion (Cl−)

A base (in this equation, ammonia [NH_3]) is a substance that can *accept* protons (hydrogen ion [H^+]):

$$\text{(Ammonia)NH}_3 + \text{H}^+ \rightarrow \text{NH}_4^+\text{(base)}$$(Ammonia)NH3+H+⟶NH4+(base)

The acid–base pairs commonly encountered in clinical practice are listed in Table 71-1.

TABLE 71-1

Acid–Base Pairs

Carbonic acid/bicarbonate	H_2CO_3/HCO_3^-
Monobasic/dibasic phosphate	H_2PO_4/HPO_4^-
Ammonium/ammonia	NH_4^+/NH_3
Lactic acid/lactate	$H_6C_3O_2/H_5C_3O_2^-$

The acidity of body fluids is quantified in terms of the hydrogen ion concentration. By convention, the degree of acidity is expressed as pH, or the negative logarithm (base 10) of the hydrogen ion concentration. Thus, hydrogen ion concentration and pH are inversely related. Normally, the pH of blood is maintained at 7.4 ([H^+] of 4×10^{-8} M) with a range of 7.35 to 7.45. A pH of less than 6.7 ([H^+] of 2×10^{-7} M), representing a fivefold increase in hydrogen ion concentration, or greater than 7.7 ([H^+] of 2×10^{-8} M), representing a 50% decrease in hydrogen ion concentration, is considered incompatible with life.

The hydrogen ion concentration in blood may not be indicative of that in other body compartments. For example, the pH within cells, within the cerebrospinal fluid, or on the surface of bone can all be altered without causing an alteration in blood pH.[1] Recognizing this caveat, the acid–base status of the body is usually analyzed based on measurement of blood pH. Alterations in blood pH serve as the basis for the diagnosis of acid–base disorders.

The dissociation of acid–base pairs is an equilibrium reaction. This allows the relationship between hydrogen ion concentration or pH and the relative concentrations of the acid and base to be described mathematically in terms of the dissociation constant for the acid–base buffer pair. When expressed as a logarithmic relationship, where p*K* is the negative logarithm of the dissociation constant *K*, this is known as the Henderson–Hasselbalch equation:

$$\text{pH} = \text{p}K + \log([\text{base}]/[\text{acid}])$$pH=pK+log([base]/[acid])

BUFFERS

The ability of a weak acid and its corresponding anion (base) to resist change in the pH of a solution with the addition of a strong acid or base is

referred to as *buffering*. An acid–base pair is most efficient in functioning as a buffer at a pH close to its p*K*. The principal extracellular buffer is the carbonic acid/bicarbonate (H_2CO_3/HCO_3^-) system. Other physiologic buffers include plasma proteins, hemoglobin, and phosphates. The complex buffering of biologic fluids can be analyzed based on a single buffer pair because the isohydric principle requires that all buffer systems remain in chemical equilibrium.

The carbonic acid/bicarbonate buffer system plays a unique role in acid–base homeostasis. In addition to being the most abundant extracellular buffer, the components of this buffer pair exist under dynamic regulation by the body. In the presence of carbonic anhydrase, carbonic acid, $[H_2CO_3]$, is in equilibrium with carbon dioxide (CO_2) gas. Changes in pulmonary ventilation that alter the partial pressure of CO_2 (PCO_2) in the blood regulate the carbonic acid level in the blood. Conversely, the bicarbonate concentration is independently regulated by the kidney. Because the p*K* for the carbonic acid/bicarbonate system is 6.1, the relationship between pH, carbonic acid, and bicarbonate concentrations can be described by the Henderson–Hasselbalch equation. The concentration of carbonic acid is directly proportional to the amount of CO_2 dissolved in blood, which is equal to the product of PCO_2 and its solubility in physiologic fluids ($PCO_2 \times 0.03$ for PCO_2 expressed in mm Hg or $PCO_2 \times 0.226$ for PCO_2 expressed in kPa). This term can, therefore, be substituted into the equation below in place of $[H_2CO_3]$.

$$pH = 6.1 + \log\left([HCO_3^-]/[H_2CO_3]\right)$$

$$pH = 6.1 + \log\left([HCO_3^-]/[PCO_2 \times 0.03]\right) \text{ for } PCO_2 \text{ in mm Hg}$$

or

$$pH = 6.1 + \log\left([HCO_3^-]/[PCO_2 \times 0.226]\right) \text{ for } PCO_2 \text{ in kPa}$$

Thus, hydrogen ion concentration and pH are determined not by the absolute amounts of bicarbonate and PCO_2 present but by their ratio.[2] Under normal physiologic conditions, the kidneys maintain the serum bicarbonate at approximately 24 mEq/L (mmol/L), whereas the lungs maintain the PCO_2 at approximately 40 mm Hg (5.3 kPa). The normal physiologic pH is thus 7.4:

$$pH = 6.1 + \log[24/(0.03 \times 40)] \quad (\text{or } pH = 6.1 + \log[24/0.226 \times 5.3])$$

$$pH = 6.1 + 1.3 = 7.4$$

If, in response to an acid load, the serum bicarbonate concentration decreases to 12 mEq/L (mmol/L), then the predicted pH would be:

$$[HCO_3^-] = 12 \text{ mEq/L (mmol/L)}$$

$$PCO_2 = 40 \text{ mm Hg} (5.3 \text{ kPa})$$

$$pH = 6.1 + \log[12/0.03 \times 40] \text{ or}$$

$$pH = 6.1 + \log([12/(0.226 \times 5.3)])$$

$$pH = 6.1 + 1.0 = 7.1$$

However, the normal respiratory response to an acid load is hyperventilation. As a result, if the PCO_2 decreased to approximately 26 mm Hg (3.5 kPa), then the change in pH would be less:

$$[HCO_3^-] = 12 \text{ mEq/L} (\text{mmol/L})$$

$$PCO_2 = 26 \text{ mm Hg } (3.5 \text{ kPa})$$

$$pH = 6.1 + \log[12/0.03 \times 26]$$

$$\text{or } pH = 6.1 + \log[12/(0.226 \times 3.5)]$$

$$pH = 6.1 + 1.19 = 7.29$$

Thus, the physiologic regulation of both PCO_2 and $[HCO_3^-]$ permits the carbonic acid/bicarbonate system to provide more effective buffering of the extracellular fluids (ECFs) than could be achieved on the basis of chemical buffering alone.

REGULATION OF ACID–BASE HOMEOSTASIS

Cellular metabolism results in the production of large quantities of hydrogen that need to be excreted to maintain acid–base balance. In addition, small amounts of acid and alkali are also presented to the body through the diet. The bulk of acid production is in the form of CO_2, with the average adult producing approximately 15,000 mmol of CO_2 each day from the catabolism of carbohydrate, protein, and fat.[2] When respiratory function is normal, the amount of CO_2 produced metabolically is equal to the amount lost by respiration, and the blood CO_2 concentration remains constant.

Digestion of dietary substances and tissue metabolism also result in the production of nonvolatile acids. These acids are derived primarily from the

sulfur-containing amino acids cysteine and methionine, as well as from ingested sulfur. In addition, phosphates are generated from the metabolism of proteins and phospholipids. Neutral substances such as glucose can also be incompletely metabolized to intermediates, such as lactic and pyruvic acid, and fatty acids can be incompletely metabolized to acetoacetic acid and β-hydroxybutyric acid. These dietary and metabolic fixed acids are excreted primarily by the kidney to maintain acid–base homeostasis. On average, daily fixed acid excretion is approximately 0.8-1 mEq/kg/day (mmol/kg/day).[3]

Three processes, each of which varies in its onset, collectively maintain acid–base balance: extracellular buffering, ventilatory regulation of carbon dioxide elimination, and kidney regulation of hydrogen ion and bicarbonate excretion. Extracellular buffering occurs rapidly and is the body's first defense against a sudden increase in hydrogen ion concentration. Hyperventilation then results in a decrease in PCO_2, returning blood pH toward normal. Finally, over a period of day(s), the kidney will excrete the excess hydrogen ion and acid–base balance will return to normal.

Extracellular Buffering

The body's buffering system can be divided into three components: bicarbonate/carbonic acid, proteins, and phosphates. The bicarbonate/carbonic acid buffer system is the most abundant of the body's buffers making it the first line of the defense of changes in pH, because (a) there is more bicarbonate present in the ECF than any other buffer component; (b) the supply of CO_2 is unlimited; and (c) the acidity of ECF can be regulated by controlling either the bicarbonate concentration or the PCO_2.

Carbonic acid represents the respiratory component of the buffer pair because its blood concentration is directly proportional to the PCO_2, which is determined by ventilation. Bicarbonate represents the metabolic component because the kidney may alter its concentration by reabsorption, generating new bicarbonate, or altering elimination.[2] The bicarbonate buffer system easily adapts to changes in acid–base status by alterations in ventilatory elimination of acid (PCO_2) and/or renal elimination of base (HCO_3^-).

The phosphate buffer system consists of serum inorganic phosphate (3.5-5 mg/dL [1.13-1.62 mmol/L]), intracellular organic phosphate, and calcium phosphate in bone. Extracellular phosphate is present only in low concentrations, so its usefulness as a buffer is limited; however, as an intracellular buffer, phosphate is more useful. Calcium phosphate in bone is relatively inaccessible as a buffer, but prolonged metabolic acidosis will result in the release of phosphate from bone.

Intracellular and extracellular proteins also act as buffering systems. The charged side chains of amino acids provide the buffering action. Because the concentration of protein is much greater intracellularly than extracellularly, protein is much more important as an intracellular buffer.

Respiratory Regulation

1 The second process involved in maintenance of acid–base homeostasis is ventilatory regulation of CO_2 elimination. Both the rate and depth of ventilation can be varied to allow for excretion of CO_2 generated by diet and tissue metabolism. Medullary chemoreceptors in the brainstem sense changes in PCO_2 and pH and modulate the control of breathing. Increasing minute ventilation (the total amount of air exhaled over a 1-minute period), by increasing RR and/or tidal volume (the amount of air exhaled in one breath), will increase CO_2 excretion and decrease the blood PCO_2. Conversely, decreasing minute ventilation decreases CO_2 excretion and increases blood PCO_2. This system rapidly adjusts to changes in acid–base balance.[4]

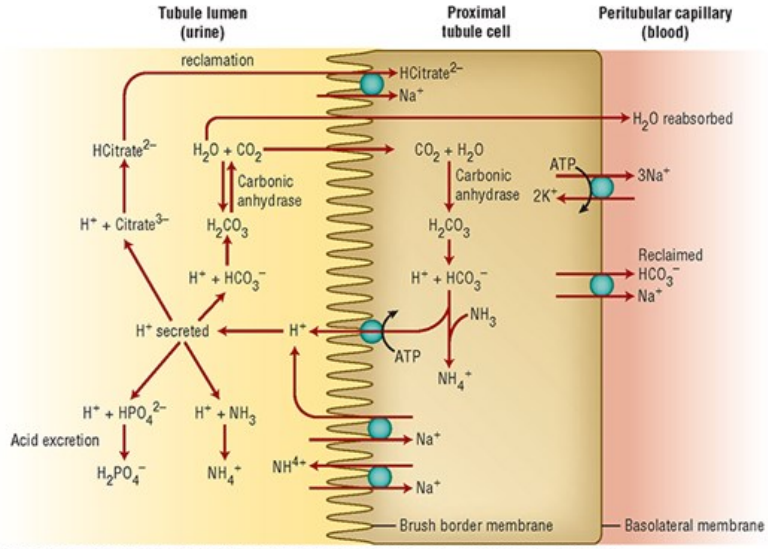
Kidney Regulation

2 Bicarbonate is freely filtered at the glomerulus because it is a small ion. The bicarbonate load delivered to the nephron is approximately 4,500 mEq/day (mmol/day).[2] To maintain acid–base balance, this entire filtered bicarbonate load must be reabsorbed. Bicarbonate reabsorption occurs primarily in the proximal tubule (Fig. 71-1). In the tubular lumen, filtered bicarbonate combines with hydrogen ion, secreted by the apical sodium ion (Na^+)–H^+-exchanger, to form carbonic acid. The carbonic acid is rapidly broken down to CO_2 and water by carbonic anhydrase, an enzyme located on the luminal surface of the brush border membrane. The CO_2 then diffuses into the proximal tubular cell, where it reforms carbonic acid in the presence of intracellular carbonic anhydrase. The carbonic acid dissociates to form hydrogen ions that can again be secreted into the tubular lumen, and

bicarbonate that exits the cell across the basolateral membrane and enters the peritubular capillary.

FIGURE 71-1

Proximal tubular bicarbonate reabsorption and renal acid secretion. The diagram shows the cellular processes involved in bicarbonate (HCO_3^-) reabsorption and renal acid (H^+) secretion in the lumen of proximal tubule lumen (left), proximal tubular cell (in the middle), and peritubular capillary (on the right). In the tubular lumen, filtered HCO_3^- combines with a H^+ secreted by an apical sodium ion (Na^+)–H^+ exchanger to form carbonic acid (H_2CO_3). Carbonic anhydrase located on the luminal surface of the brush border membrane rapidly breaks down H_2CO_3 to carbon dioxide (CO_2) and water (H_2O). The H_2O is absorbed from the tubular lumen into the cell and then into the peritubular capillary. The CO_2 then diffuses into the proximal tubular cell, where it reforms H_2CO_3 in the presence of intracellular carbonic anhydrase. Within the tubular cell, H_2CO_3 dissociates into H^+ and HCO_3^-. Ammonium ion (NH_4^+) is also produced and excreted into the tubular lumen. The HCO_3^- exits the tubular cell across the basolateral membrane into the peritubular capillary along with Na^+. The H^+ is secreted back into the tubular lumen where it is used to generate additional HCO_3^- through the above process and facilitate urinary acid secretion through formation of NH_4^+ and dihydrogen phosphate ion ($H_2PO_4^-$). The secreted H^+ may also titrate citrate^{3-} to form HCitrate^{2-} in the tubular lumen which is equivalent to reabsorption of alkali when transported into the tubular cell.



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

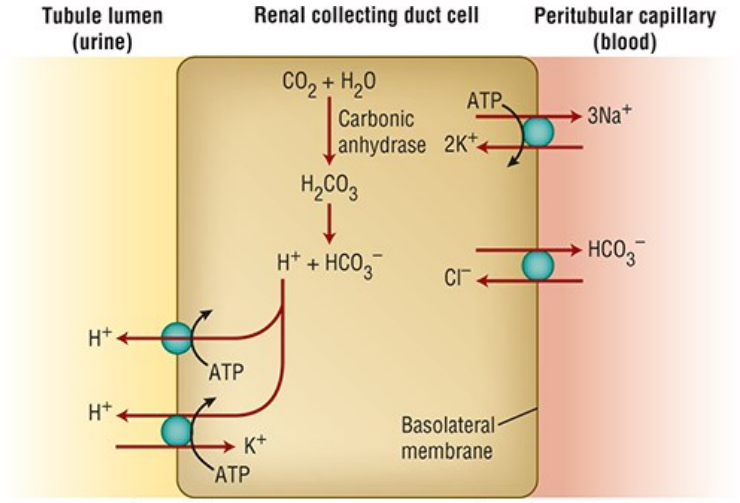
Excretion of metabolic fixed acids and generation of new HCO_3^- are achieved in nearly equal parts by renal ammoniagenesis and distal tubular hydrogen ion secretion. Ammoniagenesis plays a critical role in acid–base homeostasis, with ammonium (NH_4^+) excretion comprising approximately 50% of renal net acid excretion. Ammonium is generated from the deamination of glutamine in the proximal tubule. For each ammonium ion excreted in the urine, one bicarbonate ion is regenerated and returned to the circulation.[2]

Distal tubular hydrogen ion secretion accounts for the remaining 50% of net acid excretion. Although the distal tubule consists of multiple distinct functional segments and cell types, the carbonic anhydrase–containing intercalated cells are primarily responsible for acid–base transport. Specifically, type A intercalated cells function as hydrogen ion secreting cells (Fig. 71-2). In these cells, CO_2 combines with water in the presence of intracellular carbonic anhydrase to form carbonic acid, which dissociates to H^+ and HCO_3^-. The H^+ is actively transported into the tubular lumen by a H^+–adenosine triphosphatase. The bicarbonate exits the cell across the basolateral membrane and enters the circulation.[2]

FIGURE 71-2

Collecting duct acid excretion. The diagram shows the cellular processes involved in acid excretion in the lumen of the collecting duct of the nephron

(left), renal collecting duct cell (in the middle), and peritubular capillary (on the right). Hydrogen ion (H^+) and bicarbonate (HCO_3^-) are generated intracellularly from carbon dioxide (CO_2) and water (H_2O) in the presence of intracellular carbonic anhydrase. The H^+ is actively secreted into the tubular lumen for excretion by H^+–adenosine triphosphatase located in the apical (luminal) membrane. The HCO_3^- exits the renal collecting duct cell across the basolateral membrane and enters the peritubular capillary as chloride ion (Cl^-) enters the cell.



