Chapter 15: Acid-Base Disorders

Gabor D. Kelen; David D. Nicolaou; David M. Cline

INTRODUCTION

Controversy has existed concerning acid-base physiology and the ideal method to assess acid-base disorders for 130 years.[1] The two most common methods advocated to analyze acid-base disorders are the traditional bicarbonate-centered method[2,3] and the Stewart, or strong ion, method.[4,5] The traditional approach teaches that acid-base homeostasis is maintained by respiratory control of the partial pressure of carbon dioxide (P_{CO_2}) through changes in alveolar ventilation and control of HCO_3^- reabsorption and H^+ excretion by the kidneys. Peter Stewart proposed that acid-base physiology involves the dynamic interaction of body fluids and multiple chemical species including strong ions (primarily Na^+, K^+, Ca^{2+}, Mg^{2+}, and Cl^-) and weak acids, as well as P_{CO_2} control by the lungs.

Each of these methods has limitations. The traditional bicarbonate-centered model continues to be the most commonly used at the bedside[3] but is criticized for failing to identify acid-base abnormalities that are due to alterations in plasma free water or in complex cases of mixed acid-base disorders.[6,7] The Stewart method is praised for its accuracy in identifying acid-base disorders but is criticized for the difficulty of application at the bedside.[7,8,9,10,11] This chapter does not detail the Stewart method, but we acknowledge its importance and its contribution to underscoring the limitations of the traditional method, which has led to modifications that improve the performance of the traditional method at the bedside.[8] For example, using a correction factor for the albumin level (detailed in this chapter), the traditional method performs as well as the Stewart method for identifying complex acid-base abnormalities in critically ill patients.[8,9,10,11,12]

Many diseases, including those that present an imminent threat to life, produce acid and base (acid-base) disturbances that provide important clues concerning the nature of the underlying illness and suggest immediate therapeutic interventions. Further, ED treatments

such as rapid resuscitation of critically ill patients may create unintended acid-base disorders. This chapter describes a practical approach to the clinical evaluation and treatment of acid-base disorders.

PATHOPHYSIOLOGY

MEASUREMENT OF PLASMA ACIDITY

Plasma hydrogen ion concentration ($[H^+]$)* is normally 40 nmol/L, corresponding to a pH of 7.4. Because pH is a logarithmic transformation of $[H^+]$, the relation of $[H^+]$ to pH is not linear for all pH values (**Table 15–1**). However, for pH values from 7.20 to 7.50, the relation between $[H^+]$ and pH is nearly linear; pH changes of 0.01 correspond to approximately 1 nmol/L change in $[H^+]$. This linear relation allows for rapid bedside interpretation of blood gas and electrolyte results.

Table 15–1

pH and Hydrogen Ion Concentrations

pH	$[H^+]$, nmol/L
6.8	158
6.9	126
7.0	100
7.1	79
7.2	63
7.3	50
7.4	40
7.5	32
7.6	25
7.7	20

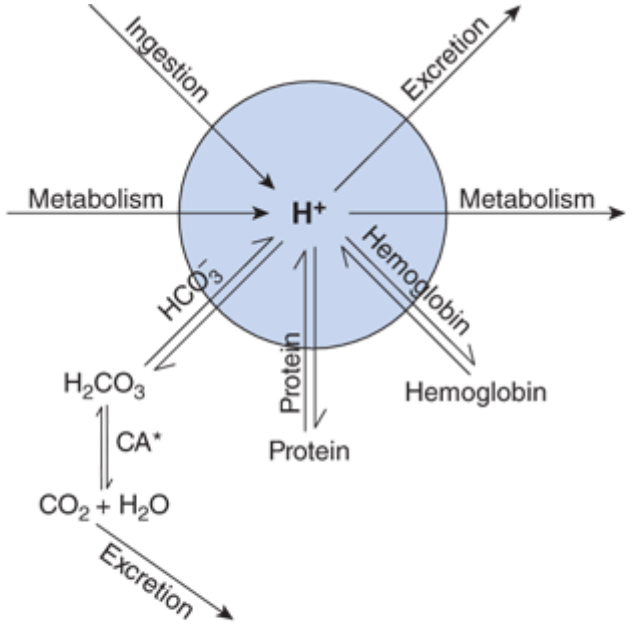
*Standard nomenclature is used in this chapter. The presence of brackets, [ ], surrounding an element or molecule implies the term concentration. Without the brackets, the chemical expressions simply refer to the element or molecule.

PLASMA ACID-BASE HOMEOSTASIS

Plasma [H^+] is influenced by the rate of endogenous production, the rate of excretion, exogenous addition (e.g., acetylsalicylic acid ingestion), and the buffering capacity of the body. Buffers mitigate the impact of large changes in available hydrogen ion on plasma pH.

Buffer systems that are effective at physiologic pH include hemoglobin, phosphate, proteins, and bicarbonate (**Figure 15–1**). One can consider the [H^+] to be the result of all physiologic buffers acting on the common pool of hydrogen ions.

FIGURE 15–1.
Schematic representation of hydrogen ion homeostasis.



*Carbonic anhydrase

The familiar Henderson-Hasselbalch equation, shown in Eq. (1),

$$\mathrm{pH} = \mathrm{p}K + \log \frac{[\mathrm{HCO_3^-}]}{[\mathrm{H_2CO_3}]} \qquad (1)$$

specifies the relationship between carbonic acid, bicarbonate, and pH; any two of these determine the value of the third. The clinical use of the Henderson-Hasselbalch equation is limited. However, if all constants are inserted into the Henderson-Hasselbalch equation and

the anti-logarithm of all its terms is taken, the result is the Kassirer-Bleich equation [Eq. (2)], which is of great clinical utility.

$$[H^+] = 24 \times \frac{P_{CO_2}}{[HCO_3^-]} \qquad (2)$$

The Kassirer-Bleich equation may be used to estimate the concentration of any component of the bicarbonate buffer system provided the concentrations of the other two components are known. Therefore, it allows clinicians to determine, for example, what the pH must be when the P_{CO_2} and $[HCO_3^-]$ are known.† Note that when $[HCO_3^-]$ is normal, the Kassirer-Bleich equation demonstrates that $[H^+] = P_{CO_2}$, using their respective units of measure.

ACID PRODUCTION AND EXCRETION

The quantity of $[HCO_3^-]$ in relation to carbonic acid buffer in the system is not fixed, but varies according to physiologic need. This flexibility is largely provided by pulmonary exhalation of carbon dioxide (CO_2), which can vary significantly and change rapidly as required by alterations in the underlying acid-base status.

Renal Influence on Acid-Base Balance

The kidney regulates HCO_3^- excretion and the formation of new HCO_3^-. The rate of these processes is dependent on the underlying acid-base status. The renal response to pulmonary acid-base disturbances begins within 30 minutes of onset, but requires hours to days to achieve equilibrium.[13] Bicarbonate is filtered into the urine and must be reclaimed to maintain homeostasis. Eighty-five percent of bicarbonate that is filtered is reclaimed by the proximal convoluted tubule in a sodium-dependent process. H^+ is secreted into the tubular lumen, and Na^+ is absorbed from the tubular lumen into the cell. Sodium is then extruded from the tubular cell into the plasma in exchange for K^+ via the Na^+/K^+-ATPase pump. Thus, the H^+ secreted into the tubule combines with the filtered HCO_3^- in the lumen to produce carbonic acid (H_2CO_3), which in turn is converted to CO_2 and H_2O by carbonic anhydrase. The CO_2 diffuses down its concentration gradient into the tubule cell, where cytoplasmic carbonic anhydrase regenerates H_2CO_3, which then dissociates into HCO_3^- and H^+ (creating a supply of H^+ for extrusion). If tubular disease inhibits H^+ extrusion, a proximal renal tubular acidosis results, in which serum $[HCO_3^-]$ decreases to a steady-state level, i.e., reclaimed HCO_3^- effectively equals H^+ extrusion.

The balance (15%) of HCO_3^- reclamation occurs in the distal tubule via a sodium-independent process. Cytoplasmic carbonic anhydrase generates $H_2CO_3^-$, which dissociates. HCO_3^- diffuses into plasma, and H^+ is secreted into the lumen by an H^+-ATPase pump, thereby maintaining cellular electrical neutrality. H^+ is trapped in the lumen by inorganic phosphate or ammonia (NH_4^+). Failure of H^+ secretion is the underlying mechanism of distal renal tubular acidosis.