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

ACID–BASE DISTURBANCES

3 4 Alterations in blood pH are designated by the suffix "-emia"; *acidemia* is an arterial blood pH less than 7.35 and *alkalemia* is an arterial blood pH more than 7.45. The pathophysiologic processes that result in alterations in blood pH are designated by the suffix "-osis." These disturbances are classified as either metabolic or respiratory in origin. In metabolic acid–base disorders, the primary disturbance is in the plasma bicarbonate concentration. Metabolic acidosis is characterized by a decrease in the plasma bicarbonate concentration, whereas in metabolic alkalosis the plasma bicarbonate concentration is increased. Respiratory acid–base disorders are caused by alterations in alveolar ventilation that produce corresponding changes in the partial pressure of carbon dioxide from arterial blood ($PaCO_2$). In respiratory acidosis, the $PaCO_2$ is elevated; in respiratory alkalosis, it is decreased. Each disturbance has a compensatory (secondary) response that attempts to correct the HCO_3^--to-$PaCO_2$ ratio toward normal and mitigate the change in pH (Table 71-2). Although the time course of the respiratory compensatory response to metabolic disturbances is rapid, the metabolic compensation for respiratory disturbances is slow. As a result, respiratory disturbances are characterized as acute (minutes to hours in duration), indicating that there has not been sufficient time for metabolic compensation, or chronic (days), indicating that sufficient time for metabolic compensation has elapsed.

TABLE 71-2

Interpretation of Simple Acid–Base Disorders

Acid–Base Disorder	pH	Primary Disturbances	Compensation
Acidosis			
Respiratory	Decrease	Increase $PaCO_2$	Increase HCO_3^-
Metabolic	Decrease	Decrease HCO_3^-	Decrease $PaCO_2$
Alkalosis			
Respiratory	Increase	Decrease $PaCO_2$	Decrease HCO_3^-
Metabolic	Increase	Increase HCO_3^-	Increase $PaCO_2$

CLINICAL ASSESSMENT OF ACID–BASE STATUS

A blood gas is measured to determine not only a patient's acid–base status but also their oxygenation. Under normal circumstances, the pH difference between arterial and mixed venous blood is not clinically significant. However, the oxygenation difference between arterial and mixed venous blood is always substantial. Arterial samples are designated with the letter "a" (eg, partial pressure of oxygen from arterial blood [PaO_2] and $PaCO_2$), whereas mixed venous samples are labeled with the letter "v" or not labeled (eg, partial pressure of oxygen from venous blood [PvO_2] and partial pressure of carbon dioxide from venous blood [$PvCO_2$]). The normal values for arterial and venous blood gases are shown in Table 71-3. Arterial blood reflects how well the blood is being oxygenated by the lungs (an accurate measurement of PaO_2), whereas venous blood reflects how much oxygen tissues are using. Arterial blood rather than venous blood should be used whenever possible because venous blood obtained from an extremity can provide misleading information. If metabolism in the extremity is altered by hypoperfusion, exercise, infection, or some other cause, the difference in the amount of dissolved oxygen between arterial and venous blood can be dramatic. The venous pH and PCO_2 during cardiopulmonary resuscitation might be significantly lower and higher, respectively, than the arterial pH and arterial PCO_2. This indicates a severe tissue acidosis from CO_2 accumulation caused by hypoperfusion.

TABLE 71-3

Normal Blood Gas Values

	Arterial Blood	Mixed Venous Blood
pH	7.40 (7.35-7.45)	7.38 (7.33-7.43)
PO_2	80-100 mm Hg (10.6-13.3 kPa)	35-40 mm Hg (4.7-5.3 kPa)
SaO_2	95% (0.95)	70-75% (0.70-0.75)
PCO_2	35-45 mm Hg (4.7-6.0 kPa)	45-51 mm Hg (6.0-6.8 kPa)
HCO_3^-	22-26 mEq/L (mmol/L)	24-28 mEq/L (mmol/L)

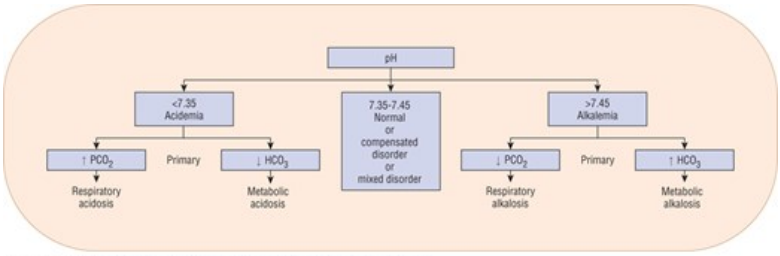
HCO_3^-, bicarbonate; PCO_2, partial pressure of carbon dioxide; PO_2, partial pressure of oxygen; SaO_2, saturation of arterial oxygen.

Analysis of Arterial Blood Gas Data

5 ABGs provide an assessment of the patient's acid–base status.[4] Low pH values (less than 7.35) indicate an acidemia, whereas high pH values (more than 7.45) indicate an alkalemia (Fig. 71-3). In a metabolic acidosis, the pH is decreased in association with a decreased serum bicarbonate concentration and a compensatory decrease in $PaCO_2$. In a respiratory acidosis while the pH is decreased, the $PaCO_2$ is elevated. The serum bicarbonate concentration is variable, depending on whether it is an acute disturbance (minimal increase in serum bicarbonate) or a chronic respiratory acidosis (substantial increase in serum bicarbonate). In a metabolic alkalosis, the pH is elevated in association with an increased bicarbonate concentration and a compensatory increase in $PaCO_2$. In a respiratory alkalosis, while the pH is also elevated, the $PaCO_2$ is decreased. As with respiratory acidosis, the metabolic compensation is variable: a minimal decrease in serum bicarbonate is often noted in acute respiratory alkalosis, while a larger decrease in $[HCO_3^-]$ is common with chronic respiratory alkalosis. Although each measurement has a normal range (see Table 71-3), it is often easiest to consider the midpoint of each range as the normal value. This would correlate to a pH of 7.4, $PaCO_2$ of 40 mm Hg (5.3 kPa), and HCO_3^- of 24 mEq/L (mmol/L). Steps in acid–base interpretation, using this physiologic approach, are described in Table 71-4. While beyond the scope of this chapter, two other approaches to assess acid–base status (ie, the physicochemical [Stewart's] approach and the base excess approach) are sometimes used in clinical practice.[5,6]

FIGURE 71-3

Analysis of arterial blood gases. (HCO_3^-, bicarbonate; PCO_2, partial pressure of carbon dioxide.)



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

TABLE 71-4

Steps in Acid–Base Diagnosis

1. Obtain ABG and electrolyte panel simultaneously
2. Compare [HCO_3^-] on ABG and electrolyte panel to verify accuracy
3. Calculate SAG (corrected for albumin when appropriate)
4. Is acidemia (pH <7.35) or alkalemia (pH >7.45) present?
5. Is the primary abnormality respiratory (alteration in $PaCO_2$) or metabolic (alteration in HCO_3^-)?
6. Estimate compensatory response (Table 71-7)
7. Compare change in [Cl^-] with change in [Na^+]
8. Compare the relative change of HCO_3^- and SAG to rule out mixed disorder(s)

[Cl^-], chloride ion; [Na^+], sodium ion.

When ABGs differ significantly from those expected on the basis of the patient's clinical condition and previous laboratory determinations, additional venous blood samples should be drawn to assess plasma electrolyte concentrations. The bicarbonate calculated from the patient's $PaCO_2$ and pH of the blood gas should be compared with the measured total CO_2 content (the amount of CO_2 gas extractable from plasma, consisting of HCO_3^-, H_2CO_3, and PCO_2). Ordinarily, the blood gas bicarbonate value is approximately 1 to 2 mEq/L (mmol/L) less than the total CO_2 content.[7] If these values do not correspond, the results should be interpreted with caution because the difference can reflect an error in the blood collection or storage of the sample, or in the calibration of the blood gas analyzer.

METABOLIC ACID–BASE DISORDERS

Metabolic Acidosis

Metabolic acidosis is characterized by a decrease in pH as the result of a primary decrease in serum bicarbonate concentration.

Pathophysiology

Metabolic acidosis can result from the buffering (consumption of HCO_3^-) of an exogenous acid, an organic acid accumulating because of a metabolic disturbance (eg, lactic acid or ketoacids), or the progressive accumulation of endogenous acids secondary to impaired kidney function (eg, phosphates and sulfates).[8] The serum HCO_3^- can also be decreased as the result of a loss of bicarbonate-rich body fluids (eg, diarrhea, biliary drainage, or pancreatic fistula) or occur secondary to the rapid administration of non-alkali–containing IV fluids (dilutional acidosis).[8]

The SAG, as defined below, can be used to determine whether an organic or mineral acidosis is present.

$$SAG = [Na^+] - [Cl^-] - [HCO_3^-]$$ SAG=[Na+]−[Cl−]−[HCO3−]

To maintain electroneutrality, the total concentration of cations in the serum must equal the total concentration of anions.

$$[Na^+] + [UCs] = ([Cl^-] + [HCO_3^-]) + [UAs]$$ [Na+]+[UCs]=([Cl−]+[HCO3−])+[UAs]

The cation concentration is equal to the sodium concentration plus that of "unmeasured" cations (UCs), predominantly magnesium, calcium, and potassium. The anion concentration is equal to the concentrations of chloride, bicarbonate, and "unmeasured" anions (UAs), including proteins, sulfates, phosphates, and organic anions. Therefore, as the result of the combination of the two equations above, the SAG can be expressed as:

$$SAG = [UAs] - [UCs]$$ SAG=[UAs]−[UCs]

The normal SAG is approximately 10 mEq/L (mmol/L), with a range of 8 to 12 mEq/L (mmol/L). Differences exist in SAG based on clinical laboratories;

therefore, the clinician should identify the normal SAG where practicing.[7] Increases in the anion gap (AG) to values of greater than or equal to 20 mEq/L (mmol/L) are indicative of the accumulation of UAs in ECF. The SAG calculation assumes normal serum albumin. In cases of hypoalbuminemia, the SAG may be underestimated. For every decrease in serum albumin by 1 g/dL (10 g/L) below the normal value of 4.5 g/dL (45 g/L), the SAG is decreased by 2.5 mEq/L (mmol/L).[7]

These UAs are generated as the result of the consumption of HCO_3^- by endogenous organic acids such as lactic acid, acetoacetic acid, or β-hydroxybutyric acid or from the ingestion of toxins such as methanol or ethylene glycol. The degree of elevation in the SAG is dependent on the clearance of the anion, and the multiple factors that influence HCO_3^- concentrations. Thus, the SAG is a relative rather than an absolute indication of the cause of metabolic acidosis. The SAG can also be elevated in metabolic acidosis because of kidney disease, as a result of the accumulation of various organic anions, phosphates, and sulfates.

A delta ratio may be calculated in patients with an elevated SAG to help determine if another acid–base disorder exists. The general rule is that for every 1 mmol of acid present causing a 1 mEq increase in SAG, the serum bicarbonate should drop by 1 mEq leading to a delta gap of 1. A delta ratio equal to 1 indicates an uncomplicated or pure elevated SAG metabolic acidosis. A delta ratio less than 1 indicates a mixed elevated SAG and non-SAG metabolic acidosis. A delta ratio greater than 1 indicates an elevated SAG metabolic acidosis and metabolic alkalosis.[9]

In hyperchloremic metabolic acidosis, bicarbonate losses from the ECF are replaced by chloride, and the SAG remains normal. This decrease in bicarbonate may be due to gastrointestinal (GI) tract losses, dilution of bicarbonate in the ECF as a result of the addition of sodium chloride solutions or chloride-containing acids. Common causes of metabolic acidosis with an increased or a normal SAG are listed in Table 71-5.

TABLE 71-5

Common Causes of Metabolic Acidosis

Increased Serum Anion Gap	Normal Serum Anion Gap/Hyperchloremic States
Ketoacidosis	Acid ingestion/administration (ammonium chloride, hydrochloric acid)
Alcoholic	GI bicarbonate loss
Diabetic	Diarrhea, high output ileostomy
Starvation	External pancreatic or small bowel drainage (fistula)
Kidney disease	Ureteroenterostomy (urinary diversion)
AKI	Calcium chloride (acidifying agent)
CKD	Magnesium sulfate (diarrhea)
Lactic acidosis (see Table 71-7)	Cholestyramine (bile acid diarrhea)
5-Oxyprolinemia (acetaminophen)	Excessive administration of chloride salts (eg, sodium chloride, PN)
Toxins/overdoses	Renal bicarbonate loss
Ethylene glycol	Adrenal insufficiency
Methanol	Carbonic anhydrase inhibitors (eg, acetazolamide, topiramate)
Propyl alcohol	Hypoaldosteronism
Propylene glycol	RTA (see Table 71-6)
Salicylate	

ACE, angiotensin-converting enzyme; NSAIDs, nonsteroidal anti-inflammatory drugs; PN, parenteral nutrition; RTA, renal tubular acidosis.

Hyperchloremic Metabolic Acidosis

Hyperchloremic metabolic acidosis can result from increased GI bicarbonate loss, renal bicarbonate wasting, impaired renal acid excretion, exogenous acid gain, topiramate, or chloride-containing IV fluids.[8] GI disorders such as diarrhea, biliary, or pancreatic drainage through either a surgical drain or

fistula can result in the loss of large volumes of bicarbonate-containing fluids. Severe diarrhea, the most common cause of hyperchloremic metabolic acidosis, can lead to significant bicarbonate losses as increased GI motility precludes absorption of bicarbonate in the GI tract. Patients who have undergone ureteral diversion into the sigmoid colon or isolated ileal loop can also develop a hyperchloremic metabolic acidosis. This is the result of a net loss of bicarbonate, given that chloride is reabsorbed, and bicarbonate is secreted by GI epithelial cells in the presence of the urine that is retained in the colon or bowel loop.

Hyperchloremic metabolic acidosis caused by renal bicarbonate wasting is the defining disturbance in proximal or Type II renal tubular acidosis (RTA) and is a complication of therapy with carbonic anhydrase inhibitors, particularly when they are administered for multiple doses.[8] Topiramate, an anticonvulsant that inhibits carbonic anhydrase, has been reported to cause hyperchloremic metabolic acidosis, proximal RTA and nephrolithiasis, particularly when administered at higher doses and for prolonged periods.[10] The metabolic acidosis observed in patients with kidney disease is initially hyperchloremic but can progress to an anion-gap acidosis as kidney disease progresses and sulfates, phosphates, and other anions accumulate.[7] Hyperchloremic metabolic acidosis can also result from the exogenous administration of acid (hydrochloric acid, ammonium chloride) or the unbuffered administration of acid salts from the amino acids in parenteral nutrition.[11]

Renal Tubular Acidosis

6 Renal tubular disorders can involve the proximal tubule, with a resultant failure to reabsorb filtered bicarbonate, or affect acid excretion in the distal tubule. The distal RTAs are the most common and are all characterized by impaired net acid excretion. The distal RTAs are subdivided into those that are associated with hypokalemia (type I) and those associated with hyperkalemia (type IV). Type II represents proximal RTA. Type III is extremely rare and will not be discussed. Common causes of RTAs are presented in Table 71-6.

TABLE 71-6

Renal Tubular Acidosis

	Type I	Type II	Type IV
Location	Distal tubules	Proximal tubules	Adrenal/Distal tubules
Primary defect	Impaired urinary H^+ secretion	Decreased urinary HCO_3^- reabsorption	Aldosterone deficiency or resistance
Acidosis	Yes (severe)	Yes	Yes (mild)
UAG	Positive	Negative	Positive
Urine pH	>5.5	<5.5	<5.5
Serum potassium	Low	Low/normal	High
Etiology*	Heredity Autoimmune diseases Primary biliary cirrhosis Rheumatoid arthritis Sjögren syndrome SLE Thyroiditis Hypercalcemia Medications Amphotericin B Cisplatin Ifosfamide Lithium Pentamidine Trimethoprim	Heredity Amyloidosis Fanconi Syndrome Medications Acetazolamide Aminoglycosides Cisplatin Foscarnet Ifosfamide 6-Mercaptopurine Tetracyclines (expired) Topiramate Valproate Multiple myeloma Nephrotic syndrome Sjögren syndrome Toxic metal exposure	Heredity Adrenal insufficiency, primary Autoimmune adrenalitis Adrenal suppression 21-hydroxylase deficiency Adrenal insufficiency, secondary ACEI/ARB/renin inhibitors CKD Diabetes mellitus type 2 Hypertension Hypothalamic-pituitary disease Aldosterone resistance Aldosterone antagonists NSAIDs Potassium sparing diuretics Trimethoprim Chronic interstitial nephropathy (nephritis, obstructive uropathy, HIV nephropathy) General distal tubule defect Sickle cell nephropathy SLE Amyloidosis Renal transplant rejection Chronic cyclosporine toxicity

*Not a comprehensive list, but includes common clinically important disease associations and medications; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; NSAID, nonsteroidal anti-inflammatory drug; SLE, systematic lupus erythematosus.

Data from References 7, 12, and 13.

Patients with classic distal (type I) RTA have impaired hydrogen ion secretion and are unable to excrete the daily acid load necessary to maintain acid–base balance.[12,13] These patients are unable to maximally acidify their urine (ie, attain urine pH less than 5.5), even in the face of an acid challenge. Type I RTA may be the result of a primary tubular defect or develop secondary to a wide variety of medications (eg, amphotericin B, ifosfamide, lithium), hypercalcemia, and autoimmune disorders such as systemic lupus erythematosus.[7,12,13] The primary form of this disorder usually occurs in children and can result in severe acidosis, slowed growth, nephrocalcinosis, and kidney stones. In adults, clinical complications include osteomalacia, nephrocalcinosis, and recurrent kidney stones.

Proximal (type II) RTA is characterized by defects in proximal tubular reabsorption of bicarbonate. Normally, 80% to 85% of filtered bicarbonate is reabsorbed in the proximal tubule.[7,14] Defects in proximal tubular bicarbonate reabsorption result in increased delivery of bicarbonate to the distal nephron, which has a limited capacity for bicarbonate reabsorption. As a result, at a normal serum bicarbonate concentration, the filtered bicarbonate load is incompletely reabsorbed, and is lost in the urine. Thus, patients with proximal RTA present with a chronic, nonprogressive hyperchloremic metabolic acidosis. These patients are able to acidify their urine in response to an acid load but develop bicarbonaturia at a reduced serum bicarbonate concentration following bicarbonate loading. The impaired bicarbonate reabsorption results in salt wasting and secondary hyperaldosteronism. Hypokalemia, which can be severe, usually develops as a result of the hyperaldosteronism and bicarbonaturia.[7,14] Proximal RTA usually presents as an acquired disorder, secondary to carbonic anhydrase inhibitor therapy, or as a result of a variety of diseases (eg, amyloidosis, multiple myeloma, nephrotic syndrome) or exposure to toxins (eg, lead, cadmium, mercury, expired tetracyclines).

The hyperkalemic distal (type IV) RTAs are a heterogeneous group of disorders characterized by hypoaldosteronism or generalized distal tubule defects. The most common form of type IV RTA is hyporeninemic hypoaldosteronism. This syndrome is most commonly associated with diabetic nephropathy, but can also be seen in a variety of other disorders, including chronic interstitial nephritis, sickle-cell disease, human immunodeficiency virus (HIV) nephropathy, and obstructive uropathy.[7,12] The clinical presentation of this syndrome is often exacerbated by medications that can interfere with the renin–angiotensin–aldosterone system, such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, renin inhibitors, and nonsteroidal anti-inflammatory drugs (NSAIDs). Patients with this form of RTA are able to maximally acidify their urine (urine pH less than 5.5). The primary defect in acid excretion is impaired ammoniagenesis caused by decreased kidney function. Treatment to control the hyperkalemia is usually sufficient to reverse the metabolic acidosis, and mineralocorticoid replacement is frequently unnecessary.

Hyperkalemic distal (type IV) RTA resulting from generalized distal tubule defects is less common than hyporeninemic hypoaldosteronism but is more common than classic distal (type I) RTA. Patients with this defect have impaired tubular potassium secretion in addition to impaired urinary acidification (urine pH more than 5.5, despite acidemia or acid loading). Urinary obstruction is the most frequent cause of this disorder, but it can also be associated with sickle-cell nephropathy, systemic lupus erythematosus, HIV nephropathy, analgesic misuse nephropathy, amyloidosis, kidney transplant rejection, and chronic cyclosporine nephrotoxicity.

Elevated Anion Gap Metabolic Acidosis

Metabolic acidosis with an increased SAG commonly results from increased endogenous organic acid production.[15] In lactic acidosis, lactic acid accumulates as a by-product of anaerobic metabolism.[16] Accumulation of the ketoacids β-hydroxybutyric acid and acetoacetic acid defines the ketoacidosis of uncontrolled diabetes mellitus (see Chapter 94, Diabetes Mellitus), alcohol intoxication (see Chapter 55, Portal Hypertension and Cirrhosis, and Chapter 86, Substance Use Disorders II), and starvation (see Chapter e83, Eating Disorders) (Table 71-5).[17] Toxic ingestions of methanol and ethylene glycol are also associated with high anion gap metabolic acidosis and can be differentiated from other causes of SAG by the presence of an elevated osmolar gap. An elevated osmolar gap is considered when the measured serum osmolality is more than 10 mOsm/kg (mmol/kg) greater than the calculated serum osmolality.[7] In advanced kidney disease, accumulation of phosphate, sulfate, and organic anions is responsible for the increased SAG, which is usually less than 24 mEq/L (mmol/L).[2] The severe metabolic acidosis seen in myoglobinuric acute kidney injury (AKI) as a result of rhabdomyolysis may be caused by the metabolism of large amounts of sulfur-containing amino acids released from myoglobin. The mechanisms responsible for the development of acidosis in these settings are diverse.

The presence of mild elevations in the SAG cannot be automatically attributed to the presence of a high SAG metabolic acidosis. Elevations in the SAG are commonly seen in hospitalized patients, especially those who are critically ill.[18] A variety of factors can contribute to this nonspecific elevation in the SAG, including the presence of alkalemia, which increases the anionic charge of albumin and other plasma proteins. The usefulness of the SAG as a marker of acid–base status is dependent on proper interpretation of a patient's clinical status. Despite these limitations, when the SAG is greater than

or equal to 20 mEq/L (mmol/L), it is generally considered a high anion gap or a significant organic acidosis.

Lactic Acidosis

Serum lactate levels are often elevated in acutely ill patients and can be used as a marker for severity of illness and response to therapy.[19] Serum lactate levels are considered normal in healthy subjects at approximately 1 mmol/L (mEq/L).[16] Hyperlactatemia is defined as a serum lactate greater than 2 mmol/L with lactic acidosis considered when serum lactate levels are greater than 4 mmol/L with concomitant acidosis.[19] Lactic acid is the end product of anaerobic metabolism of glucose (glycolysis).[13] In normal individuals, lactic acid derived from pyruvate enters the circulation in small amounts and is promptly removed by the liver. In the liver, and to a lesser extent in the kidney, lactic acid is reoxidized to pyruvic acid, which is then metabolized to CO_2 and H_2O.

Classically, lactic acidosis has been differentiated into disorders associated with tissue hypoxia (type A lactic acidosis) and disorders associated with deranged oxidative metabolism (type B lactic acidosis), although the distinction between them is blurred (Table 71-7).[16,19] Metabolic disturbances can result in increased tissue pyruvate production or impaired utilization, with proportional increases in lactate concentrations. Increased lactate production is more commonly associated with alterations in tissue redox state, resulting in preferential conversion of pyruvate to lactate. During anaerobic metabolism, reduced nicotinamide adenine dinucleotide accumulates, driving the conversion of pyruvate to lactate and increasing the lactate-to-pyruvate ratio. States of enhanced metabolic activity (eg, grand mal seizures, strenuous exercise, hyperthermia), decreased tissue oxygen delivery (eg, severe anemia, hypoxia, circulatory shock, carbon monoxide poisoning), or impaired oxygen utilization (eg, cyanide toxicity) are all associated with lactic acidosis. Impaired hepatic clearance of lactate, as seen in hypoperfusion states, liver failure, and alcohol intoxication, can also result in lactic acidosis.

TABLE 71-7

Causes of Lactic Acidosis

Type A (hypoxia)	Type B (metabolic derangement)
Carbon monoxide poisoning	D-lactic acidosis
Increased oxygen demands	Diabetes mellitus
Hyperthermia	Inborn errors of metabolism and mitochondrial myopathies
Seizures	Medications/Toxins
Shivering	Alcohols
Vigorous exercise	Ethanol
	Ethylene glycol
Regional tissue ischemia	Methanol
Severe anemia	Propofol (prolonged, high dose infusions)
Severe hypoxemia	Propylene glycol (IV formulations of lorazepam, pentobarbital, phenytoin, trimethoprim/sulfamethoxazole)
Shock	Beta-adrenergic agonists (albuterol, epinephrine)
Cardiogenic	Cyanide (sodium nitroprusside)
Hemorrhagic	Entecavir
Hypovolemic	Isoniazid
Septic	Iron
	Linezolid
	Metformin
	NRTIs (abacavir, lamivudine, stavudine, tenofovir)
	Ombitasvir, paritaprevir, ritonavir, dasabuvir (Viekira Pak®)
	Phentermine-topiramate (Qsymia®)
	Salicylates
	Telbivudine
	Theophylline
	Systemic disease
	Malignancy
	Liver failure
	Thiamine deficiency

Cardiovascular and septic shock, with resultant tissue hypoperfusion, are the most common causes of lactic acidosis.[16] Poor tissue perfusion and hypoxia influence enzymatic pyruvate and lactate metabolism to stimulate anaerobic glycolysis and to decrease lactate utilization. This leads to hyperlactatemia and lactic acidosis. The mortality rate of this type of lactic acidosis can be 50% or greater and correlates with the degree of hyperlactatemia.[20]

Lactic acidosis associated with liver disease, toxins, and congenital enzyme deficiency can be caused by deranged oxidative metabolism or impaired lactate clearance.[19] The exact role of diabetes mellitus in the induction of lactic acidosis is not clear. It may involve a decrease in pyruvate dehydrogenase activity, the enzyme responsible for pyruvate metabolism. Lactic acidosis in neoplastic disease is uncommon and reported mostly in patients with myeloproliferative disorders. Leukocytes and neoplastic cells in general have high rates of glycolysis. In the case of a large tumor or tightly packed bone marrow, oxygenation can be decreased, favoring the accumulation of lactate. Lactic acidosis has been reported in patients with massive liver tumors, and it has been postulated that the liver uptake of lactate is decreased in these patients. Lactic acidosis associated with seizures is usually transient and occurs because of excessive muscle activity.[16,19]

A number of medications have been associated with the development of lactic acidosis. Metformin (0.03 cases per 1,000 person-years) remains the

most common medication associated with lactic acidosis.[21] The primary suspected mechanism for metformin-induced lactic acidosis is inhibition of liver gluconeogenesis as the result of its inhibitory effects on pyruvate carboxylase, which is necessary for the conversion of pyruvate to glucose. Other possible pathways for metformin-associated lactic acidosis include a decrease in both hepatic intracellular pH and cardiac output, an increase in lactate production in the gut, and increased renal loss of bicarbonate. Risk factors for metformin-induced lactic acidosis include impaired kidney function, liver disease, dehydration, advanced age, excessive alcohol use, concomitant carbonic anhydrase inhibitor use, and supratherapeutic dosing.[19,22] Metformin should be discontinued during periods of tissue hypoxia (eg, myocardial infarction, sepsis), at the time of or before iodinated contrast imaging procedures in patients with eGFR 30 to 60 mL/min/1.73 m^2, withheld on the day of surgery and during periods of restricted food intake.[23,24] Metformin should only be reinstituted when the patient's kidney function is stable, and the patient is tolerating adequate oral diet.

The older nucleoside-analog reverse transcriptase inhibitors (NRTIs), particularly stavudine, have been associated with lactic acidosis (3.9 cases per 1,000 person-years) in patients with hepatic steatosis.[25] The proposed mechanism of NRTI-induced lactic acidosis is the inhibition of the enzyme DNA polymerase gamma that is responsible for mitochondrial DNA synthesis.[26] Lactic acidosis has been rarely reported with tenofovir, lamivudine, abacavir, and entecavir.

Linezolid impairs mitochondrial function and has been rarely reported to cause lactic acidosis, usually after prolonged (more than or equal to 4 weeks) therapy.[27] The weight loss combination medication phentermine-topiramate (Qsymia®) has been reported to cause lactic acidosis.[28] Use of the Viekira Pak® (ombitasvir, paritaprevir, ritonavir, dasabuvir) may cause lactic acidosis in patients without severe liver dysfunction when used to treat hepatitis C.[29]

Propylene glycol is commonly used as a solubilizing agent in IV medications (eg, lorazepam, pentobarbital, phenytoin, trimethoprim/sulfamethoxazole) and is predominantly metabolized to lactic acid via the hepatic enzyme alcohol dehydrogenase.[30-32] The administration of large doses of propylene glycol, particularly to patients with impaired kidney or liver function, can lead to a lactic acidosis with an osmolar gap. Thus, serial measurement of the osmolar gap can be used to detect propylene glycol accumulation.[30,31]

The association between propofol and lactic acidosis was initially described in children.[33] This association is now recognized in adults and has come to be known as the propofol-related infusion syndrome. In addition to lactic acidosis, cardiac failure, rhabdomyolysis, and AKI have been observed primarily because of uncoupling of oxidative phosphorylation and impaired oxidation of free fatty acids. To minimize the risk of propofol infusion syndrome, it is recommended not to exceed 4 mg/kg/hour for more than 48 hours unless the perceived benefit exceeds the risk.[33]

Clinical Presentation

Chronic metabolic acidosis is usually not associated with severe acidemia and is relatively asymptomatic. The major manifestations are bone demineralization with growth failure and short stature in children and both osteomalacia and osteopenia in adults.[6,28] Chronic metabolic acidosis is also associated with nonspecific symptoms including anorexia, nausea, weight loss, and muscle weakness.

Severe metabolic acidosis is usually associated with acute processes. The manifestations of severe acidemia (pH less than 7.20) involve the cardiovascular, respiratory, and central nervous system (CNS). Hyperventilation is often the first sign of metabolic acidosis. At a pH of 7.2, pulmonary ventilation increases approximately fourfold, and an eightfold increase has been noted at a pH of 7.[34,35] Respiratory compensation can occur as Kussmaul respirations—the deep, rapid respirations seen commonly in patients with diabetic ketoacidosis. In extremely severe acidosis (pH less than 6.8), CNS function is disrupted to such a degree that the respiratory center is depressed.