New HCO_3^- can also be created by the kidney. A sodium-dependent process allows synthesis of HCO_3^- in the distal tubule. Intracellular glutamine generates HCO_3^- and ammonia NH_4^+. The Na^+/K^+ pump moves Na^+ into the lumen, but Na^+ diffuses back across the cell membrane, and NH_4^+ is secreted into the lumen in exchange. The generated HCO_3^- remains in the cell. Formation of HCO_3^- by this process increases during acidosis, but may require 4 to 5 days to reach equilibrium. Drugs that alter uptake or delivery of Na^+ to the distal tubule can significantly alter HCO_3^- synthesis. The process of acid secretion allows the regeneration of HCO_3^- in proportion to the daily production of acid. Urine, especially under conditions of acidosis, can be made almost entirely without HCO_3^-.

$^{-\dagger}$The "bicarbonate concentration" measured by the clinical laboratory is actually the total CO_2, which is the sum of bicarbonate, dissolved CO_2, and H_2CO_3. H_2CO_3 is the P_{CO_2} multiplied by the solubility coefficient of CO_2 in blood (α), 0.03. Thus, total CO_2 = [HCO3] + (0.03) (P_{CO_2}). Most clinicians simply neglect the second term when the P_{CO_2} is normal; when hypercapnia is present, however, the second term measurably contributes to total CO_2.

FUNDAMENTAL ACID-BASE DISORDERS

Any condition that acts to increase [H^+]—whether through endogenous production, decreased buffering capacity, decreased excretion, or exogenous addition—is known as acidosis. Similarly, any condition that acts to decrease [H^+] is termed alkalosis. The terms acidemia and alkalemia refer to the net imbalance of [H^+] in the blood. The difference between acidosis and acidemia is not merely semantic, but of great clinical importance. For example, a patient with acidosis and alkalosis of equal magnitude will have a normal pH. A patient with these disturbances thus has neither acidemia nor alkalemia (resulting in the normal pH), but nevertheless has both acidosis and alkalosis. It is important to appreciate that, although acidemia is diagnostic of acidosis and alkalemia of alkalosis, a normal or high pH does not exclude acidosis and a normal or low pH does not exclude alkalosis.

Acid-base disturbances are further classified as respiratory or metabolic. Respiratory acid-base disorders are due to primary changes in P_{CO_2}, and metabolic acid-base disorders reflect primary changes in $[HCO_3^-]$. Compensatory mechanisms are, by definition, not "disorders," but rather normal physiologic responses to acid-base derangements. Terms such as compensatory respiratory alkalosis are therefore misleading. The clinician is nonetheless concerned with the adequacy of compensation, because failure of appropriate compensatory response implies the presence of another primary acid-base disturbance.

It is important to note that compensatory mechanisms return the pH toward normal but do not reach baseline.‡ The fact that compensatory mechanisms cannot reach completion is evident when one considers that complete compensation would necessarily remove the physiologic stimulus driving the compensation.[2]

The "normal" values of pH, P_{CO_2}, and $[HCO_3^-]$ for given laboratory ranges are intended to include 95% of patients without an acid-base disorder. The normal pH range is 7.35 to 7.45, the normal P_{CO_2} range is 35 to 45 mm Hg, and the normal $[HCO_3^-]$ is usually 21 to 28 mEq/L. However, a patient's values may all fall within the "normal range" and still have significant acid-base disturbances. As detailed further below, a patient with metabolic acidosis and a concomitant metabolic alkalosis of nearly approximate magnitude will have a "normal" pH, P_{CO_2}, and $[HCO_3^-]$. In contrast, abnormal values may be appropriate for a given simple acid-base disturbance. For example, in the presence of a metabolic acidosis where $[HCO_3^-] = 15$ and pH = 7.3, an appropriate respiratory compensation should result in a P_{CO_2} of about 30 mm Hg. This P_{CO_2} value is below the "normal" range, but at the expected level of physiologic respiratory compensation for the degree of metabolic acidosis. In this example, the finding of P_{CO_2} in the normal (35 to 45 mm Hg) range actually implies the presence of a respiratory acidosis, because the expected physiologic respiratory response is inadequate.

THE ANION GAP

The principle of electrical neutrality requires that plasma have no net charge. The charge of the predominant plasma cation, Na^+, must therefore be "balanced" by the charge of plasma anions. Although HCO_3^- and Cl^- constitute a significant fraction of plasma anions, the sum of their concentrations does not equal that of sodium. Therefore, there must be other anions present in the serum to maintain electrical neutrality. These anions are primarily serum proteins (albumin, phosphate, sulfate, and organic anions, such as lactate) and the conjugate bases of ketoacids. Because these substances are not commonly measured, they are termed unmeasured anions.

Unmeasured cations also exist, largely in the form of Ca^{2+} and Mg^{2+}. Because all cations (measured cations [MC] and unmeasured cations [UC]) must equal all anions (measured anions [MA] and unmeasured anions [UA]):

$$MC + UC = MA + UA \quad (3)$$

it follows that:

$$MC - MA = UA - UC = AG \quad (4)$$

Thus, substituting measured ions produces:

$$[Na^+] - ([HCO_3^-] + [Cl^-]) = AG \quad (5)$$

The unmeasured anion concentration is commonly called the anion gap (AG), i.e., the difference between the serum $[Na^+]$ and the sum of serum $[Cl^-]$ and $[HCO_3^-]$ equals the concentration of the unmeasured anions. The contribution of $[K^+]$, largely an intracellular ion, is usually neglected (although some hospital laboratories still include the $[K^+]$ as part of the reported AG value). For the purposes of AG determination, correction of serum $[Na^+]$ in the face of hyperglycemia is unnecessary, because this condition similarly dilutes $[Cl^-]$. The normal value of the AG is generally considered to be 12 ± 4 mEq/L, assuming no major deviations in expected concentration of unmeasured anions or cations. Reports have suggested that a normal AG value of 7 ± 4 mEq/L may be more appropriate to electrolyte measurements made with ion-specific electrodes.[14] However, normal range values used by the clinician should reflect institutional practice. As with other acid-base concepts, the accepted "normal" range for the AG is less important than whether it has changed in relation to the patient's steady-state baseline value. Thus, a relative change in the AG, referred to as the delta gap, may be more important than the actual AG value. Virtually all AG values above 15 mEq/L can be considered abnormal, even when there are no previous comparison values available.

The AG may change even in the absence of acid-base disturbances. It may rise when (unmeasured) cations decrease, as in severe states of hypomagnesemia, hypokalemia, and hypocalcemia. A reduced, narrow, or even negative AG may result from an increase in the concentration of unmeasured cations, such as lithium; unmeasured positively charged proteins resulting from myeloma and polyclonal gammopathies; or a significant decrease in unmeasured anions, such as albumin and γ-globulin. Albumin is a major component of the AG. Critically ill patients are frequently hypoalbuminemic, which may decrease the AG into the normal range, effectively masking the presence of a wide AG acidosis.[15] The AG should be corrected [$AG\text{-}Corr_{(albumin)}$][6,8] for an abnormal albumin level to improve the sensitivity of using the AG to identify a metabolic acidosis:[#]

$$\text{AG-Corr}_{(\text{albumin})} = \text{AG} + 0.25 \times ([\text{albumin}]_{\text{Reference}} - [\text{albumin}]_{\text{measured}}) \qquad (6)^{f}$$

A factitiously narrow or even negative AG may result from a number of conditions including measurement artifact. Bromide toxicity yields false elevations of chloride, unless Cl^- specific electrodes are used for detection;[**] triglyceride levels greater than 600 mg/dL falsely elevate chloride levels and lower sodium levels, resulting in an apparently narrow or even negative AG.[16] If these can be excluded, a narrow AG may imply an excess of unmeasured cations such as may occur with hypergammaglobulinemias and myeloma proteins.

Although increases in the AG are traditionally considered in the context of metabolic acidosis, elevation of the AG may be seen with other acid-base disturbances. Metabolic and respiratory alkalosis, for example, may elevate the AG by 2 to 3 mEq/L, due to elevations in lactate (an unmeasured anion) produced by enhancement of glycolysis.[††] Penicillin and carbenicillin, as unmeasured anions, produce elevations in the AG and may be accompanied by a hypokalemic alkalosis.

Elevations of the AG are usually clinically importance in the emergency setting and most commonly associated with metabolic acidosis (**Table 15–2**). Traditional mnemonics for the differential diagnosis of an elevated AG acidosis (MUDPILES, CAT MUDPILES, GOLDMARK, KARMEL, KUPIN, ACE GIFTs) can help the clinician recall elements of the differential diagnosis for this condition. However, these mnemonics leave the dangerous impression that lactic acidosis is a diagnostic endpoint for elevated AG acidosis. It is not. For example, propylene glycol, iron, seizures from isoniazid, carbon monoxide poisoning, and aspirin ingestions, as well as alcoholic ketoacidosis, may produce significant lactic acidosis. We suggest that the differential diagnosis of metabolic acidosis with an elevated AG should emphasize distinctions between endogenous and exogenous unmeasured anion sources and avoid mixing the etiology of lactic acidosis with that of other increased unmeasured anions. Some authors suggest correcting for lactate in patients known to have lactate elevations at baseline;[17,18] if lactate correction is calculated, the delta lactate should be used.