CNS depression correlates more closely with spinal fluid pH than with blood pH. For this reason, neurologic symptoms tend to occur more frequently and to a greater degree in patients with respiratory acidosis because the CO_2 accumulated in the respiratory form readily crosses the blood–brain barrier to cause acidosis in the CNS.[4] Because of the slow penetration of administered bicarbonate into the CNS, the CNS pH fails to normalize as rapidly as blood pH. Therefore, patients continue to hyperventilate because of sustained CNS acidity, and severe respiratory alkalosis can occur. Sustained lowering of the $PaCO_2$ within 12 to 36 hours is to be anticipated during the correction of any metabolic acidosis.[4]

Systemic acidosis can cause peripheral arteriolar dilatation, characterized by flushing, a rapid HR, and wide pulse pressure. Initially, cardiac output can

be increased, but as acidosis becomes more severe, myocardial contractility becomes impaired, and cardiac output decreases. The effects of vagal stimulation are also enhanced at reduced pH levels, likely a consequence of inhibition of acetylcholinesterase. This increases the danger of vagally mediated bradycardia and heart block during acidosis.[36]

GI symptoms of metabolic acidosis include loss of appetite, nausea, and vomiting. Severe acidosis (pH less than 7.1) interferes with carbohydrate metabolism and insulin utilization, and results in hyperglycemia. Metabolic acidosis alters potassium homeostasis and contributes to the development of hyperkalemia. The magnitude of the effect on serum potassium depends on the type of acidosis: Acidosis caused by mineral acids (eg, hydrochloric acid) is associated with a greater change in potassium levels than acidosis caused by organic acids (eg, lactic acidosis), in which the increase in potassium attributable to the acidosis is minimal.[37]

Compensation

The patient's primary means to compensate for metabolic acidosis is to increase carbon dioxide excretion by increasing the RR. This results in a decrease in $PaCO_2$. This ventilatory compensation results from stimulation of the respiratory center by changes in cerebral bicarbonate concentration and pH.[4,38] For every 1 mEq/L (mmol/L) decrease in bicarbonate concentration below the average of 24, the $PaCO_2$ decreases by approximately 1 to 1.5 mm Hg (0.13-0.20 kPa) from the normal value of 40 mm Hg (5.3 kPa). General guidelines for the assessment and interpretation of acid–base disorders based on observed compensatory responses are presented in Table 71-8.[7]

TABLE 71-8

Guidelines for Interpretation of Acid–Base Disorders Based on Compensatory Responses

Acidosis	**Compensation**
Metabolic	$PaCO_2$ (in mm Hg) should decrease by 1.25 times the fall in plasma [HCO_3^-] (in mEq/L or mmol/L)
Acute respiratory	Plasma [HCO_3^-] should increase by 0.1 times the increase in $PaCO_2$ (in mm Hg)
Chronic respiratory	Plasma [HCO_3^-] should increase by 0.4 times the increase in $PaCO_2$ (in mm Hg)
Alkalosis	**Compensation**
Metabolic	$PaCO_2$ (in mm Hg) should increase by 0.6 times the rise in plasma [HCO_3^-] (in mEq/L or mmol/L)
Acute respiratory	Plasma [HCO_3^-] should decrease by 0.2 times the decrease in $PaCO_2$ (in mm Hg), but usually not to <18 mEq/L (mmol/L)
Chronic respiratory	Plasma [HCO_3^-] should fall by 0.4 times the decrease in $PaCO_2$ (in mm Hg), but usually not to <14 mEq/L (mmol/L)

HCO_3^-, bicarbonate; $PaCO_2$, partial pressure of carbon dioxide from arterial blood; multiply values expressed in kPa by 7.519 to convert to mm Hg.

Data from Reference 7.

The anticipated $PaCO_2$ associated with a given bicarbonate concentration for patients with uncomplicated metabolic acidosis can also be calculated using the Winters' formula[7]:

$\mathrm{PaCO_2} = (1.5 \times [\mathrm{HCO_3^-}] + 8) \pm 2 \text{ for } \mathrm{PaCO_2} \text{ in mm Hg}$
$(\mathrm{PaCO_2} = (0.2 \times [\mathrm{HCO_3^-}] + 1.1) \pm 0.3 \text{ for } \mathrm{PaCO_2} \text{ in kPa})$
PaCO2 = (1.5 × [HCO3−] + 8) ± 2 for PaCO2 in mm Hg(PaCO2 = (0.2 × [HCO3−] + 1.1) ± 0.3 for PaCO2 in kPa)

For example, 95% of patients with a plasma bicarbonate of 16 mEq/L (mmol/L) should have an arterial PCO_2 of 30 to 34 mm Hg (4.0-4.5 kPa). An

observed arterial PCO_2 within this range is consistent with physiologic respiratory compensation for a metabolic acidosis and suggests that there is no respiratory disturbance. In contrast, if the PCO_2 is less than 30 mm Hg (4.0 kPa), a superimposed respiratory alkalosis can be present, whereas if the PCO_2 is greater than 34 mm Hg (4.5 kPa), a superimposed respiratory acidosis is likely present.

CLINICAL PRESENTATION: Metabolic Acidosis

General

- The patient usually is relatively asymptomatic if the acidosis is acute and mild. In those with severe acidemia (pH less than 7.20), the cardiovascular, respiratory, and CNS systems can be affected.

Symptoms

- The patient may complain of loss of appetite, nausea, and vomiting.

Signs

- Cardiac: Flushing, a rapid HR, wide pulse pressure, and an increase in cardiac output can be seen initially. This can be followed by a reduction in cardiac output, BP, and liver and kidney blood flow.
- Cerebral: Obtundation or coma.
- Metabolic: Insulin resistance; increased protein degradation; increased metabolic demands.
- GI: Nausea, vomiting, loss of appetite.
- Respiratory: Dyspnea, hyperventilation with deep, rapid respirations is seen in those with severe acidosis.
- Chronic acidemia causes bone demineralization with the development of growth failure and short stature in children and osteomalacia and osteopenia in adults.

Laboratory Tests

- Serum CO_2 is low. Hyperglycemia and hyperkalemia are common. Patients with a pH of less than 7.2 are deemed to have a severe acidosis.

TREATMENT OF METABOLIC ACIDOSIS

7 Asymptomatic patients with mild to moderate degrees of acidemia (plasma bicarbonate of 12-20 mEq/L [mmol/L]; pH 7.2-7.4) do not require emergent therapy. They can usually be managed with gradual correction of the acidemia, over a period of days to weeks, using oral sodium bicarbonate or other alkali preparations (Table 71-9). In all forms of chronic metabolic acidosis, primary therapy should be directed at treating the underlying disease state. GI pathology should be treated to reduce ongoing bicarbonate losses, and factors that exacerbate RTA should be treated. If acidemia persists, alkali therapy should be instituted with the goal of normalization of blood pH. The loading dose (LD) of alkali to initially correct the acidemia can be calculated as follows:

$$\text{LD (mEq or mmol/L)} = (V_D \times BW) \times (\text{desired}[HCO_3^-] - \text{current } [HCO_3^-])$$LD (mEq or mmol/L) = (VD × BW) × (desired[HCO3−] − current [HCO3−])

TABLE 71-9

Therapeutic Alternatives for Oral Alkali Replacement

Product	Milliequivalents of Alkali	Dosage Form(s)
Sodium citrate/citric acid	1 mL contains 1 mEq sodium and is equivalent to 1 mEq bicarbonate	Solution, sodium citrate 500 mg, citric acid 334 mg per 5 mL
Sodium bicarbonate	3.9 mEq bicarbonate per tablet (325 mg) 7.8 mEq bicarbonate per tablet (650 mg) 60 mEq bicarbonate per teaspoon (5 g per teaspoon)	Tablet, 325 mg Tablet, 650 mg Baking soda powder
Potassium citrate	Each tablet contains 5, 10, or 15 mEq potassium and delivers approximately 5, 10, or 15 mEq bicarbonate	Tablet Extended Release, 5 mEq Tablet Extended Release, 10 mEq Tablet Extended Release, 15 mEq
Potassium bicarbonate/potassium citrate	Each tablet contains 10, 20, or 25 mEq potassium and delivers approximately 10, 20, or 25 mEq bicarbonate	Tablet Effervescent, 10 mEq Tablet Effervescent, 20 mEq Tablet Effervescent, 25 mEq
Potassium citrate/citric acid	Each packet contains 30 mEq potassium and delivers approximately 30 mEq bicarbonate Each mL contains 2 mEq potassium and delivers approximately 2 mEq bicarbonate	Powder for solution, potassium citrate monohydrate 3,300 mg, citric acid monohydrate 1,002 mg per packet Solution, potassium citrate monohydrate 1,100 mg, citric acid monohydrate 334 mg per 5 mL
Sodium citrate/potassium citrate/citric acid	1 mL contains 1 mEq potassium and 1 mEq sodium ion, and delivers approximately 2 mEq bicarbonate	Solution, citric acid 334 mg, sodium citrate 500 mg, and potassium citrate 550 mg per 5 mL

where V_D is the volume of distribution of bicarbonate (0.5 L/kg) and BW is body weight in kg.[8,39]

Thus, for a 60-kg patient with a serum bicarbonate of 15 mEq/L (mmol/L), the LD is calculated:

$$\begin{aligned} \text{LD(mEq)} &= (0.5\ \text{L/kg} \times 60\ \text{kg}) \times (24\ \text{mEq/L} - 15\ \text{mEqL}) \\ \text{LD} &= 30\ \text{L} \times 9\ \text{mEq/L} \\ \text{LD} &= 270\ \text{mEq} \end{aligned}$$ LD(mEq)=(0.5 L/kg × 60 kg) × (24 mEq/L - 15 mEqL)LD=30 L × 9 mEq/LLD=270 mEq

The calculated LD of alkali should be administered over several days to avoid volume overload from the accompanying sodium load. For this scenario, a regimen of 60 to 70 mEq (mmol) three times a day for 3 to 5 days should result in an increase in HCO_3^- levels toward normal. In addition to the calculated LD, supplemental alkali must also be provided to replace ongoing losses, which can be approximated to be 2 mEq/kg (mmol/kg) per day or 40 mEq (mmol) three times a day. In patients with associated volume depletion, bicarbonate replacement can be provided simultaneously with volume resuscitation by substituting bicarbonate for chloride in IV crystalloid solutions.

In patients with chronic metabolic acidosis because of GI bicarbonate losses, maintenance therapy should provide enough alkali to replace ongoing bicarbonate losses. The magnitude of this replacement is variable and can be substantial (more than 10 mEq/kg [mmol/kg] per day). In addition, associated losses of other electrolytes, such as potassium and magnesium, may need to be replaced (see Chapter 70, Potassium and Magnesium Homeostasis).

Proximal (type II) RTA is a bicarbonate-wasting disorder that requires the administration of large maintenance doses of alkali (10-15 mEq/kg [mmol/kg] per day). As alkali replacement raises the serum bicarbonate concentration toward normal, the proximal tubule's capacity to reabsorb bicarbonate is overwhelmed, and renal bicarbonate wasting increases. In children, aggressive therapy of proximal RTA is necessary to avoid growth retardation and

osteopenia. Because this is generally a mild, nonprogressive acidosis in adults, the benefit of alkali therapy is frequently outweighed by the risks of increased potassium wasting. In patients with classic distal (type I) RTA, maintenance therapy usually requires only enough alkali to buffer the amount of acid generated from dietary intake and metabolism. This usually approximates 1 to 3 mEq/kg/day (mmol/kg/day).

8 After initial potassium deficits are replaced, ongoing potassium supplementation may not be required, as renal potassium losses decrease following initiation of appropriate alkali therapy. The use of potassium alkali salts can, however, be desirable in patients with associated nephrolithiasis, because sodium salts can increase urinary calcium excretion.

The metabolic acidosis associated with hyperkalemic distal (type IV) RTA with hyporeninemic-hypoaldosteronism that is often seen in patients with diabetes mellitus can be corrected by the treatment of hyperkalemia alone (see Chapter 70). The use of supplemental alkali (1-2 mEq/kg [mmol/kg] per day) to increase sodium intake and stimulate distal tubular potassium secretion can be beneficial. Some patients may require the administration of pharmacologic amounts of fludrocortisone.[8] Type IV RTA resulting from a generalized distal tubular disorder often responds to low doses of alkali (1.5-2.0 mEq/kg [mmol/kg] per day).[12,14] Corrections of the acidosis along with modest dietary potassium restriction (to 1 mEq/kg [mmol/kg] per day) will often result in the maintenance of serum potassium concentrations of 5 mEq/L (mmol/L) or less.

Veverimer

Veverimer is an investigational medication designed to be used in the treatment of metabolic acidosis of chronic kidney disease (CKD). It is a non-absorbable polymer designed to bind hydrogen chloride in the GI tract with subsequent removal in the feces.[40] Every hydrogen ion bound results in HCO_3^- entering the blood, thus producing an increase in serum HCO_3^- without administering sodium, a mechanism thought to be potentially useful in sodium retentive patients.[41] No changes in fluid or serum concentrations of sodium, potassium, calcium, magnesium, and phosphate have been observed in patients treated with veverimer.[41,42] Adverse medication reactions are primarily GI including nontreatment limiting diarrhea (most common), flatulence, nausea, and constipation.[42] Administration is orally as a suspension in water. Since veverimer does not slow CKD progression in patients with metabolic acidosis and CKD, the FDA denied approval in August 2020.

Acute Severe Metabolic Acidosis

9 The management of life-threatening acute metabolic acidosis (plasma bicarbonate of 8 mEq/L [mmol/L] and pH less than 7.20) is dependent on the underlying cause and the patient's cardiovascular status. In some cases, patients will require emergent hemodialysis therapy (see Chapter 64). Patients with hyperchloremic acidosis (eg, diarrhea-induced) are unable to regenerate bicarbonate, and the generation of new bicarbonate by the kidneys can require several days before one can observe a meaningful change in their status. Thus, IV alkali therapy is often required for these patients.

Although conventional wisdom recommends the use of alkali replacement in patients with severe acidemia, studies have not demonstrated that its administration improves patient outcomes.[16,39,43] Alkali therapies may either improve or worsen clinically relevant endpoints such as $[H^+]$, $PaCO_2$, lactate concentrations, and cardiac output. The specific patient populations most likely to benefit or be harmed from alkalinizing therapy are presented in Table 71-10.

TABLE 71-10

Patient Populations Likely to Benefit or Suffer from Alkalinizing Therapy

Patients with Potential for Benefit	Patients with Potential for Harm
Distal (type I) renal tubular acidosis	Hypernatremia
Severe hyperchloremic metabolic acidosis secondary to diarrhea or surgical diversion	Hypervolemia
Specific poisonings and intoxications (eg, salicylate overdose with metabolic acidosis)	AKI
	Chronic heart failure
	Pulmonary disease resulting in decreased ventilation
	Acute lung injury where a lung protective ventilation strategy is used
	Diabetic ketoacidosis

There are several therapeutic alternatives available for the acute correction of severe metabolic acidosis. Sodium acetate, sodium citrate, and sodium lactate are unreliable sources of alkali because their alkalinizing effect is dependent on their oxidative conversion to bicarbonate by the liver. This process is often impaired in critically ill patients, especially those with hepatic disease or circulatory failure. Although sodium bicarbonate is the most widely used IV alkalotic agent, it is frequently ineffective and can actually be deleterious, especially in patients with lactic acidosis.[16,39,44] Among the two remaining alternatives, dichloroacetate (DCA) is investigational and not available in most clinical settings. Tromethamine, or THAM, is a carbon dioxide–consuming, commercially available solution that buffers respiratory as well as metabolic acids but was discontinued by its sole US manufacturer in 2016.

Sodium Bicarbonate

While sodium bicarbonate administration provides fluid and electrolyte replacement and increases arterial pH, it does not improve cardiac function, organ perfusion, or intracellular pH.[17,39,44,45] In patients with AKI, sodium bicarbonate may reduce mortality at 28 days.[43] However, additional research is required to further evaluate the role of sodium bicarbonate in patients with severe metabolic acidemia and AKI given the potential role of renal replacement therapy in this setting. In addition, sodium bicarbonate administration can have paradoxical adverse effects on intracellular pH. When bicarbonate is given by IV infusion, the carbon dioxide generated diffuses more readily than bicarbonate across cell membranes and into cerebrospinal fluid. Therefore, the intracellular pH can be decreased by administration of bicarbonate.[8,43]

Excessive sodium bicarbonate administration can result in (a) a shift of the oxyhemoglobin saturation curve to the left, thereby impairing oxygen release from hemoglobin to tissues; (b) sodium and water overload, with subsequent pulmonary congestion and hypernatremia; (c) paradoxical tissue acidosis as a result of the production of CO_2 that freely diffuses into myocardial and cerebral cells; and (d) decreased ionized calcium with a resultant decrease in myocardial contractility.[8,39] If there is an endogenous source of bicarbonate, such as can occur in the case of ketoacidosis or lactic acidosis, a bicarbonate “overshoot” can develop because the ketoacids (acetoacetic acid and β-hydroxybutyric acid) or lactic acid are converted in the liver to bicarbonate once the underlying cause of acidosis is corrected. Alkalosis can also result if too much sodium bicarbonate is administered too quickly.[8,39]

If IV sodium bicarbonate is used, one must be mindful that the goals are to increase, not normalize, pH (to approximately 7.2) and plasma bicarbonate

(to 8-10 mEq/L [mmol/L]). There is no calculative method that will assure attainment of these goals with a given dose of sodium bicarbonate because of the multiplicity of competing processes that can affect acid–base status (eg, vomiting, potential increases in endogenous acid production, and kidney disease) and the marked variability in the volume of distribution of bicarbonate (50% of BW in patients with mild acidosis to approximately 100% in those with severe acidosis).[8,46] The dose of sodium bicarbonate may be calculated using a distribution volume of 50% of BW for all patients to avoid overtreatment.[8] The total dose calculated as described previously in the RTA section should be administered as an infusion over one-half to several hours. Follow-up monitoring of ABGs, beginning no sooner than 30 minutes after the end of the infusion, should be used to guide further therapeutic decisions.[46]

Bicarbonate therapy is generally not necessary for patients with cardiac arrest, even if the initial arrest was unmonitored. The American Heart Association Advanced Cardiac Life Support (ACLS) guidelines state the routine use of sodium bicarbonate is not recommended for patients in cardiac arrest, but may be useful in patients with life-threatening hyperkalemia.[47] The initial dose of sodium bicarbonate in this situation is (1 mEq/kg [mmol/kg]) administered by rapid, direct IV injection.[47] Subsequent doses of sodium bicarbonate should be based on measurements of arterial blood pH and $PaCO_2$ given the propensity for it to cause alkalemia.[46]

Tromethamine (THAM)

THAM, no longer available in the United States, is a highly alkaline, sodium-free organic amine that acts as a proton acceptor to prevent or correct acidosis.[8,48] THAM combines with hydrogen ions from carbonic acid to form bicarbonate and a cationic buffer, and also acts as an osmotic diuretic to increase urine flow, urine pH, and the excretion of fixed acids, CO_2, and electrolytes.[7,48] It should be administered via a central line and used with extreme caution in patients with severe liver or kidney failure.

Dichloroacetate (DCA)

DCA, another investigational agent, facilitates aerobic lactate metabolism by stimulating the activity of lactate dehydrogenase, thus reversing hyperlactatemia and elevating blood pH.[49-51] DCA does not improve hemodynamic parameters or clinical outcomes compared to conventional management.[49-51] DCA can cause mild drowsiness and peripheral neuropathy that is reversible upon discontinuation.[51] The future role of DCA in the management of metabolic acidosis, particularly lactic acidosis, remains to be clarified.[16]

Metabolic Alkalosis

Pathophysiology

Metabolic alkalosis is a simple acid–base disorder that presents as alkalemia (increased arterial pH) with an increase in plasma bicarbonate. Metabolic alkalosis is predominantly maintained because of an abnormality in kidney function and does not occur or cannot be corrected in a matter of hours. Normally, the kidneys are capable of excreting all of the excess bicarbonate presented to them, even during periods of increased bicarbonate loads.[2] As the serum bicarbonate concentration increases, the filtered bicarbonate load exceeds the maximal rate for bicarbonate reabsorption, and the excess bicarbonate is excreted in the urine. Thus, evaluation of patients with metabolic alkalosis must consider two separate issues: (a) the initial process that generates the metabolic alkalosis; and (b) alterations in kidney function that maintain the alkalemia state.[52]

10 The generation of metabolic alkalosis can result from reduced renal bicarbonate excretion, excessive losses of hydrogen ions from the kidneys or stomach, or from a gain secondary to the ingestion or administration of bicarbonate-rich fluids.[52,53] In general, these mechanisms can be divided into volume-mediated processes (sodium chloride–responsive), volume-independent processes (sodium chloride–resistant), or not classified by either (Table 71-11).[7,53] Patients with a sodium chloride–responsive metabolic alkalosis will have a urinary chloride concentration less than 10 mEq/L (mmol/L) and patients with a sodium chloride–resistant alkalosis will have a urinary chloride concentration greater than 20 mEq/L (mmol/L).[7]

TABLE 71-11

Causes of Metabolic Alkalosis

Sodium chloride–responsive (urinary chloride concentration <10 mEq/L [mmol/L])
GI disorders
Vomiting
Gastric drainage
Villous adenoma of the colon
Chloride diarrhea
Diuretic therapy (distant)
Correction of chronic hypercapnia
Cystic fibrosis
Excessive bicarbonate therapy of an organic acidosis
Mild/moderate potassium deficiency
Sodium chloride–resistant (urinary chloride concentration >20 mEq/L [mmol/L])
Excess mineralocorticoid activity
Hyperaldosteronism
Cushing syndrome
Bartter syndrome (sodium transport defect in loop of Henle)
Gitelman syndrome (sodium transport defect in collecting duct)
Excessive black licorice intake
Profound potassium depletion
Magnesium deficiency
Liddle syndrome (enhanced sodium reabsorption in collecting duct)
Diuretic therapy (recent)
Estrogen therapy
Unclassified
Alkali administration
Milk-alkali syndrome
Massive blood or plasma protein fraction transfusion
Non-parathyroid hypercalcemia
Carbohydrate refeeding after starvation
Large doses of penicillin

Sodium Chloride Responsive

11 Gastric juice, rich in chloride and hydrogen ions, is secreted at a rate of less than 50 mL/hr in the basal state, but can increase up to fivefold with stimulation. In the gastric parietal cells, the hydrogen ion and bicarbonate are generated from CO_2 and water.[1] The hydrogen ion is secreted into gastric fluid, and the bicarbonate is retained in the ECF. Normally, an amount of bicarbonate equal to the bicarbonate generated in the stomach is eliminated in the alkaline pancreatic and small-bowel secretions, maintaining hydrogen ion balance. With vomiting and nasogastric suctioning, the hydrogen ion is lost externally and metabolic alkalosis results. Diarrhea, as seen with secretory villous adenomas and other secretory diarrheas, often results in excessive GI losses of chloride-rich, bicarbonate-poor fluid, and thus leads to the generation of metabolic alkalosis.

12 Diuretic agents acting on the thick ascending limb of the loop of Henle (eg, furosemide, bumetanide, and torsemide) and distal convoluted tubule (eg, thiazides) have most commonly been associated with the generation of metabolic alkalosis.[1,54] These agents promote the excretion of sodium and

potassium almost exclusively in association with chloride, without a proportionate increase in bicarbonate excretion. Collecting duct hydrogen ion secretion is stimulated directly by the increased luminal flow rate and sodium delivery, and indirectly by intravascular volume contraction, which results in secondary hyperaldosteronism. Renal ammoniagenesis can also be stimulated by concomitant hypokalemia, further augmenting net acid excretion.

Sodium Chloride Resistant

Mineralocorticoid excess plays a significant role in the maintenance of metabolic alkalosis given that it stimulates collecting duct hydrogen ion secretion. Elevated mineralocorticoid levels directly stimulate collecting duct hydrogen ion secretion, indirectly increase ammoniagenesis by causing hypokalemia, and is associated with both acute and chronic causes including profound potassium deficiency, magnesium deficiency, and estrogen therapy.[1,7,54]

Unclassified

Metabolic alkalosis can also be generated by the gain of exogenous alkali. This is a result of bicarbonate administration or from the infusion of organic anions that are metabolized to bicarbonate, such as acetate, lactate, and citrate. The milk-alkali syndrome was historically a common cause of metabolic alkalosis in patients with peptic ulcer disease secondary to the ingestion of large quantities of milk products and antacids. Administration of high doses of penicillins (eg, ticarcillin) can produce metabolic alkalosis because they act as non-reabsorbable anions, which enhances the secretion of potassium and hydrogen ions and results in hypokalemia and metabolic alkalosis.[55]

Clinical Presentation

There are no unique signs or symptoms associated with mild-to-moderate metabolic alkalosis, but patients may complain of symptoms related to the underlying cause of the disorder (eg, muscle weakness with hypokalemia or postural dizziness with volume depletion).[52,56] They may have a history of vomiting, gastric drainage, or diuretic use, all of which contribute to the development of metabolic alkalosis. Severe alkalemia (blood pH greater than 7.55) has been associated with cardiac arrhythmias, particularly in patients with heart disease, hyperventilation, and hypoxemia.[56] Neuromuscular irritability can be present, with signs of tetany or hyperactive reflexes, possibly caused by the decreased ionized calcium concentration that occurs secondary to the increase in pH. This decrease in ionized calcium may be caused by a conformational change in the albumin molecules to which the calcium is bound, resulting in increased binding, or by decreased competition from hydrogen ions for binding sites on the albumin molecule. Mental confusion, muscle cramping, and paresthesia can also occur.[52] Lastly, patients will be more difficult to liberate from mechanical ventilation.

Compensation

The respiratory response to metabolic alkalosis is hypoventilation, which results in an increased $PaCO_2$. Respiratory compensation is initiated within hours when the central and peripheral chemoreceptors sense an increase in pH. The $PaCO_2$ increases 6 to 7 mm Hg (0.8-0.9 kPa) for each 10 mEq/L (mmol/L) increase in bicarbonate, up to a $PaCO_2$ of approximately 50 to 60 mm Hg (6.7-8.0 kPa) (see Table 71-8) before hypoxia sensors react to prevent further hypoventilation.[7] If the $PaCO_2$ is normal or less than normal, one should consider the presence of a superimposed respiratory alkalosis, which can be secondary to fever, gram-negative sepsis, or pain.

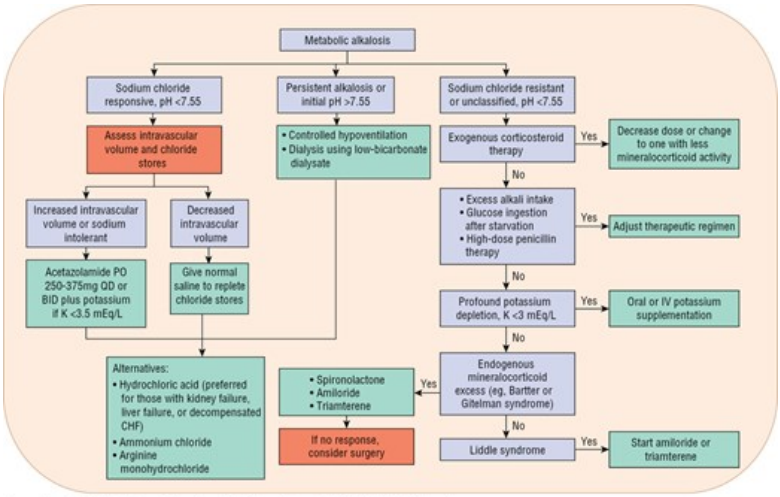
TREATMENT OF METABOLIC ALKALOSIS

Treatment of metabolic alkalosis should be aimed at correcting the factor(s) responsible for the maintenance of the alkalosis.[56] For example, vomiting should be treated with antiemetics; gastric losses of hydrogen ions during nasogastric suction can be modulated by giving histamine blockers such as famotidine or proton pump inhibitors such as omeprazole, and reducing or discontinuing diuretic therapy.[56,57] Metabolic alkalosis will persist until the renal mechanism responsible for maintaining the disorder is corrected, despite the fact that the original cause of the elevated plasma bicarbonate may have resolved. For example, hypovolemia should be treated with sodium chloride to allow excretion of bicarbonate by the kidney. However, patients with severely compromised cardiovascular function may not be able to tolerate this therapeutic approach. In situations such as this and/or the presence of life-threatening alkalosis, a reduction in pH by controlled hypoventilation sometimes using inspired CO_2 with supplemental oxygen to

prevent hypoxia has been used. Dialysis using a low bicarbonate dialysate is also indicated in such patients.[7,58] Therapy for metabolic alkalosis can be conceptualized on the basis of the sodium chloride responsiveness of the disorders (Fig. 71-4).

FIGURE 71-4

Treatment algorithm for patients with primary metabolic alkalosis. (BID, twice daily; CHF, chronic heart failure; K, potassium [serum potassium in mEq/L is numerically equivalent to mmol/L]; PO, orally; QD, every day.)



Sodium Chloride–Responsive Metabolic Alkalosis

Sodium chloride–responsive disorders usually result from volume depletion and chloride loss, which can accompany severe vomiting, prolonged nasogastric suction, and diuretic therapy. Initially, therapy is directed at expanding intravascular volume and replenishing chloride stores. Sodium chloride– and potassium chloride–containing solutions should be administered to patients who can tolerate the volume load.[52] Patients with metabolic alkalosis who are volume overloaded or intolerant to volume administration because of chronic heart failure can benefit from the carbonic anhydrase inhibitor acetazolamide. This agent inhibits the action of carbonic anhydrase, thereby inhibiting renal bicarbonate reabsorption. Unfortunately, it also increases the renal losses of potassium and phosphate. Administration of acetazolamide (250-375 mg once or twice daily) can promote a sufficient bicarbonate diuresis and return the pH toward normal.[52,59] Among mechanically ventilated chronic obstructive pulmonary disease patients having metabolic alkalosis, administration of acetazolamide 500 to 1,000 mg twice daily (initiated within 48 hours of ICU admission and continued to ICU discharge) appears to reduce the degree of alkalosis while not affecting duration of mechanical ventilation or any other clinically relevant outcome.[60]

Hemodialysis using a low-bicarbonate dialysate can be used for the rapid correction of severe (pH greater than 7.55) metabolic alkalosis.[7,58] Acidifying agents including hydrochloric acid, ammonium chloride, and arginine monohydrochloride can also be used in such situations; however, availability limits their use as first line.[61,62] In general, this management is reserved for patients who are unresponsive to conventional fluid and electrolyte management or who are unable to tolerate the requisite volume load because of decompensated heart failure or advanced kidney disease.[58]

Hydrochloric Acid

Hydrochloric acid is usually infused IV via a large central vein as a 0.1 to 0.25 N HCl solution in either 5% dextrose or normal saline, although sterile water has also been used. Extemporaneously prepared solutions can be made by adding 100 to 250 mEq (mmol) of HCl through a 0.22-mm filter into a glass container of saline or dextrose. The rate of infusion should be 100 to 125 mL/hr (10-25 mEq/h [mmol/h]). A severe transient respiratory acidosis can occur if the hydrochloric acid is infused too quickly because of a slower reduction of the elevated bicarbonate concentration in the cerebrospinal fluid than in the ECF. Improvement is usually seen within 24 hours of initiating therapy. To prevent overcorrection, the infusion should be stopped when the arterial pH decreases to 7.5.[7,61] ABGs and serum electrolytes should be drawn every 4 to 8 hours to evaluate and adjust therapy.