Table 15–2

Unmeasured Anions Associated with an Elevated Anion Gap and Metabolic Acidosis

Diagnostic Category	Anion Species	Origin	Diagnostic Adjuncts
Renal failure (uremia)	$[PO_4^{2-}]$, $[SO_4^{2-}]$	Protein metabolism	BUN/creatinine
Ketoacidosis	Ketoacids, lactate	Fatty acid metabolism	Serum/urine ketones
Diabetic	β-Hydroxybutyrate, lactate	Fatty acid metabolism	Specific test now available (older nitroprusside test yields false-negative result for β-hydroxybutyrate)
Alcoholic	Acetoacetate, lactate	Fatty acid metabolism	
Starvation			Consider coexistent dehydration
Lactic acidosis*	Lactate	Metabolism	Lactate level for subtypes
Sepsis	Lactate	Hypoperfusion, anaerobic metabolism	Culture/organism-specific tests
Cardiac arrest	Lactate	Hypoperfusion/reperfusion injury	Consider other acidosis

Diagnostic Category	Anion Species	Origin	Diagnostic Adjuncts
Liver failure	Lactate	Decreased lactate clearance	Liver function tests
Iron	Lactate	Disruption of cellular metabolism,	Serum iron level
Metformin	Lactate	Inhibition of gluconeogenesis	
Cyanide	Lactate	Mitochondrial dysfunction, histotoxic hypoxia	
Carbon monoxide	Lactate	Hypoxia, anaerobic metabolism	Carbon monoxide level
Thiamine deficiency	Lactate	Aerobic metabolism interrupted, lactate accumulates	Assess peripheral sensory and motor function for neuropathy
Exogenous poisoning*			
Methanol	Formate	Methanol metabolism	Osmolal gap
Ethylene glycol (EG)	Oxalate and organic anions	EG metabolism favors pyruvate conversion to lactate	Osmolal gap Oxalate crystals (urine)
Salicylate	Salicylate	Salicylate, lactate, ketoacids	Concomitant respiratory alkalosis and metabolic acidosis
Isoniazid	Lactate	Anaerobic metabolism, lactate accumulation	

*This is not an exhaustive list; several other causes exist.

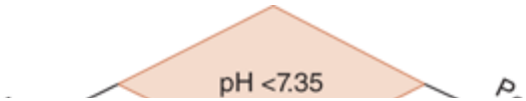
Clinical use of AG values requires an appreciation of their limitations. Although an AG greater than 30 mEq/L is usually caused by lactic acidosis or diabetic ketoacidosis, these conditions may exist even when the AG is normal.[19] Thus, a "normal" AG does not exclude the possibility of the presence of increased concentrations of unmeasured cations. An AG increased from baseline but still within the "normal" range may be a clue (delta gap). Direct measurements of lactate, formate (parent of formic acid), ketoacids, methanol, ethylene glycol (parent of oxalic acid and numerous other organic acids), and salicylate should be ordered when the presence of any of these substances is suspected, but the AG is "normal," (when a delta gap exists, or the AG is in the upper range of normal). Measurement of serum osmolarity and subsequent comparison to calculated serum osmolarity are necessary to detect small unmeasured molecules (such as toxic alcohols).[20] Finally, it is important to recognize that several concomitant causes of wide AG–type metabolic acidosis may be present.

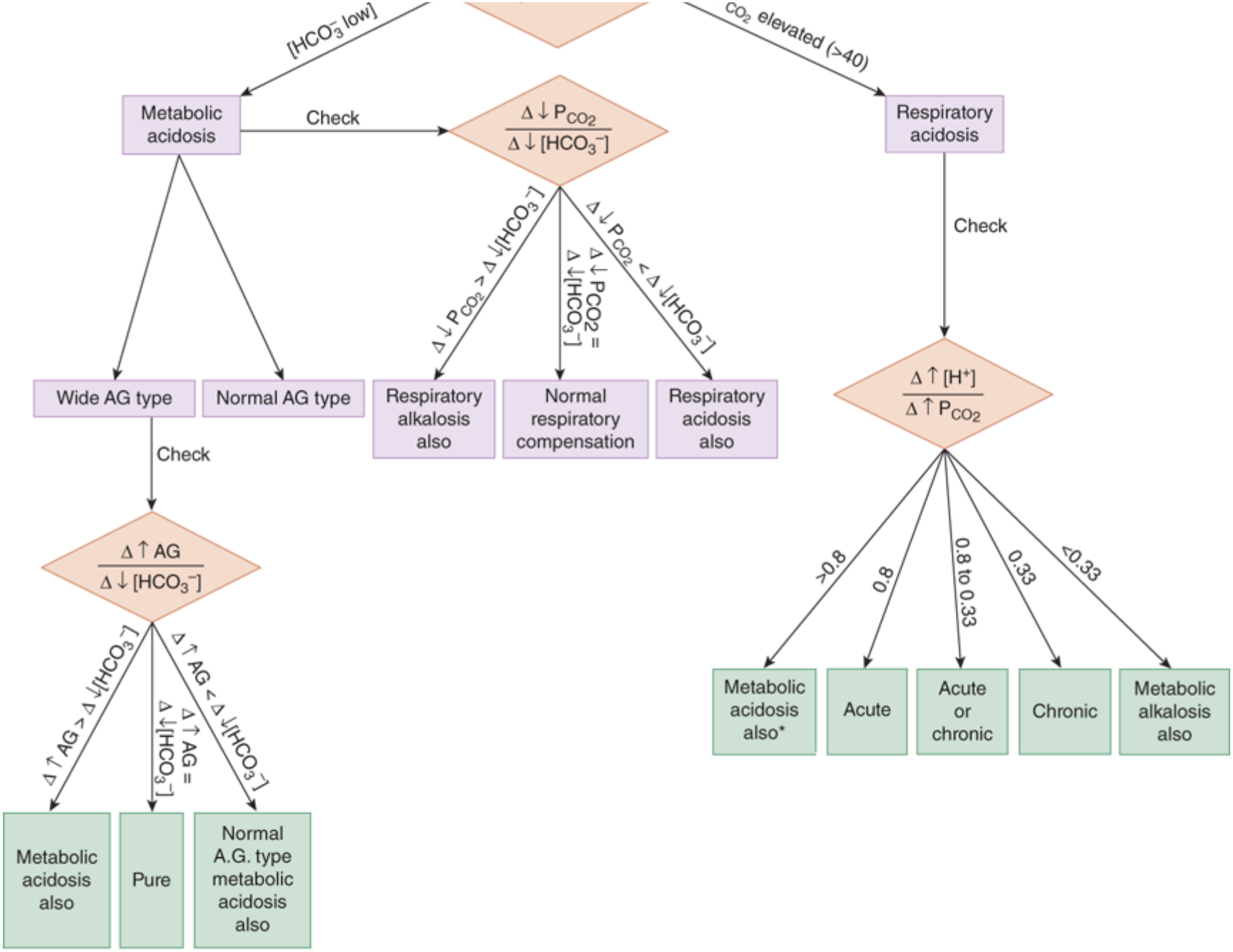
A common clinical problem is the diagnosis of mixed acid-base disturbances in the presence of an elevated AG. Simple acid-base disturbances that produce elevated AGs are referred to as wide AG metabolic acidoses. If a wide AG metabolic acidosis is the only disturbance, then the change (elevation from baseline) in value of the AG (the delta gap) should exactly equal the net decrease in the $[HCO_3^-]$. This is a one-to-one relationship. This concept is represented mathematically in Eq. (7).

$$\Delta \text{ increase in AG} = \Delta \text{ decrease in } [HCO_3^-] \qquad (7)$$

If the $[HCO_3^-]$ is lower than the value predicted by the delta AG, then there must be a concomitant hyperchloremic (i.e., normal AG type) metabolic acidosis (**Figure 15–2A**). Similarly, if the $[HCO_3^-]$ is higher than expected based on the delta AG, there must be a concomitant metabolic alkalosis present. Note that acute respiratory conditions (respiratory acidosis or alkalosis) do not affect these determinations, although chronic respiratory conditions may have substantial metabolic compensatory effects. Potential acid-base disturbances related to respiratory status must be further determined, as discussed below (**Figure 15–2A–C**).

FIGURE 15–2.
A. Algorithm for determination of type of acidosis and mixed acid-base disturbances when pH indicates acidemia. **B**. (next page) Algorithm for determination of type of alkalosis and mixed acid-base disturbances when pH indicates alkalemia. **C**. (next page) Algorithm to check for acid-base disturbances when pH is within the "normal" range.