The dose of hydrochloric acid can be based on an estimate of the total body chloride deficit[61]:

$$\text{Dose HCl (in mEq or mmol)} = [0.2\ \text{L/kg} \times \text{BW (in kg)}] \times [103\text{-observed serum chloride}]$$Dose HCl (in mEq or mmol)=[0.2 L/kg × BW (in kg)]×[103-observed serum chloride]

where the estimated chloride space is 0.2 times the BW, and the average serum chloride is 103 mEq/L (mmol/L). Alternatively, the dose can be calculated based on the estimated base deficit[63]:

$$\text{Dose HCl (in mEq or mmol)} = [0.5\ \text{L/kg} \times \text{BW (in kg)}] \times (\text{observed } [HCO_3^-] - 24)$$Dose HCl (in mEq or mmol) = [0.5 L/kg × BW (in kg)] × (observed [HCO3−] - 24)

Ammonium Chloride

Ammonium chloride has a limited role in the treatment of metabolic alkalosis. The liver converts ammonium chloride (NH_4Cl) to urea and free hydrochloric acid[64]:

$$2NH_4Cl + 2HCO_3^- \rightarrow CO(NH_2)_2 + CO_2 + 3H_2O + 2Cl^-$$2NH4Cl+2HCO3−⟶CO(NH2)2 + CO2 + 3H2O + 2Cl−

The dose of ammonium chloride can be calculated based on the chloride deficit using the same method as for HCl and assuming that 20 g ammonium chloride will provide 374 mEq (mmol) of H^+. However, only one-half of the calculated dose of ammonium chloride should be administered to avoid ammonia toxicity. Ammonium chloride is available as a 26.75% solution containing 100 mEq (mmol) of H^+ in 20 mL, which should be further diluted prior to administration. A dilute solution can be prepared by adding 20 mL of ammonium chloride to 500 mL of normal saline and infusing the solution at a rate of no more than 1 mEq/min (mmol/min). Improvement in metabolic status is usually seen within 24 hours. CNS toxicity, marked by confusion, irritability, seizures, and coma, has been associated with more rapid rates of administration. Ammonium chloride must be administered cautiously to patients with impaired kidney or hepatic function. In patients with impaired hepatic function, decreased conversion of ammonia to urea can result in increased ammonia levels and worsened encephalopathy. In patients with kidney disease, the increased urea synthesis can exacerbate uremic symptoms.[63,64]

Arginine Monohydrochloride

Although not FDA-approved, arginine monohydrochloride at a dose of 10 g/hr given IV has been used to treat metabolic alkalosis. Like ammonium chloride, arginine must undergo metabolism by the liver to produce hydrogen ions, with a conversion of 100 g to 475 mEq (mmol) of H^+. Unlike ammonium chloride, arginine combines with ammonia in the body to synthesize urea; thus, it can be used in patients with relative hepatic insufficiency. Patients with kidney disease should not receive arginine monohydrochloride because it can significantly elevate blood urea nitrogen and is associated with severe hyperkalemia.[64,65] The increase in potassium is caused by arginine-induced shifts of potassium from the intracellular to the extracellular space.

Sodium Chloride–Resistant Metabolic Alkalosis

13 Management of these disorders usually consists of treatment of the underlying cause of the mineralocorticoid excess. For patients taking a corticosteroid, a dosage reduction or a switch to a corticosteroid with less mineralocorticoid activity (eg, methylprednisolone) should be considered. Patients with an endogenous source of excess mineralocorticoid activity can require surgery or the administration of spironolactone, amiloride, or triamterene.[2,52]

Spironolactone is a competitive antagonist of the mineralocorticoid receptor. Amiloride and triamterene are potassium-sparing diuretics that inhibit the epithelial sodium channel in the distal convoluted tubule and collecting duct. All three agents inhibit aldosterone-stimulated sodium reabsorption in the collecting duct. In addition, spironolactone directly inhibits aldosterone stimulation of the hydrogen ion secretory pump. Thus, most patients with mineralocorticoid excess, including Bartter and Gitelman syndromes, respond to therapy with these agents.[7] Liddle syndrome, which is a form of pseudohypoaldosteronism caused by overactivity of the epithelial sodium channel, is not responsive to spironolactone but can be treated with either amiloride or triamterene.[52] Although experience is limited, some patients with Bartter and Gitelman syndromes may respond to NSAIDs or ACE inhibitors.[7,66,67] Finally, aggressive potassium repletion can correct the alkalosis in those who have not responded to the approaches outlined above (see Chapter 70).

RESPIRATORY ACID–BASE DISORDERS

As with the metabolic acid–base disturbances, there are two cardinal respiratory acid–base disturbances: respiratory acidosis and respiratory alkalosis. These disorders are generated by a primary alteration in CO_2 excretion, which changes the concentration of CO_2, and therefore the carbonic acid concentration in body fluids.[4] A primary reduction in $PaCO_2$ causes an increase in pH (respiratory alkalosis), and a primary increase in $PaCO_2$ causes a decrease in pH (respiratory acidosis). Unlike the metabolic disturbances, for which respiratory compensation is rapid, metabolic compensation for the respiratory disturbances is slow. Hence, these disturbances can be further divided into acute disorders, with a duration of minutes to hours, and where metabolic compensation has yet to occur, and chronic disorders that have been present long enough for metabolic compensation to be complete.

Respiratory Alkalosis

Respiratory alkalosis is characterized by a primary decrease in $PaCO_2$ that leads to an elevation in pH. The $PaCO_2$ decreases when the excretion of CO_2 by the lungs exceeds the metabolic production of CO_2. It is the most frequently encountered acid–base disorder, occurring physiologically in normal pregnancy and in persons living at high altitudes.[68] Respiratory alkalosis also occurs frequently among hospitalized patients (Table 71-12).[68,69]

TABLE 71-12

Causes of Respiratory Alkalosis

Medications (stimulation of central nervous system respiration)	Xanthine derivatives (theophylline, aminophylline, caffeine)
	Nicotine
	Catecholamines (epinephrine, norepinephrine, dopamine)
	Salicylate overdose
	Topiramate
Central nervous system stimulation of respiration	Brain tumors
	Encephalitis, meningitis
	Head trauma
	Vascular accidents
	Anxiety
	Pain
	Fever
	Pregnancy
Hypoxia	High altitudes
	Hyperventilation
	Hypoxemia
	Pneumonia
	Pulmonary edema
	Severe anemia
Peripheral stimulation of respiration	Pulmonary embolus
	Asthma
Other	Thyrotoxicosis
	Cirrhosis

Pathophysiology

A decrease in $PaCO_2$ occurs when ventilatory excretion exceeds metabolic production. Because endogenous production of CO_2 is relatively constant, negative CO_2 balance is primarily caused by an increase in ventilatory excretion of CO_2 (hyperventilation). The metabolic production of CO_2, however, can be increased during periods of stress or with excess carbohydrate administration (eg, parenteral nutrition). Hyperventilation can develop from an increase in neurochemical stimulation via either central or peripheral mechanisms, or by the result of voluntary or mechanical (iatrogenic) hyperventilation.

A decrease in $PaCO_2$ can occur in patients with cardiogenic, hypovolemic, or septic shock because oxygen delivery to the carotid and aortic chemoreceptors is reduced. This relative deficit in PaO_2 stimulates an increase in ventilation. The hyperventilation in sepsis is also mediated via a central mechanism. Hyperventilation-induced respiratory alkalosis with an elevation in cardiac index and hypotension without peripheral vasoconstriction can therefore be an early sign of sepsis.

Clinical Presentation

Although most patients are asymptomatic, respiratory alkalosis can cause adverse neuromuscular, cardiovascular, and GI effects.[68] During periods of decreased $PaCO_2$, there is a decrease in cerebral blood flow, which can be responsible for symptoms of light-headedness, confusion, decreased intellectual functioning, syncope, and seizures. Nausea and vomiting can occur, probably as a result of cerebral hypoxia. In severe respiratory alkalosis, cardiac arrhythmias can occur because of sensitization of the myocardium to the arrhythmogenic effects of circulating catecholamines.[70] Acute respiratory alkalosis has no effect on BP or cardiac output in awake individuals. Anesthetized patients, however, can experience a decrease in both cardiac output and BP, possibly owing to the lack of a tachycardic response.[68]

The concentration of serum electrolytes can also be altered secondary to the development of respiratory alkalosis.[7] The serum chloride concentration is usually slightly increased, and serum potassium concentration can be slightly decreased. Clinically significant hypokalemia can be a consequence of extreme respiratory alkalosis, although the effect is usually very small or negligible.[71] Serum phosphorus concentration can decrease by as much as 1.5 to 2 mg/dL (0.48-0.65 mmol/L) because of the shift of inorganic phosphate into cells. Reductions in the blood ionized calcium concentration can be partially responsible for symptoms such as muscle cramps and tetany. Approximately 40% of calcium is bound to albumin, and an increase in pH results in an increase in binding.[72]

Compensation

The initial response of the body to acute respiratory alkalosis is chemical buffering: hydrogen ions are released from the body's buffers—intracellular proteins, phosphates, and hemoglobin—and titrate down the serum bicarbonate concentration. This process occurs within minutes. Acutely, the bicarbonate concentration can be decreased by a maximum of 3 mEq/L (mmol/L) for each 10-mm Hg (1.3 kPa) decrease in $PaCO_2$ (see Table 71-8).[7] When only physicochemical buffering has occurred, the disturbance is referred to as acute respiratory alkalosis.

Metabolic compensation occurs when respiratory alkalosis persists for more than 6 to 12 hours. In response to the alkalemia, proximal tubular bicarbonate reabsorption is inhibited, and the serum bicarbonate concentration decreases. Renal compensation is usually complete within 1 to 2 days. The renal bicarbonaturia as well as decreased NH_4^+ and titratable acid excretion are direct effects of the reduced $PaCO_2$ and pH on renal reabsorption of chloride and bicarbonate.[2,73] The acuity of the respiratory alkalosis can be assessed on the basis of the degree of renal compensation (see Table 71-8). In fully compensated respiratory alkalosis, the bicarbonate concentration decreases by 4 mEq/L (mmol/L) below 24 for each 10-mm Hg (1.3 kPa) drop in $PaCO_2$. For example, a sustained decrease in $PaCO_2$ of 20 mm Hg (2.7 kPa) will lower serum bicarbonate from 24 to 16 mEq/L (mmol/L) with a resultant pH of 7.46. Bicarbonate concentrations differing from those anticipated using the preceding guidelines suggest a mixed acid–base disorder.

TREATMENT OF RESPIRATORY ALKALOSIS

Because most patients with respiratory alkalosis, especially chronic cases, have few or no symptoms and pH alterations are usually mild (pH not exceeding 7.5), treatment is often not required.[70] The first consideration in the treatment of acute respiratory alkalosis with pH more than 7.5 is the

identification and correction of the underlying cause. Relief of pain, correction of hypovolemia with IV fluids, treatment of fever or infection, treatment of salicylate overdose, and other direct measures can prove effective. A rebreathing device, such as a paper bag, can be useful in controlling hyperventilation in patients with the anxiety/hyperventilation syndrome. Oxygen therapy should be initiated in patients with severe hypoxemia.[68,70] Patients with life-threatening alkalosis (pH more than 7.55), particularly if it is a mixed respiratory and metabolic condition, tend to have complications, such as arrhythmias or seizures, which can require mechanical ventilation with sedation and/or paralysis to control hyperventilation.[64,68]

Respiratory alkalosis in patients receiving mechanical ventilation is usually iatrogenic. It can often be corrected by decreasing either the set RR or tidal volume, although other measures can also be employed. The use of a capnograph and spirometer in the breathing circuit enables a more precise adjustment of the ventilator settings. Another method of treating respiratory alkalosis is to increase the amount of dead space in the ventilator circuit by placing a known length of tubing between the artificial airway and the "T" piece of the ventilator. This results in "rebreathing" of expired gas, and therefore an increase in the inspired carbon dioxide concentration, which should increase the carbon dioxide tension of the patient, correcting the respiratory alkalosis. In patients breathing more rapidly than the ventilator settings, sedation with or without paralysis can be employed.

CLINICAL PRESENTATION: Respiratory Alkalosis

General

- The patient is usually asymptomatic if the condition is chronic and mild.

Symptoms

- The patient may complain of light-headedness, confusion, muscle cramps and tetany, and decreased intellectual functioning.
- Nausea and vomiting can occur, probably as a result of cerebral hypoxia.

Signs

- In severe respiratory alkalosis, pH is more than 7.55.

Laboratory Tests

- Serum chloride concentration is usually slightly increased. Serum ionized calcium through increased calcium binding to albumin, potassium, and phosphorus concentration can be decreased.

Respiratory Acidosis

Pathophysiology

Respiratory acidosis occurs when the lungs fail to excrete CO_2 resulting in a lower pH. This can be the result of conditions that centrally inhibit the respiratory center, diseases that interfere with pulmonary perfusion or neuromuscular function, and intrinsic airway or parenchymal pulmonary disease (Table 71-13).[68,69] Acute respiratory acidosis with hypoxemia, hypercarbia, and acidosis is life threatening. Those disorders that produce an increase in $PaCO_2$ and hypoxemia to a degree compatible with life (eg, chronic obstructive pulmonary disease), with or without oxygen therapy, can result in chronic respiratory acidosis (Table 71-14).[68,69] These patients can function normally without noticeable neurologic defects with higher than normal range $PaCO_2$ concentrations, provided that adequate oxygenation is maintained.

TABLE 71-13

Causes of Acute Respiratory Acidosis

Airway and pulmonary abnormalities	Acute airway obstruction

	Acute asthma exacerbation
	Acute cardiogenic pulmonary edema
	Acute respiratory distress syndrome
	Aspiration
	Chronic obstructive pulmonary disease exacerbation
	Obesity hypoventilation syndrome
	Laryngeal spasms
	Obstructive sleep apnea
	Pneumonia
	Pneumothorax
	Smoke inhalation
	Trauma
Central	Anesthetics (bupivacaine, mepivacaine)
	Meningitis
	Neuromuscular blockers (succinylcholine, vecuronium, cisatracurium, rocuronium, pancuronium)
	Opioids (fentanyl, hydromorphone, morphine, oxycodone, codeine)
	Sedatives (alprazolam, diazepam, lorazepam, propofol)
	Status epilepticus
	Stroke
Mechanical ventilator	Inadequate frequency or tidal volume setting
	Large dead space
	Ventilator malfunction
Metabolic	Overfeeding
Neuromuscular abnormalities	Brainstem or cervical cord injury
	Guillain-Barre syndrome
	Myasthenia gravis

Perfusion abnormalities	Cardiac arrest
	Massive pulmonary embolus

TABLE 71-14

Causes of Chronic Respiratory Acidosis

Airway abnormalities	Airway stenosis
Metabolic	Chronic overfeeding
Neuromuscular abnormalities/disorders	Amyotrophic lateral sclerosis
	Brainstem lesions
	Critical illness myopathies
	Diaphragmatic paralysis
	Extreme obesity (Pickwickian syndrome)
	Myasthenia gravis
	Multiple sclerosis
	Poliomyelitis
	Primary alveolar hypoventilation syndrome
	Tumors
Pulmonary abnormalities/disorders	Bronchitis
	Chronic obstructive pulmonary disease
	Chronic pulmonary embolism
	Emphysema
	Extreme obesity
	Fibrothorax
	Kyphoscoliosis
	Pulmonary fibrosis

Clinical Presentation

Respiratory acidosis can produce neurologic symptoms, including altered mental status, abnormal behavior, seizures, stupor, and coma. Hypercapnia can mimic stroke or CNS tumors by producing headache, papilledema, focal paresis, and abnormal reflexes. These CNS symptoms are attributable to the vasodilator effects of CO_2 in the brain that result in an increase in cerebral blood flow.[2] The CNS response to hypercapnia is extremely variable between patients and is most influenced by the acuity of presentation. Given that chronic hypercapnia blunts the usual respiratory stimulus of an elevated $PaCO_2$, hypoxemia rather than hypercapnia provides the primary ventilatory stimulus in patients with severe chronic respiratory acidosis.[18]

The degree to which cardiac contractility and HR are altered depends on the severity of the acidosis and the rapidity with which it develops. Modest acute hypercapnia ($PaCO_2$ of 50-55 mm Hg [6.7-7.3 kPa]) stimulates a stress-like response, with elevated catecholamines and corticosteroid hormone levels, and can result in increased cardiac output and pulmonary artery pressure. As the severity increases, cardiac output declines and vascular resistance decreases leading to refractory hypotension in some patients.[68]

In respiratory acidosis, the serum potassium concentration increases modestly secondary to cellular shifts. The increases are less than those seen with inorganic metabolic acidosis and are difficult to predict for individual patients.[71]

Compensation

The body responds to acute respiratory acidosis with chemical buffering. The increase in $PaCO_2$ results in increased carbonic acid levels. The carbonic acid dissociates, releasing hydrogen ions, which are buffered by non-bicarbonate buffers (ie, proteins, phosphate, and hemoglobin) and bicarbonate. Thus, based on physicochemical factors, increases in $PaCO_2$ raise the serum bicarbonate concentration. In general, in acute respiratory acidosis, the bicarbonate concentration increases by 1 mEq/L (mmol/L) above 24 for each 10 mm Hg (1.3 kPa) increase in $PaCO_2$ above 40 mm Hg (5.3 kPa) (see Table 71-8).[7]

CLINICAL PRESENTATION: Respiratory Acidosis

General

- The patient is usually symptomatic.