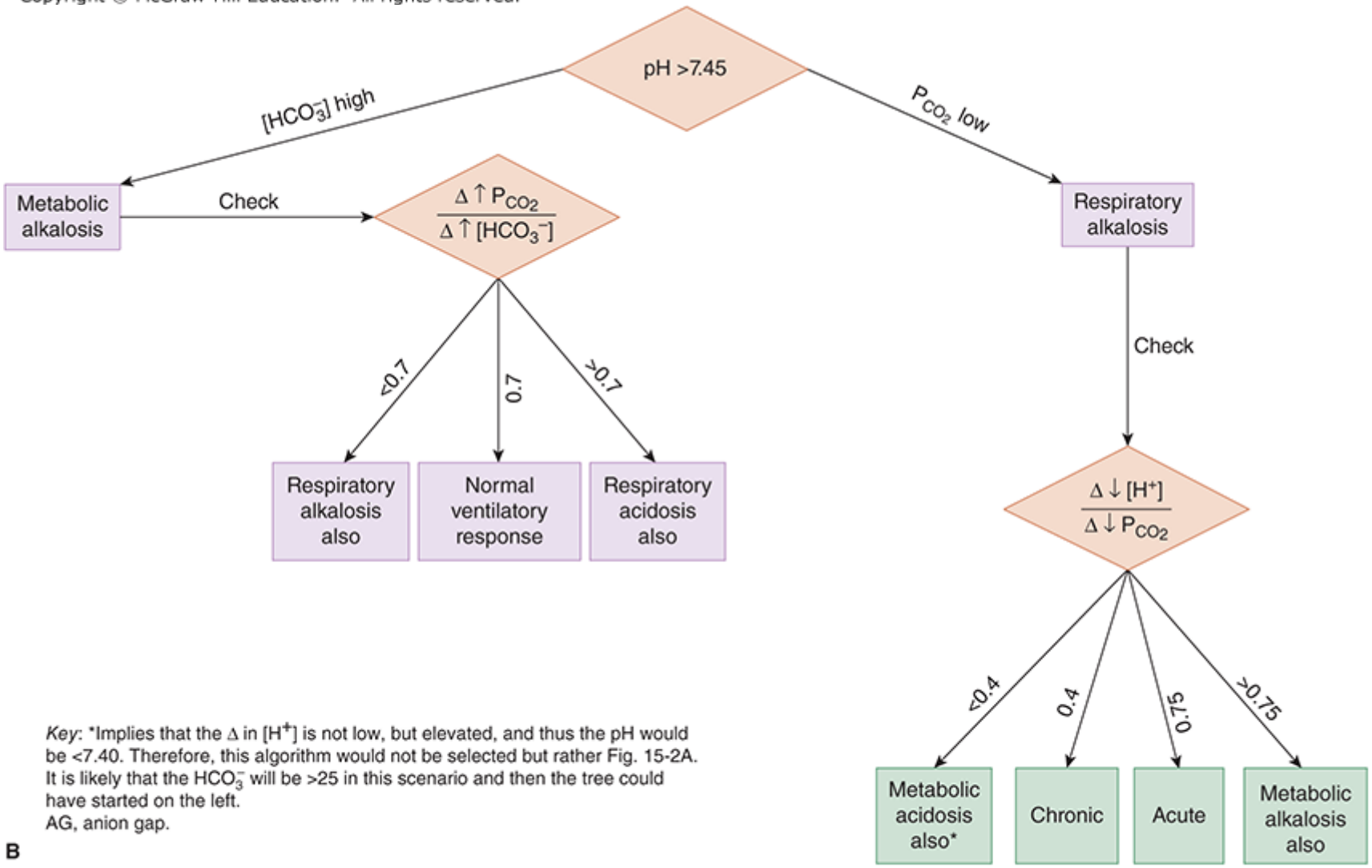




Key: * It is likely that $[HCO_3^-]$ is <25 in this scenario and the tree could have been started on the left.
AG, anion gap.

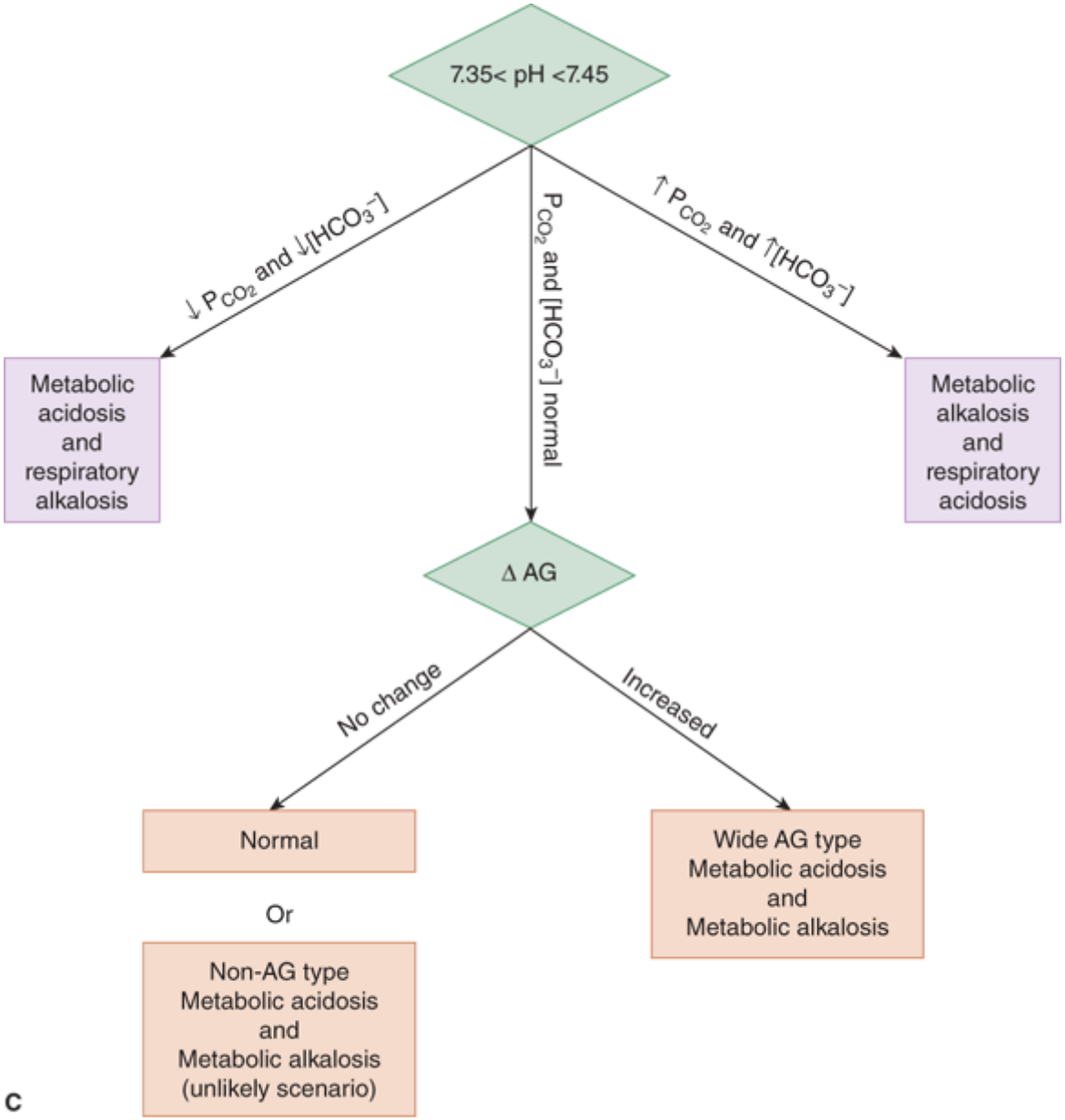
A

Source: J.E. Tintinalli, J.S. Stapczynski, O.J. Ma, D.M. Yealy, G.D. Meckler, D.M. Cline:



Key: *Implies that the Δ in $[H^+]$ is not low, but elevated, and thus the pH would be <7.40. Therefore, this algorithm would not be selected but rather Fig. 15-2A. It is likely that the HCO_3^- will be >25 in this scenario and then the tree could have started on the left.
AG, anion gap.

B



C

Source: J.E. Tintinalli, J.S. Stapczynski, O.J. Ma, D.M. Yealy, G.D. Meckler, D.M. Cline: Tintinalli's Emergency Medicine: A Comprehensive Study Guide, 8th Edition
www.accessmedicine.com

PARAMETERS REQUIRED FOR CLINICAL ACID-BASE EVALUATION

When taking a medical history, one should emphasize events that may result in the gain or loss of acid or base, such as vomiting, diarrhea, medications, or ingestions of toxins, and seek evidence of dysfunction of the organs of acid-base homeostasis—the liver, kidneys, and lungs.

Laboratory evaluation requires blood samples for determination of blood gases (pH, P_{CO_2}, and [HCO_3^-]), electrolytes ([Na^+], [K^+], [Cl^-], and [HCO_3^-]), and other factors that affect the patient's acid-base status (albumin, lactic acid, creatinine, BUN, drug levels of suspected ingestions such as salicylate). Based on current history and physical and past medical history, consider the need for calcium, magnesium, phosphate, serum ketones and glucose, serum osmolality, and urine electrolytes, osmolality, and glucose. Most clinical laboratories measure two of the parameters reported in blood gas results (most commonly the pH and P_{CO_2}) and use the Henderson-Hasselbalch equation to calculate the third ([HCO_3^-]).

Blood samples for acid-base evaluation were historically obtained by arterial puncture, but there is increasing evidence that, in many clinical situations, venous or capillary blood may be used instead.[21] Venous P_{CO_2} may be a sensitive screen for hypercarbia (cutoff 45 mm Hg), but the venous and arterial P_{CO_2} values exhibit wide variation and are not interchangeable.[22] With increasing attention to early goal-directed therapy, point-of-care venous lactate levels are useful to screen for hyperlactatemia.[23] Confirming an elevated venous lactate with an arterial sample[24] is not necessary.[22,23]

Inexperienced clinicians frequently resort to arterial blood gas (ABG) determination as a means to determine the pH. However, **the pH per se is often the least important value for diagnosis and management**. When respiratory status is not compromised (which should be presumed only with caution), the pH can be calculated with the aid of the Kassirer-Bleich equation [see Eq. (2)] from the venous [HCO_3^-] alone, as described below.

‡The sole exception is in chronic respiratory alkalosis, where bicarbonate levels may decline to a level that nearly normalizes the pH, such that differentiating the actual pH from normal falls within the range of laboratory error.

#This correction is generally not of clinical importance in emergency medicine because even a large decrease in albumin will have negligible effect on the anion gap and the delta gap, particularly in patients with severe acidosis.

fFor SI units (g/L); if the lab reports g/dL, the factor is increased 10-fold, i.e., 2.5 × Δ albumin.

**Other techniques cause reactions where bromide is falsely read as chloride.

††This form of lactate is not associated with acid production as occurs with states resulting in anaerobic metabolism.

METABOLIC ACIDOSIS

Metabolic acidosis may result from HCO_3^- loss, administration or ingestion of acid, or endogenous production and accumulation of acid. Loss of HCO_3^- occurs by externalization of intestinal contents (e.g., vomiting, enterocutaneous fistulae) and renal wasting of bicarbonate (e.g., renal tubular acidosis, carbonic anhydrase inhibitor therapy). Administration of acid, unlikely to be seen in the ED, occurs primarily with total parenteral nutrition, whereby patients receive hydrochloric salts of basic amino acids. Endogenous acids accumulate in renal tubular acidosis, ketoacidosis, and lactic acidosis. Acidosis from rapid infusion of normal saline, called dilutional acidosis, has been shown to involve endogenous accumulation from CO_2 hydration.[25]

Unopposed metabolic acidosis results in a decreased serum $[HCO_3^-]$ and an increase in serum $[H^+]$. The increased $[H^+]$ stimulates the respiratory center, resulting in increased minute ventilation. The physiologically based "respiratory compensation" is an attempt to lower the $[H^+]$ by a reduction in P_{CO_2} through increased ventilation. The steady-state relationship between the P_{CO_2} and the $[HCO_3^-]$ is shown in Eq. (8).‡‡ [12]

$$P_{CO_2} = (1.5 \times [HCO_3^-] + 8) \pm 2 \qquad (8)$$

While equation (8) expresses the steady-state values after 24 hour of metabolic acidosis, the respiratory response is almost immediate. When $[HCO_3^-]$ is greater than ~8 mEq/L, the relationship between P_{CO_2} and $[HCO_3^-]$ is simpler. With normal respiratory compensation, P_{CO_2} decreases by 1 mm Hg for every 1 mEq/L net decrease in $[HCO_3^-]$. Using these relationships allows the clinician to calculate the expected P_{CO_2} from the measured $[HCO_3^-]$, assuming respiratory compensation is normal. If the expected P_{CO_2} value differs from the measured value in steady-state metabolic acidosis, then respiratory compensation is compromised, and a primary respiratory disorder exists in conjunction with the metabolic acidosis. As an example, if the $[HCO_3^-]$ is 15 mEq/L, the expected P_{CO_2} is ~30 mm Hg. If the actual measured value is higher than expected (e.g., 35 mm Hg), then by definition there is a concomitant respiratory acidosis (Figure 15–2A). If the measured value is lower than expected (e.g., 25 mm Hg), then there is a concomitant respiratory alkalosis. This latter

case is not an example of overcompensation, but rather a second, simultaneous primary acid-base disturbance. These are important concepts. The body cannot tolerate metabolic and respiratory mechanisms for acidosis simultaneously, as one cannot buffer or compensate for the other.

Physiologic studies of otherwise healthy persons with acute metabolic acidosis caused by diarrhea found that the completeness of the respiratory response to metabolic acidosis depends on the duration of the acidosis, the time course of its development, and its severity. When $[HCO_3^-]$ is held constant, steady-state P_{CO_2} is reached in 11 to 24 hours. When acidosis develops slowly, there is no lag in respiratory compensation. If acidosis develops more quickly, the P_{CO_2} is often higher than values observed in steady state; the more rapid and severe the acidosis, the larger is the difference between the observed P_{CO_2} and the predicted steady-state CO_2. The delay in full compensation again indicates the presence of concomitant respiratory acidosis, and the clinician must recognize the contribution of inadequate ventilation to the level of acidosis (e.g., $[H^+]$). Thus, in the ED setting, the delay in reaching steady state is of passing interest as the labs results signify the reality of the moment. Unfortunately, the ED patient's illness can rarely be assumed to be in steady state.

There are limits to the adequacy of respiratory compensation during metabolic acidosis. Respiratory minute volume actually declines when pH decreases below 7.10. This finding has led clinicians to initiate bicarbonate therapy when pH falls below 7.10. It is particularly important to appreciate any contribution to the acidosis from inadequate respiratory response. Administration of HCO_3^- in the presence of hypoventilation may exacerbate the respiratory acidosis, because the HCO_3^- converts to CO_2 and H_2O.

The development of metabolic acidosis that drives the pH below 7.10 is likely associated with a very high risk of inadequate ventilation response, since there is a limit to respiratory compensation. The lowest P_{CO_2} level achievable is ~12 mm Hg. This lower limit in obtainable P_{CO_2} is due to resistance in airflow and increased CO_2 generated by the exertion required for rapid ventilation, both offsetting the ventilator exhalation of CO_2. The superimposition of respiratory acidosis on a patient in such a condition will result in a rapid decline of pH to levels at which organ function drops and pharmacotherapy will fail. Mechanical ventilation usually should be instituted in such situations to ensure the ventilatory rate and volume are sufficient to prevent an increase in P_{CO_2} at this critical time.

The serum $[K^+]$ level is affected by metabolic acidosis. The movement of H^+ into cells is associated with extrusion of K^+. Changes in $[K^+]$ are more substantial during inorganic acidosis, although elevated serum $[K^+]$ is typically seen in diabetic ketoacidosis. In general, for each 0.10 change in the pH, serum $[K^+]$ will change by approximately 0.5 mEq/L, in an inverse relationship. Whatever the mechanism of

the acidosis, it is important to remember that normal values as well as low serum [K^+] likely reflect severe intracellular K^+ depletion. As the acidosis is corrected, serum [K^+] should fall, possibly to levels that may produce clinical symptoms, dysrhythmias, and other adverse outcomes.

CLINICAL FEATURES AND PHYSIOLOGIC CONSEQUENCES OF ACIDOSIS

Symptoms of the primary disorder causing metabolic acidosis dominate the clinical presentation; however, several symptoms are common to various etiologies. Patients may complain of abdominal pain, headache, nausea with or without vomiting, and generalized weakness, and because acidosis stimulates the respiratory center, the patient may complain of dyspnea.