Symptoms

- The patient may complain of confusion or difficulty thinking and headache.

Signs

- In severe respiratory acidosis.
- Cardiac: Increased cardiac output if moderate that decreases if severe. Refractory hypotension can be present in some patients.
- CNS: Abnormal behavior, seizures, stupor, and coma. Papilledema, focal paresis, and abnormal reflexes can also be present.

Laboratory Tests

- Serum potassium concentration can be modestly increased. Hypercapnia can be moderate ($PaCO_2$ of 50-55 mm Hg [6.7-7.3 kPa]) to severe ($PaCO_2$ of more than 80 mm Hg [10.6 kPa]). Hypoxia (PaO_2 is less than 70 mm Hg [9.3 kPa]) is often present.

Metabolic compensation occurs when respiratory acidosis is prolonged beyond 12 to 24 hours. In response to hypercapnia and acidemia, proximal tubular bicarbonate reabsorption, ammoniagenesis, and distal tubular hydrogen secretion are enhanced, resulting in an increase in the serum bicarbonate concentration that raises the pH toward normal. Renal compensation for chronic hypercapnia generally results in the plasma bicarbonate concentration increasing by 4 mEq/L (mmol/L) above 24 for each 10 mm Hg (1.3 kPa) increase in $PaCO_2$ above 40 mm Hg (5.3 kPa) (see Table 71-8).[7] The

new steady state in acid–base values is generally achieved within 5 days of the onset of hypercapnia in dogs; the time interval necessary for compensation in humans has not been established.[74]

TREATMENT OF RESPIRATORY ACIDOSIS

The treatment of respiratory acidosis is dependent on the chronicity of the patient's condition. Respiratory decompensation in patients with chronic elevations in $PaCO_2$ is frequently seen in those with acute infections and those recently started on narcotic analgesics or oxygen therapy. Aggressive treatment of these conditions can offer considerable benefit and should be initiated. Furthermore, tranquilizers and sedatives should be avoided and supplemental oxygen, if used, should be minimized.[68]

Acute Respiratory Acidosis

When carbon dioxide excretion is severely impaired ($PaCO_2$ more than 80 mm Hg [10.6 kPa]) and/or life-threatening, hypoxia is present (PaO_2 less than 40 mm Hg [5.3 kPa]); the immediate therapeutic goal is to provide adequate oxygenation. Under these circumstances, hypoxia, not acidemia, is the principal threat to life. A patent airway needs to be established, which can necessitate intubation. Excessive secretions must be cleared from the airway and oxygen administered to restore adequate oxygenation. Mechanical ventilation is usually required.

14 The underlying cause of the acidosis should be treated aggressively (ie, bronchodilators for treatment of severe bronchospasm; narcotic or benzodiazepine antagonists to reverse the deleterious effects of these agents on the respiratory center). Bicarbonate administration is rarely necessary in the treatment of respiratory acidosis. Furthermore, rapid correction of acidosis with bicarbonate can eliminate the patient's respiratory drive or precipitate metabolic alkalosis. Cautious use of alkali (bicarbonate) can restore the responsiveness of bronchial muscles to β-adrenergic agonists and thus can be beneficial for those patients with severe bronchospasm.[74] ABGs should be monitored closely to ensure that the respiratory acidosis is resolving without creating a metabolic alkalosis as the result of compensatory elevation in HCO_3^- and decrease in $PaCO_2$. ABGs should be obtained every 2 to 4 hours during the acute phase and less frequently (every 12-24 hours) as the acidosis improves.

Acute Respiratory Acidosis in a Compensated Chronic Respiratory Acidotic Patient

Patients with a history of chronic respiratory acidosis (eg, those with chronic obstructive pulmonary disease) can experience an acute worsening of their respiratory acidosis. This can result in severe life-threatening hypoxemia. As with acute respiratory acidosis, the goals of therapy are maintenance of a patent airway and adequate oxygenation. Individuals with chronic respiratory acidosis are routinely able to tolerate a low PaO_2 and an elevated $PaCO_2$ because of compensation (increased number of red blood cells, hemoglobin content, and 2,3-diphosphoglycerate). The drive to breathe in these patients is dependent on hypoxemia rather than hypercarbia. Administration of oxygen to a patient with chronic respiratory acidosis can eliminate this drive to breathe and result in the syndrome of carbon dioxide narcosis. In this case, if the PaO_2 is 50 mm Hg (6.7 kPa), no oxygen treatment is necessary. If the PaO_2 is less than 50 mm Hg (6.7 kPa), oxygen therapy should be initiated carefully using a controlled flow of oxygen.[68]

ABGs should be checked periodically to ensure adequate oxygenation. If the $PaCO_2$ increases during oxygen therapy, it can be a sign of impending carbon dioxide narcosis and oxygen therapy may need to be discontinued. The underlying cause of the acute exacerbation should be aggressively managed. Pulmonary infections should be treated with the appropriate antibiotics and bronchodilators administered as necessary. Excess secretions should be cleared from the airway to allow proper gas exchange. This can involve increasing oral fluid intake to decrease the viscosity of secretions, deep breathing, and postural drainage, suction, or bronchoscopy.

MIXED ACID–BASE DISORDERS

Diagnosis

The diagnosis of a mixed disorder depends on an understanding of the appropriate quantitative response of the compensatory mechanisms for each of the simple acid–base disturbances.[38,75] To diagnose mixed disorders, one must know how each of the four simple disorders alters pH, $PaCO_2$, and

(HCO_3^-) (see Table 71-8). If a given set of blood gases does not decrease within the range of expected responses for a simple acid–base disturbance, a mixed disorder should be suspected. In addition to laboratory information, a thorough history and physical examination of the patient will often lead to the diagnosis, even before the laboratory data are available. Examples of common mixed disturbances follow.

Mixed Respiratory Acidosis and Metabolic Acidosis

A mixed respiratory and metabolic acidosis disturbance is characterized by a failure of compensation. The respiratory disorder prevents the compensatory decrease in $PaCO_2$ expected in the defense against metabolic acidosis. The metabolic disorder prevents the buffering and renal mechanisms from raising the bicarbonate concentration as expected in the defense against respiratory acidosis. In the absence of these compensatory mechanisms, the pH decreases markedly.

Mixed respiratory and metabolic acidosis may develop in patients with cardiorespiratory arrest, in those with chronic lung disease who are in shock, and in metabolic acidosis patients who develop respiratory failure. When treating this mixed disorder, clinicians need to respond to both the respiratory and metabolic acidosis. Improved oxygen delivery must be initiated to improve hypercarbia and hypoxia. Mechanical ventilation may be needed to reduce $PaCO_2$. During the initial stage of therapy, appropriate amounts of alkali should be given to reverse the metabolic acidosis (see section "Treatment," for "Metabolic Acidosis").

Mixed Respiratory Alkalosis and Metabolic Alkalosis

The combination of respiratory and metabolic alkalosis is the most common mixed acid–base disorder. This mixed disorder occurs frequently in critically ill surgical patients with respiratory alkalosis caused by mechanical ventilation, hypoxia, sepsis, hypotension, neurologic damage, pain, or medications, and with metabolic alkalosis caused by vomiting or nasogastric suctioning and massive blood transfusions. It can also occur in patients with hepatic cirrhosis who hyperventilate, receive diuretics, or vomit, as well as in patients with chronic respiratory acidosis and an elevated plasma bicarbonate concentration who are placed on mechanical ventilation and undergo a rapid decrease in $PaCO_2$.

The renal excretion of bicarbonate that usually occurs as compensation for the respiratory alkalosis is prevented by the complicating metabolic alkalosis. Likewise, the retention of $PaCO_2$ expected to compensate for metabolic alkalosis is prevented by the primary respiratory alkalosis. The failure of compensation that occurs with mixed respiratory and metabolic alkalosis can result in a severe alkalemia.

Administration of sodium chloride and potassium chloride solutions will help correct the metabolic component of a mixed respiratory and metabolic alkalosis, and adjustment of the ventilator and/or treatment of an underlying process that is causing hyperventilation can correct or ameliorate the respiratory component of this mixed disorder.

Mixed Metabolic Acidosis and Respiratory Alkalosis

This mixed disorder is often seen in patients with advanced liver disease, salicylate intoxication, and pulmonary-renal syndromes. The respiratory alkalosis will decrease the $PaCO_2$ beyond the appropriate range for the respiratory compensation usually seen with metabolic acidosis. The plasma bicarbonate concentration also decreases below the level expected in compensation for a simple respiratory alkalosis. In a sense, the defense of pH for either disorder alone is enhanced; thus, the pH can be normal or close to normal, with a low $PaCO_2$ and a low (HCO_3^-). Treatment of this disorder should be directed at the underlying cause. Because of the enhanced compensation, the pH is usually closer to normal than in either of the two simple disorders.

Mixed Metabolic Alkalosis and Respiratory Acidosis

This mixed disorder often occurs in patients with chronic obstructive pulmonary disease and chronic respiratory acidosis who are treated with salt restriction, diuretics, and possibly glucocorticoids. When diuretics are initiated, the plasma bicarbonate may increase because of increased renal bicarbonate generation and reabsorption, providing mechanisms for both generating and maintaining metabolic alkalosis. The elevated pH diminishes respiratory drive and may therefore worsen the respiratory acidosis.

Although the pH may not deviate significantly from normal, treatment may need to be initiated to maintain PaO_2 and $PaCO_2$ at acceptable levels.

Because it is often difficult to correctly identify this mixed disorder, it is helpful to observe the patient's response to discontinuation of diuretics and administration of sodium and potassium chloride.[38] The $PaCO_2$ will normalize if the patient has a simple metabolic alkalosis, but it will be minimally affected in the setting of a mixed disorder. Treatment should be aimed at decreasing the plasma bicarbonate with sodium and potassium chloride therapy, thereby allowing the renal excretion of retained bicarbonate from the diuretic-induced metabolic alkalosis. This therapy should be used cautiously to avoid exacerbating any underlying chronic heart failure.

CONCLUSION

Acid–base disorders are a common and widespread problem, and clinicians can play a key role in identifying, preventing, and properly treating them. Acid–base disorders do not occur only in the intensive care unit setting. Patients in ambulatory and extended care settings have many chronic conditions and medication therapies that commonly affect acid–base balance. Thus, clinicians in all practice settings should strive to identify patients at high risk for developing medication-related problems that affect acid–base balance and to undertake appropriate prevention and treatment measures to improve the quality of life of their patients.

ABBREVIATIONS

AKI	acute kidney injury
ABG	arterial blood gas
BP	blood pressure
BW	body weight
CKD	chronic kidney disease
CNS	central nervous system
DCA	dichloroacetate
ECF	extracellular fluid
GI	gastrointestinal
HR	heart rate
H^+	hydrogen ion
HCO_3^-	bicarbonate
H_2CO_3	carbonic acid
HIV	human immunodeficiency virus
IV	intravenous
NH_4^+	ammonium
$PaCO_2$	partial pressure of carbon dioxide from arterial blood

PaO_2	partial pressure of oxygen from arterial blood
PCO_2	partial pressure carbon dioxide in the blood
pH	the negative logarithm (base 10) of the hydrogen ion concentration
p*K*	the negative logarithm of the dissociation constant
$PvCO_2$	partial pressure of carbon dioxide from venous blood
PvO_2	partial pressure of oxygen from venous blood
RTA	renal tubular acidosis
RR	respiratory rate
SAG	serum anion gap
SCr	serum creatinine
THAM	tromethamine (Tris[hydroxymethyl]-aminomethane)
UAs	unmeasured anions
UCs	unmeasured cations

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SELF-ASSESSMENT QUESTIONS

1. A 31-year-old man, LG, was found to be unresponsive and apneic and transferred to the emergency department. His arterial blood gas (ABG) sample on arrival revealed the following: pH 7.08, PCO_2 80 mm Hg (10.6 kPa), and HCO_3^- 23 mEq/L (mmol/L). His serum labs demonstrated Na 130 mEq/L (mmol/L); Cl 111 mEq/L (mmol/L), and TCO_2 23 mEq/L (mmol/L). His acid–base disturbance is:

   A. Respiratory acidosis with an elevated anion gap

   B. Respiratory acidosis with a normal anion gap

   C. Metabolic acidosis with a normal anion gap

   D. Metabolic acidosis with an elevated anion gap

2. A 31-year-old man, LG, was found to be unresponsive and apneic and transferred to the emergency department. His ABG sample on arrival revealed the following: pH 7.08, PCO_2 80 mm Hg (10.6 kPa), and HCO_3^- 23 mEq/L (mmol/L). His serum labs demonstrated Na 130 mEq/L (mmol/L); Cl 111 mEq/L (mmol/L), and TCO_2 23 mEq/L (mmol/L). Which statement is *most true* about extracellular buffering?

A. The bicarbonate buffer system is the most important because it is not dependent on the amount of bicarbonate filtered by the kidney.

B. The carbonic acid buffer system plays a minimal role given the low amount of CO_2 produced by the body.

C. The stomach plays an important role given its ability to easily adjust the amount of gastric acid produced.

D. The phosphate buffer system plays a limited role given the low concentrations of extracellular phosphate.

3. A 45-year-old female, AR, is transferred to the intensive care unit with septic shock due to acute peritonitis. Her ABG sample revealed the following: pH 7.25, PCO_2 29 mm Hg (3.9 kPa), and HCO_3^- 15 mEq/L (mmol/L). Her serum labs demonstrated Na 142 mEq/L (mmol/L); Cl 105 mEq/L (mmol/L), and TCO_2 15 mEq/L (mmol/L), lactate 5.8 mEq/L (mmol/L). Which statement is *most true* regarding the expected compensation for AR's acid–base disturbance?

A. Compensation is initiated within days through increased renal elimination of bicarbonate.

B. Compensation is initiated within hours through renal accumulation of bicarbonate.

C. Compensation is initiated within hours through increased respiratory rate.

D. Compensation is initiated within days through decreased respiratory rate.

4. A 68-year-old man, KL (weight: 70 kg; height: 69 in. [175 cm]), with a long-standing history of poorly controlled diabetes mellitus, is admitted to the medical floor of a hospital with a diagnosis of community-acquired pneumonia. His most recent ABG is as follows: pH 7.30, PCO_2 34 mm Hg (4.5 kPa), HCO_3^- 15 mEq/L (mmol/L), and PO_2 80 mm Hg (10.6 kPa), and his most recent serum labs demonstrate Na 135 mEq/L (mmol/L), K 5.4 mEq/L (mmol/L), Cl 116 mEq/L (mmol/L), TCO_2 15 mEq/L (mmol/L), and blood glucose 146 mg/dL (8.1 mmol/L). He is hemodynamically stable. What is his acid–base disturbance?