Acidemia has numerous negative physiologic consequences that impair the function of enzymes as well as many different organs through mechanisms not yet well understood. Cardiac contractile function is reduced, likely due to impaired oxidative phosphorylation, intracellular acidosis, and alterations in intracellular calcium concentrations. The threshold for ventricular fibrillation falls as the defibrillation threshold rises. Hepatic and renal perfusion and systemic blood pressure decline, and pulmonary vascular resistance increases. The physiologic effects of catecholamines are attenuated, and when acidosis is sufficiently severe, vascular collapse may result. A catabolic state develops, including a generalized increase in metabolism, resistance to insulin, and inhibition of anaerobic glycolysis. The effect of hypoxia on all organs is aggravated.[26]

CAUSES OF METABOLIC ACIDOSIS

The causes of elevated AG metabolic acidosis are listed in Table 15–2. A comparison with the patient's steady-state AG should be made whenever possible. Measurement and detection of specific anions may be indicated.

Differential Diagnosis of Wide AG Acidosis

The differential diagnoses to be considered in emergency practice fall into four broad categories: renal failure (uremia), ketoacidosis (diabetic ketoacidosis, alcoholic ketoacidosis, starvation ketoacidosis), lactic acidosis, and ingestions (methanol, ethylene glycol, salicylates, and many others).

Renal failure should be evident from the serum chemistries. Acidosis seen in initial stages of renal failure may be severe, but tends to be stable, with [HCO_3^-] ~15 mEq/L in cases of chronic renal failure.

Positive serum ketones point to one of the ketoacidoses. In instances of known insulin-dependent diabetes mellitus, diabetic ketoacidosis is likely, although there is usually a component of lactic acidosis. In alcoholics who have recently stopped heavy drinking, alcoholic ketoacidosis should be considered; ketoacids contribute far less to the acidosis in ketoacidosis than lactate. Starvation ketosis will be found in patients with recent oral intake that is inadequate, such as in cases of fasting, dieting, or protracted vomiting, although the magnitude of acid-base disturbance in starvation ketosis should be small. The major ketone present in the serum of a patient with untreated diabetic or alcoholic ketoacidosis may be β-hydroxybutyrate. A specific test is now available. The older nitroprusside test yields a false-negative result for β-hydroxybutyrate. See chapter 223, "Type 1 Diabetes Mellitus for a detailed discussion.

Lactic acidosis occurs whenever lactate production exceeds lactate metabolism and is classified into two types. The first, in which tissue hypoxia is present and lactate production is elevated, is referred to as **type A**. Normal tissue oxygenation and impairment of lactate metabolism define the second, called **type B**. Severe acidosis that is resistant to treatment is seen in various type B lactic acidoses and ingestions. **Lactic acidosis is not a diagnosis, but a syndrome with its own differential diagnosis**. Causes of lactic acidosis include renal failure, shock, sepsis, cardiac arrest, trauma, seizures, tissue ischemia, diabetic ketoacidosis, thiamine deficiency, malignancy (e.g., leukemia), liver dysfunction, genetic disorders (e.g., metabolic diseases), toxins (e.g., methanol), and medications (e.g., metformin, salicylates, iron, isoniazid) (Table 15–2).

Lactate levels should be measured and accounted for in an adjustment of the AG. Ethanol is frequently cited as a cause of wide AG acidosis, but **ethanol should never be considered the etiologic source of any significant metabolic acidosis**; look for other causes. Although ethyl alcohol metabolism may lead indirectly to very mild lactic acidosis, usually due to the same mechanism as alcoholic ketoacidosis, in which lactic acidosis is more substantial, neither the alcohol nor its metabolites directly contribute to the acidosis.

Determination of the osmolal gap will help identify methanol and ethylene glycol from other etiologies. Although methanol is measured in most hospital laboratories, determination of ethylene glycol levels is performed off-site in many institutions. A widened osmolal gap without clear evidence of methanol ingestion may determine the diagnosis long before confirmatory laboratory evidence is available. Calculated adjustments to the osmolal gap may need to be made if ethanol is a co-ingestant (see chapter 185, "Alcohols" for detailed discussion).

Concomitant acid-base disturbance may further assist in determining the etiology. The triple acid-base disturbance of wide AG metabolic acidosis, metabolic alkalosis, and respiratory alkalosis is seen with sepsis (lactic acidosis) and salicylate poisoning. The latter also may be associated with a mild temperature elevation.

The relation of [HCO_3^-] to the AG and the [HCO_3^-] to the expected P_{CO_2} compensation must be examined in every patient with wide AG acidosis to determine whether other acid-base disturbances, metabolic or respiratory, exist (Figure 15–2A).

Differential Diagnosis of Unchanged (Normal) AG Acidosis

The non-AG type of acidosis is often referred to as "normal" AG acidosis.[3] Some texts refer to this as **hyperchloremic metabolic acidosis**, but not all cases of normal AG acidosis are associated with hyperchloremia. If the patient has hyponatremia with a normal AG acidosis, the chloride may be in the normal range. Abnormal chloride levels alone usually signify a more serious underlying metabolic disorder, such as metabolic acidosis (elevated chloride) or metabolic alkalosis (low chloride).[27]

Normal AG acidosis results from loss of HCO_3^-, failure to sufficiently excrete H^+, or administration of H^+. Bicarbonate may be lost from the urine or GI tract and is usually accompanied by K^+ loss. However, potassium-sparing diuretics, hypoaldosteronism, urinary tract obstruction, and type IV renal tubular acidosis result in loss of HCO_3^- with retention of K^+ (**Table 15–3**). Acetazolamide exerts its effect through carbonic anhydrase inhibition, inducing a functional renal tubular acidosis.

Table 15–3

Causes of Normal Anion Gap Metabolic Acidosis

With a Tendency to Hyperkalemia	With a Tendency to Hypokalemia
Subsiding diabetic ketoacidosis	Renal tubular acidosis, type I (classical distal acidosis)
Early uremic acidosis	Renal tubular acidosis, type II (proximal acidosis)
Early obstructive uropathy	Acetazolamide
Renal tubular acidosis, type IV	Acute diarrhea with losses of HCO_3^- and K^+
Hypoaldosteronism (Addison's disease)	Ureterosigmoidostomy with increased resorption of $[H^+]$ and $[Cl^-]$ and losses of HCO_3^- and K^+
Infusion or ingestion of HCl, NH_4Cl, lysine-HCl, or arginine-HCl	Obstruction of artificial ileal bladder
Potassium-sparing diuretics	Dilution acidosis (may occur with 0.9% NaCl infusion)

One should be wary of traditional classification based on $[K^+]$, because serum $[K^+]$ itself is dependent on the actual pH. Thus, in severe acidosis, a normal range $[K^+]$ value may be falsely reassuring. As the acidosis is corrected and acidemia resolves, the $[K^+]$ will concordantly fall.

Because all diuretics may cause a contraction alkalosis, the metabolic acidosis that occurs simultaneously with potassium-sparing diuretics may not be evident, as the two may simply cancel each other out (Figure 15–2C). Because the AG is unchanged, there is no indication that two distinct opposing processes may be occurring. As with wide AG–type acidosis, **the expected P_{CO_2} compensation**

must be examined in every patient with normal AG acidosis to determine whether other respiratory acid-base disturbances exist (Figure 15–2A).

TREATMENT

The treatment of acidosis reflects that of the underlying disorder but particularly emphasizes restoration of normal tissue perfusion and oxygenation. The most important step is to determine whether there is a respiratory component to the acidosis (i.e., a primary respiratory acidosis), because the treatment approach differs. If there is inadequate respiratory compensation, the most appropriate treatment will be to first correct the respiratory problem. Address electrolyte disturbances, administer antidotes for toxins as appropriate, and initiate treatment for underlying causes such as sepsis (see chapter 150, "Toxic Shock Syndromes") or diabetic ketoacidosis (see chapter 225, "Diabetic Ketoacidosis").

Buffer Therapy in Acidosis

Slow replacement of sodium bicarbonate in patients with sodium bicarbonate loss due to diarrhea or proximal renal tubular acidosis is useful.[28] The adverse effects of acidemia make the concept of buffer therapy teleologically appealing, but its role in instances of cardiac arrest and severe metabolic acidosis is unclear. A small 2013, single-center, randomized controlled trial showed mortality benefit in the treatment of sepsis patients; this study needs confirmation.[29] The traditional therapeutic buffer, sodium bicarbonate, may have negative effects in the treatment of acidosis. Bicarbonate therapy results in the generation of significant quantities of CO_2, which diffuses readily into cells, in particular those of the CNS, which may cause paradoxical worsening of intracellular acidosis. An abrupt CO_2 increase may exceed the ventilatory capacity of a patient already at maximum minute ventilation, thereby producing abrupt and worsening respiratory acidosis. After successful treatment with bicarbonate, "overshoot" alkalosis may result. Bicarbonate therapy imposes an osmotic and sodium load (1000 mEq/L of typical 1 N solution). These concerns suggest that bicarbonate therapy should not be used in the ED treatment of mild to moderate metabolic acidosis.

Concerning use of buffer therapy for cardiac arrest, diabetic ketoacidosis, and lactic acidosis, several studies of HCO_3^- use in adult and pediatric cases, including patients with severe acidosis, failed to show any improvement in speed of recovery or decrease in complication rates with buffer therapy.[26,28,30,31,32,33] There has been some suggestion of harmful effects, particularly an increased rate of development of cerebral edema in pediatric patients with diabetic ketoacidosis who were treated with bicarbonate. However, it

remains unclear whether certain subgroups of patients (for example, those with cardiac or other disease) may benefit from bicarbonate therapy and dialysis.

The goal of bicarbonate and dialysis therapy in lactic acidosis may be to "bridge" the patient physiologically to definitive treatment of the etiology of the acidosis. Bicarbonate therapy may be appropriate for limited indications (**Table 15–4**).[26,28,30,31,32,33,34]

Table 15–4

Potential Indications for Bicarbonate Therapy in Metabolic Acidosis

Indication	Rationale
Severe hypobicarbonatemia (<4 mEq/L)	Insufficient buffer concentrations may lead to extreme increases in acidemia with small increases in acidosis.
Severe acidemia (pH <7.00 to 7.15)* in cases of wide anion gap acidosis, with signs of shock or myocardial irritability that has not responded to supportive measures including adequate ventilation and fluid resuscitation as indicated by the patient's clinical characteristics	Therapy for the underlying cause of acidosis depends on adequate organ perfusion.
Severe hyperchloremic acidemia†	Lost bicarbonate must be regenerated by kidneys and liver, which may require days.

*Presented as a range because recommendations differ among authors; data do not support a specific threshold for treatment.

†No specific threshold indication by pH exists. The presence of serious hemodynamic insufficiency despite supportive care should guide the use of bicarbonate therapy for this indication.

When given, HCO_3^- can be dosed 0.5 mEq/kg for each milliequivalent per liter rise in [HCO_3^-] desired.[26] The goal is to restore adequate buffer capacity ([HCO_3^-] >8 mEq/L) or to achieve clinical improvement in shock or dysrhythmias. Bicarbonate should be given as slowly as the clinical situation permits. Seventy-five milliliters of 8.4% sodium bicarbonate in 500 mL of dextrose 5% in water produces a nearly isotonic solution for infusion. Adequate time should be allowed for the desired effect to be achieved, and close monitoring of acid-base balance, especially in patients with organic acidosis, is critical. Other buffers appeared promising in the treatment of metabolic acidosis during early studies but have failed to provide improvement in clinical outcomes, including carbicarb, and tris-hydroxymethyl amino-methane.

–‡‡The constants in this equation (P_{CO_2} = 1.54 × [HCO_3] + 8.36 ± 2) have been rounded for ease of use.

METABOLIC ALKALOSIS

Metabolic alkalosis is typically classified as chloride-sensitive and chloride-insensitive, thus indicating the treatment approach. Metabolic alkalosis results from gain of bicarbonate or loss of acid. The relation of metabolic alkalosis to chloride balance defines pathophysiologic features of the disease and its therapy.

CLINICAL FEATURES AND PHYSIOLOGIC CONSEQUENCES OF ALKALOSIS

Symptoms of the primary disorder causing metabolic alkalosis dominate the clinical presentation; however, several symptoms are common to various etiologies. Patients may complain of generalized weakness, dizziness, myalgia, palpitations, nausea with or without vomiting, paresthesias, and possibly muscle spasm or twitching.

The physiologic effects of alkalemia are substantial. Neurologic abnormalities, especially tetany, neuromuscular instability, and seizures, are common. Reduction in [H^+] results in reductions in ionized calcium, potassium, magnesium, and phosphate levels. Serum proteins, largely polyanionic, buffer H^+; with rapid acid loss, such as that which occurs in respiratory alkalosis, the newly available buffer capacity of those proteins binds calcium and other cations instead. Constriction of arterioles occurs, resulting in reduced coronary and cerebral blood flow. Refractory dysrhythmias may develop.[26] Alkalemia may be of particular concern in patients with chronic obstructive pulmonary disease, because of the shift of the oxygen-hemoglobin dissociation curve to the left, which makes O_2 less available to the tissues. Many patients with chronic obstructive pulmonary disease take diuretics, which lead to a contraction alkalosis. Additionally, the alkalemic environment tends to further depress ventilatory drive.

CAUSES OF METABOLIC ALKALOSIS

Bicarbonate and chloride represent the major serum anions whose concentrations may be readily altered, and their homeostasis is therefore closely intertwined. Conditions that result in chloride loss, such as vomiting (which also causes acid loss), diarrhea, diuretic therapy, and chloride-wasting diseases (e.g., cystic fibrosis and chloride-wasting enteropathy), tend to reduce serum chloride concentration and extracellular volume. The reduction in extracellular volume increases mineralocorticoid activity, which enhances sodium reabsorption and potassium and hydrogen ion secretion in the distal tubule, which in turn enhance bicarbonate generation. The resulting increase in serum [HCO_3^-] eventually exceeds the tubule's maximum ability to reabsorb filtered bicarbonate. The resulting urine is alkaline, and because its anionic content is mostly bicarbonate, it is largely free of chloride (<10 mEq/L). (Nevertheless, the urine chloride may be normal when diuretics are administered.) The result is hypokalemic, hypochloremic alkalosis that responds to normal saline (chloride-responsive alkalosis).

Other diseases that cause metabolic alkalosis are usually associated with normovolemia or hypervolemia and often include hypertension. These diseases usually cause excess mineralocorticoid activity, resulting in the same pathophysiologic cascade described above. However, the excess mineralocorticoid activity is not associated with hypovolemia, so the urine chloride is generally normal or elevated (>10 mEq/L) and the alkalosis cannot be reversed with normal saline. Conditions producing "chloride-unresponsive alkalosis" and hypertension include renal artery stenosis, renin-secreting tumors, adrenal hyperplasia, hyperaldosteronism, Cushing's syndrome, Liddle's syndrome, and exogenous mineralocorticoids (e.g., licorice, fludrocortisone). Chloride-unresponsive alkalosis caused by Bartter's and Gitelman's syndromes is usually associated with normotension.

The compensation for metabolic alkalosis involves reduction in alveolar ventilation, but the exact relation between P_{CO_2} and [H^+] is not well established. Most studies to date have been conducted in dialysis patients or patients with conditions that predispose to alveolar hyperventilation (e.g., sepsis, pneumonia). As a guideline, P_{CO_2} in patients with significant metabolic alkalosis should rise by 0.7 mm Hg for each milliequivalent increase in [HCO_3^-]. The P_{CO_2} also rarely rises above 55 mm Hg in compensation for metabolic alkalosis.

TREATMENT

As with all acid-base disorders, therapy of alkalemia emphasizes treatment of the underlying cause with careful supportive care. In the emergency setting, metabolic alkalosis rarely requires active management. Acetazolamide produces significant bicarbonaturia and is effective in the treatment of metabolic alkalosis, but its use requires very careful monitoring of potassium, magnesium, and phosphate

concentrations. If alkalosis is severe ([HCO_3^-] >45 mmol/L) and associated with serious signs or symptoms not responsive to supportive care, the use of intravenous hydrochloric acid should be considered. A 0.1 normal solution (100 mmol/L) should be used, infused ideally at 0.1 mmol/kg/h but at no more than 0.2 mmol/kg/h through a central venous catheter. Higher concentrations may degrade the catheter material. An infusion rate of 100 mL/h of 0.1 N solution provides about 10 mmol/h. The dose is calculated using ideal body weight as shown in Eq. (9), with the result in mmol H^+ required.

$$\text{Dose} = (\Delta[HCO_3^-]) * 0.5 \text{ weight, in kg} \quad (9)$$

RESPIRATORY ACIDOSIS

Respiratory acidosis is defined by alveolar hypoventilation and is diagnosed when the P_{CO_2} is greater than the expected value. Acute respiratory acidosis may have origins in other conditions, such as increased CO_2 production (high-glucose diet) and abnormal gas exchange (e.g., pneumonia). However, the final common path is inadequate ventilation.

Inadequate minute ventilation most frequently results from head trauma, chest trauma, lung disease, or excess sedation. The chronic hypoventilation seen in extremely obese patients is often referred to as the **pickwickian syndrome**. Patients with severe chronic obstructive pulmonary disease have increased dead space and frequently also have decreased minute ventilation.