A. Respiratory alkalosis

B. Metabolic alkalosis

C. Respiratory acidosis

D. Metabolic acidosis

5. A 68-year-old man, KL, with a long-standing history of poorly controlled diabetes mellitus, is admitted to the medical floor of a hospital with a diagnosis of community-acquired pneumonia. His most recent ABG is as follows: pH 7.30, PCO_2 34 mm Hg (4.5 kPa), HCO_3^- 15 mEq/L (mmol/L), and PO_2 80 mm Hg (10.6 kPa), and his most recent serum labs demonstrate Na 135 mEq/L (mmol/L), K 5.4 mEq/L (mmol/L), Cl 116 mEq/L (mmol/L), TCO_2 15 mEq/L (mmol/L), blood urea nitrogen 23 mg/dL (8.2 mmol/L), SCr 1.5 mg/dL (133 µmol/L) and blood glucose 146 mg/dL (8.1 mmol/L). He is hemodynamically stable. Which condition *best* explains his current acid–base status?

A. Type IV renal tubular acidosis

B. Diabetic ketoacidosis

C. Type II renal tubular acidosis (proximal)

D. Type I renal tubular acidosis (distal)

6. A 68-year-old man, KL, with a long-standing history of poorly controlled diabetes mellitus, is admitted to the medical floor of a hospital with a diagnosis of community-acquired pneumonia. His most recent ABG is as follows: pH 7.30, PCO_2 34 mm Hg (4.5 kPa), HCO_3^- 15 mEq/L (mmol/L), and

PO_2 80 mm Hg (10.6 kPa), and his most recent serum labs demonstrate Na 135 mEq/L (mmol/L), K 5.4 mEq/L (mmol/L), Cl 116 mEq/L (mmol/L), TCO_2 15 mEq/L (mmol/L), and blood glucose 146 mg/dL (8.1 mmol/L). KL is found to be hypertensive (BP 170/92 mm Hg) and the medical resident asks if there is an antihypertensive that should be avoided in KL based on the underlying condition contributing to KL's current acid–base status. Which agent should be *avoided* in KL at this time?

A. Enalapril

B. Clonidine

C. Hydralazine

D. Amlodipine

7. A 44-year-old moderately dehydrated female was admitted with a two-day history of acute severe diarrhea. Her most recent ABG is as follows: pH 7.31, PCO_2 28 mm Hg (3.7 kPa), pO_2 93 mm Hg (12.4 kPa), HCO_3^- 16 mEq/L (mmol/L), O_2 saturation 94% [0.94], and her most recent serum labs demonstrate Na 134 mEq/L (mmol/L), K 3.1 mEq/L (mmol/L), Cl 108 mEq/L (mmol/L), TCO_2 15 mEq/L (mmol/L), BUN 31 mg/dL (11.1 mmol/L), creatinine 1.5 mg/dL (133 µmol/L). Baseline creatinine is 0.7 mg/dL (62 µmol/L). What is the *most appropriate* treatment of choice for this patient with normal anion gap metabolic acidosis?

A. Replace bicarbonate deficit with sodium bicarbonate intravenously during the first 24 hours of admission.

B. Replace ½ the bicarbonate deficit with sodium bicarbonate intravenously during the first 24 hours of admission.

C. Replace bicarbonate deficit with bicarbonate oral solution during the first 24 hours of admission.

D. Correct the underlying cause. Bicarbonate therapy not indicated.

8. Which of the following human immunodeficiency virus (HIV) medications has been *most* associated with lactic acidosis?

A. Rilpivirine

B. Efavirenz

C. Stavudine

D. Elvitegravir

9. Which statement is *most true* regarding RTA?

A. Distal RTA (type IV) can be caused by aldosterone resistance and often results in hypokalemia.

B. Proximal RTA (type II) is caused by a defect in the proximal tubule that prevents reabsorption of bicarbonate.

C. Proximal RTA (type II) and distal RTA (type I) are associated with sodium wasting and hypokalemia.

D. Renal tubular acidosis is usually associated with a high anion gap resulting from an increase in unmeasured anions.

10. A 31-year-old male presents with lethargy, weakness, confusion, and rapid breathing. He has had type 1 diabetes mellitus for 15 years and has been suffering from the "intestinal flu" for a day or so, for which he has been avoiding food to help prevent further vomiting and "make his stomachache go away." Since he stopped eating, he thought that it would be a good idea to stop taking his insulin. When seen in the emergency department his urine dipstick was positive for both glucose and ketones and his breath had a strange sweet, fruity smell. The following ABG data were obtained: pH 7.26, PCO_2 23 mm Hg (3.1 kPa), and HCO_3^- 10 mEq/L (mmol/L). His most recent serum chemistries are as follows: Na 140 mEq/L (mmol/L), Cl 100 mEq/L (mmol/L), K 4.5 mEq/L (mmol/L), TCO_2 11 mEq/L (mmol/L), and glucose 793 mg/dL (44 mmol/L). What is his acid–base disturbance?

A. Metabolic alkalosis (normal anion gap) due to rapid breathing

B. Metabolic alkalosis (elevated anion gap) due to inadequate oral intake

C. Metabolic acidosis (normal anion gap) due to vomiting

D. Metabolic acidosis (elevated anion gap) due to diabetic ketoacidosis

11. Which statement is *most true* regarding lactic acidosis?

A. Frequently reported with linezolid therapy of less than 4 weeks duration

B. Increased risk with administration of propofol at a dose of 10 mcg/kg/min for one day

C. Present when the serum lactate concentration equals 2 mEq/L (mmol/L)

D. Increased risk with high dose lorazepam IV infusions in a patient with kidney failure

12. Which of the following is *most correct* regarding administration of IV sodium bicarbonate to a patient with septic shock who has a high anion gap metabolic acidosis and an arterial pH of 7.15?

A. Sodium bicarbonate use will reduce mortality.

B. Sodium bicarbonate use may paradoxically reduce intracellular pH.

C. Sodium bicarbonate use will reduce the efficacy of norepinephrine.

D. Sodium bicarbonate IV is indicated for a patient with a pH of 7.3.

13. A 77-year-old female presents to the Emergency Department with increased bilateral lower extremity swelling, fatigue, and dyspnea upon exertion consistent with heart failure exacerbation. Due to the COVID-19 pandemic, she has been eating more canned goods and ordering take out, so she doesn't have to go to the grocery store and risk exposure. Her heart failure is managed outpatient with furosemide, metoprolol, and lisinopril. She increased her furosemide to twice daily dosing 5 days ago. Her most recent ABG is as follows: pH 7.51, PCO_2 48 mmHg (6.4 kPa), HCO_3^- 40 mEq/L (mmol/L), and PO_2 85 mm Hg (11.3 kPa), and her most recent serum labs demonstrate Na 133 mEq/L (mmol/L), K 3 mEq/L (mmol/L), Cl 91 mEq/L (mmol/L), and TCO_2 40 mEq/L (mmol/L). Urine chloride is less than 10 mEq/L (mmol/L). What is her acid–base disturbance?

A. Acute respiratory alkalosis

B. Saline responsive metabolic alkalosis

C. Saline resistant metabolic alkalosis

D. Chronic respiratory alkalosis

14. A 61-year-old female comes into your emergency department with sudden pain and swelling of her left wrist. She is status post stem cell transplant requiring high dose prednisone to help with skin graft-versus-host disease. What type of acid–base disorder *most likely* results from this therapy?

A. Saline-resistant metabolic alkalosis

B. Saline-responsive metabolic alkalosis

C. Anion gap metabolic acidosis

D. Non-anion gap metabolic acidosis

15. A patient is admitted to the ICU after emergency surgery for bowel perforation. He has been given 3 liters of 0.9% sodium chloride in the operating

room and 2 additional liters over the previous 2 hours. He has recently become drowsy and his respirations have slowed after receiving multiple doses of fentanyl IV for pain. The ABG is as follows: pH 7.29, PCO_2 34 mmHg (4.5 kPa), pO_2 98 mmHg (13.1 kPa), HCO_3^- 14 mEq/L (mmol/L) and the most recent lab values are as follows: Na 137 mEq/L (mmol/L), K 3.9 mEq/L (mmol/L), Cl 115 mEq/L (mmol/L), and TCO_2 15 mEq/L (mmol/L). What is his acid–base disturbance?

A. Metabolic alkalosis with respiratory alkalosis

B. Metabolic alkalosis with respiratory acidosis

C. Metabolic acidosis with respiratory alkalosis

D. Metabolic acidosis with respiratory acidosis

SELF-ASSESSMENT QUESTION-ANSWERS WITH RATIONALES

1. **B.** Respiratory acidosis with a normal anion gap. The pH is less than 7.35 indicating acidosis. The PCO_2 is elevated (greater than 40 mm Hg [5.3 kPa]), indicating primary respiratory disorder. The anion gap is calculated as AG = $Na^+ – (Cl^- + HCO_3^-)$ = 130 mEq/L – (111 mEq/L + 23 mEq/L) = –4 (normal). The etiology is hypoventilation due to the patient being unresponsive and apneic leading to hypercarbia and respiratory acidosis.

2. **D.** The phosphate buffer system plays a limited role given the low concentrations of extracellular phosphate. Since extracellular phosphate is present in low concentrations, its usefulness as an extracellular buffering system is limited. The bicarbonate/carbonic acid buffer system is the most important buffer system in the body as there is a high concentration of extracellular bicarbonate compared to other buffer components, high amount of CO_2 produced in the body, and the extracellular fluid acidity can be regulated by either adjustments in bicarbonate concentration by the kidneys or adjustments of PCO_2 by the lungs. Gastric acid production in the stomach isn't involved in acid–base regulation. See Regulation of acid–base homeostasis (Extracellular buffering) section for more information.

3. **C.** Compensation is initiated within hours through increased RR. This patient is presenting with elevated anion gap metabolic acidosis due to septic shock. In such cases, the lungs will increase the RR which decreases the PCO_2 in order to restore the pH to normal. Respiratory compensation begins within minutes to hours.

4. **D.** Metabolic acidosis. pH is less than 7.35 indicating acidosis. The HCO_3^- is low (less than 24 mmol/L) indicating primary metabolic disorder. The calculated AG = 135 mEq/L – (116 mEq/L + 15 mEq/L) = 4 which is considered normal.

5. **A.** Type IV renal tubular acidosis. This patient has a normal anion gap AG = 135 mEq/L – (116 mEq/L + 15 mEq/L) = 4. Renal tubular acidosis is a type of normal anion gap metabolic acidosis. The presentation of a mild acidosis (mild decrease in serum TCO_2) and elevated serum potassium fits the classification of Type IV renal tubular acidosis. Type I and II renal tubular acidosis present with low or normal serum potassium and a lower serum bicarbonate. Diabetic ketoacidosis presents as an elevated anion gap metabolic acidosis.

6. **A.** Enalapril. The underlying etiology of Type IV RTA is aldosterone deficiency or aldosterone resistance and present with hyperkalemia. Due to this, medications such as ACE inhibitors should be avoided. The other antihypertensive agents do not work within the renin–angiotensin–aldosterone system and do not potentiate hyperkalemia.

7. **D.** Correct the underlying cause – bicarbonate therapy not indicated. This patient does not have an indication for IV sodium bicarbonate due to pH (pH greater than 7.2) and current clinical condition. Fluid resuscitation (e.g., balanced crystalloid) and treatment for diarrhea is indicated.

8. **C.** Stavudine is a nucleoside-analog transcriptase inhibitor (NRTI) associated with lactic acidosis. The proposed mechanism of NRTI lactic acidosis is inhibition of DNA polymerase gamma, an enzyme responsible for mitochondrial DNA synthesis. Rilpivirine, efavirenz are non-nucleoside reverse transcriptase inhibitors (NNRTIs) and elvitegravir is an integrase inhibitor.

9. **B.** Proximal RTA (Type II) is caused by a proximal tubular defect resulting in decreased reabsorption of bicarbonate into the urine. Distal RTA (Type

IV) can be caused by aldosterone resistance but often results in hyperkalemia. Proximal (Type II) is associated with sodium wasting and hypokalemia. Distal RTA (Type I) is associated with hypokalemia but not sodium wasting. RTA is classified as a normal anion gap metabolic acidosis.

10. **D.** Metabolic acidosis (elevated anion gap) due to diabetic ketoacidosis. pH is less than 7.35 indicating acidosis. The HCO_3^- is low (less than 24 mmol/L) indicating primary metabolic disorder. The anion gap is calculated using the equation AG = Na^+ - (Cl^- + HCO_3^-). Using the laboratory values provided, the calculated AG = 140 mEq/L – (100 mEq/L + 11 mEq/L) = 29 which is elevated. All of these plus the presence of ketones in the urine dipstick, fruity breath, history of type 1 diabetes mellitus, stopping insulin therapy, and glucose of 793 mg/dL (32.9 mmol/L) lead to the diagnosis of diabetic ketoacidosis.

11. **D.** Increased risk with high-dose lorazepam IV infusions in a patient with kidney failure. Lorazepam IV is formulated in propylene glycol diluent and high doses in patients with renal and/or hepatic dysfunction can lead to lactic acidosis as it is predominantly metabolized to lactic acid via hepatic alcohol dehydrogenase. Linezolid is rarely seen with short-term therapy. Propofol-related infusion syndrome is seen with prolonged, high-dose infusions (greater than 80 mcg/kg/min for greater than 48 hours). Lactic acidosis is considered when lactate concentrations exceed 4-5 mEq/L (mmol/L).

12. **B.** Sodium bicarbonate use may paradoxically reduce intracellular pH. The carbon dioxide produced after IV infusion of sodium bicarbonate diffuses more readily over the cell membrane to the intracellular compartment compared to bicarbonate. This can lead to a paradoxical reduction in intracellular pH and produces an increased risk for intracellular acidosis adverse medication reactions. Sodium bicarbonate use has not shown to provide a mortality benefit. Severe acidosis may limit efficacy of norepinephrine due to reduced vascular responsiveness and reduction in cardiac contractility. Sodium bicarbonate IV is indicated in severe metabolic acidosis defined as a pH less than 7.2.

13. **B.** Saline responsive metabolic alkalosis. pH is greater than 7.45 indicating alkalosis. The HCO_3^- is high (greater than 24 mmol/L) indicating primary metabolic process. The urine chloride is less than 10 mEq/L (mmol/L), indicating saline responsive. Etiology is increased furosemide dosing.

14. **A.** Saline-resistant metabolic alkalosis. High-dose steroids can result in mineralocorticoid excess causing significant renal H^+ and K depletion.

15. **D.** Metabolic acidosis with respiratory acidosis. pH is less than 7.4 indicated acidosis. PCO_2 is less than 40 mm Hg (5.3 kPa) and HCO_3^- is less than 24 mEq/L (mmol/L), indicating metabolic process. Anion gap is calculated as Na – (Cl + CO_2) = 137 mEq/L – (115 mEq/L + 15 mEq/L) = 7 (normal anion gap). Using the expected PCO_2 equation to determine appropriate compensation and possible mixed acid–base disorder, the calculated expected PCO_2 is 40 - [1.2 × (24 - measured TCO_2)] = 29 mmHg (or 5.3 kPa-[0.16 x(24-measured TCO_2)]= 3.9 kPa). The actual PCO_2 of 34 mm Hg (4.5 kPa) is greater than the expected PCO_2 of 29 mm Hg (3.9 kPa), indicating a concomitant respiratory acidosis. Upon reviewing history and physical, the patient has a bowel perforation with possible ischemia, received large volume 0.9% sodium chloride infusion, has received multiple doses of IV opioid (fentanyl) with decreased respirations and drowsiness. Metabolic acidosis is due to bowel ischemia and large volume chloride-based IV fluid administration and respiratory acidosis is due to opioid-induced respiratory depression.