In general, a rise in the P_{CO_2} stimulates the respiratory center to increase respiratory rate and minute ventilation. However, if the arterial P_{CO_2} chronically exceeds 60 to 70 mm Hg, as may occur in 5% to 10% of patients with severe emphysema, the respiratory acidosis may depress the respiratory center. Under such circumstances, the stimulus for ventilation is provided primarily by hypoxemia acting on chemoreceptors in the carotid and aortic bodies. Giving oxygen could remove the main stimulus to breathe, causing the P_{CO_2} to rise abruptly to extremely dangerous levels. Consequently, when administering oxygen to patients with COPD, careful monitoring for the development of apnea or hypoventilation is required; however, do not withhold oxygen from a patient with severe dyspnea for fear of worsening hypercarbia. Evaluation of ventilation requires attention to several important clinical issues. First, the ventilation that would be expected based on assessment of the respiratory rate and depth should be compared with the actual ventilation of the patient (i.e., P_{CO_2}). A "normal" P_{CO_2} of 40 mm Hg in a tachypneic, dyspneic patient likely reflects significant ventilatory insufficiency. Second, the impact of respiratory acidosis on partial pressure of oxygen in the alveoli (P_{AO_2}) in such a patient may be considerable. The alveolar gas

equation suggests that if inspired oxygen concentration and respiratory quotient do not change, increases in P_{CO_2} will result in reductions in P_{AO_2}.

The relation of P_{CO_2} to hydrogen ion concentration in acute respiratory acidosis derived from the Kassirer-Bleich equation shown in Eq. (10):

$$\Delta[H^+] = 0.8\ (\Delta P_{CO_2}) \qquad (10)$$

Each 1-mm Hg increase in P_{CO_2} results in a 1-mmol increase in $[H^+]$. Across the linear portion of the pH-hydrogen ion concentration relationship, each 1-mm Hg increase in P_{CO_2} should theoretically produce a 0.01 decrease in pH. The actual relation between changes in P_{CO_2} (up to values of 90 mm Hg) and changes in $[H^+]$ determined in normal humans is about 8 to 10, as shown in Eq. (10). Thus, a 10-mm Hg increment in P_{CO_2} produces an 8-mmol increase in $[H^+]$, with little change in bicarbonate concentration (usually 1 mEq/L) or urinary acid excretion. If the $[H^+]$ is higher or lower than that suggested by the change in the P_{CO_2}, a mixed disorder is present.

The adaptation to chronic respiratory acidosis is complex. Over time, chronic elevation of P_{CO_2} reduces carotid sinus sensitivity to hypercapnia, and ventilatory drive is then controlled by PAO_2. The acidosis results in significant increases in renal HCO_3^- generation and avid reclamation of filtered HCO_3^-. The relation between $[H^+]$ and $[HCO_3^-]$ in chronic respiratory acidosis at steady state, derived from studies in humans, is shown in Eq. (11).

$$\Delta[H^+] = 0.3 * (\Delta P_{CO_2}) \qquad (11)$$

It is frequently uncertain whether a patient has an acute respiratory acidosis, a chronic respiratory acidosis, or a mixed disorder. Evaluation of the acid-base status in such circumstances does not require "baseline" arterial blood gas values. Instead, the change in $[H^+]$ is compared with the change in P_{CO_2}. If this ratio is 0.3, the patient has a chronic respiratory acidosis; if it is 0.8, the patient has an acute respiratory acidosis. Other ratios suggest a mixed acid-base disturbance, as shown in **Table 15–5**.

Table 15–5

Evaluation of Acid-Base Status in Respiratory Acidosis

Ratio = $\Delta[H^+]/\Delta P_{CO_2}$				
Ratio < 0.3	**Ratio = 0.3**	**0.3 < Ratio < 0.8**	**Ratio = 0.8**	**Ratio > 0.8**
Change in hydrogen ion concentration is less than accounted for by chronic change in P_{CO_2}. Metabolic alkalosis is also present.	Change in hydrogen ion concentration matches chronic change in P_{CO_2}. Chronic respiratory acidosis is present.	Change in hydrogen ion concentration is larger than accounted for by chronic change in P_{CO_2}. Chronic respiratory acidosis plus either acute respiratory acidosis or metabolic acidosis is present; examine pH.	Change in hydrogen ion concentration matches acute change in P_{CO_2}. Acute respiratory acidosis is present.	Change in hydrogen ion concentration is larger than accounted for by acute or chronic change in P_{CO_2}. Metabolic acidosis is also present.

Abbreviation: P_{CO_2} = partial pressure of carbon dioxide.

TREATMENT

Treatment of respiratory acidosis is designed primarily to improve alveolar ventilation. In general, if the minute ventilation is doubled, the P_{CO_2} will be reduced by 50%. In patients with chronic obstructive pulmonary disease, bronchodilators such as β-agonists, anticholinergics, or systemic sympathomimetic agents, with careful administration of small amounts of oxygen, may substantially improve ventilation. However, ventilatory assistance (intubation or noninvasive ventilatory support) may be required in some patients who do not respond adequately to lesser measures, particularly if the pH falls below 7.25.

In patients with a chronic respiratory acidosis, reduction of the P_{CO_2} should generally proceed slowly. The minute ventilation for a 70-kg person is normally about 6 L/min; in chronic obstructive pulmonary disease patients, it may be less than 4 L/min. It is beyond the scope of this chapter to discuss in detail the approach to management of a patient with chronic obstructive pulmonary disease and severe

hypercarbia. If treatment is indicated in the ED, it may be wise to start with a minute ventilation of about 5 L/min and then gradually increase it according to the clinical response and changes in P_{CO_2}.

In patients with a chronic respiratory acidosis, the arterial P_{CO_2} should not be reduced by more than 5.0 mm Hg/h. Rapid correction of a chronic respiratory acidosis can cause sudden development of a severe combined metabolic and respiratory alkalosis, with resulting dysrhythmias. A rapid rise in pH can cause an abrupt fall in ionized calcium levels and hypokalemia. Both may cause dangerous dysrhythmias, seizures, and decreased microvascular blood flow.

RESPIRATORY ALKALOSIS

Respiratory alkalosis is defined by alveolar hyperventilation and exists when P_{CO_2} is less than expected. It is caused by conditions that stimulate respiratory centers, including CNS tumors or stroke, infections, pregnancy, hypoxia, and toxins (e.g., salicylates). Anxiety, pain, and iatrogenic overventilation of patients on mechanical ventilators also cause respiratory alkalosis.

Whatever the etiology, the clinical symptoms of acute respiratory alkalosis are predictable from its physiologic effects. Acute reduction in P_{CO_2} produces a reduction in $[H^+]$, resulting in an increase in negative charge on anionic buffers. The now negatively charged proteins instead bind calcium, and if the effect is sufficiently large, the reduction in ionized calcium produces tetany (e.g., carpopedal spasm) and paresthesias.[26] Hypocapnia also produces substantial reductions in cerebral blood flow and results in reduced tissue oxygen delivery due to a leftward shift in the oxygen-hemoglobin dissociation curve (i.e., increased hemoglobin-oxygen binding).

The theoretical relationship of $[H^+]$ and P_{CO_2} predicted by the Kassirer-Bleich equation is that a 1-mmol decrease in $[H^+]$ results from each 1-mm Hg reduction in P_{CO_2}. The actual observed relationship is very close to the predicted values. Each 1-mm Hg reduction in P_{CO_2} results in a 0.75-mmol reduction in $[H^+]$ (Eq. 12).

$$\Delta[H^+] = 0.75 * (\Delta P_{CO_2}) \qquad (12)$$

Chronic respiratory alkalosis is unique among the acid-base disorders in that its compensation may be complete. Compensatory events include bicarbonaturia and a reduction in acid excretion, requiring 6 to 72 hours to develop fully and at least 1 week to normalize pH. The steady-state relationship between $[H^+]$ and P_{CO_2} in chronic respiratory alkalosis observed in normal human subjects at high altitude is shown in Eq. (13).

$$\Delta[H^+] = 0.4 * (\Delta Pco_2) \quad (13)$$

TREATMENT

Therapy for acute respiratory alkalosis emphasizes identification and treatment of the underlying cause. The use of "paper-bag" rebreathing in the treatment of respiratory alkalosis should be avoided because it may lead to hypoxia, and patients respond to calm reassurance, which is more effective treatment. Chronic respiratory alkalosis is seen at high altitudes, in particular among mountaineers climbing over 3700 m (12,000 ft), where the partial pressure of O_2 is significantly diminished. Acetazolamide is frequently prescribed to counter the physiologic respiratory effects of such ascents.

CLINICAL APPROACH TO ACID-BASE PROBLEMS AND MIXED ACID-BASE DISTURBANCES

Methodical interpretation of laboratory results followed by correlation with the clinical scenario is necessary to prevent erroneous acid-base evaluation. We present one method that has worked well for the authors; however, the particular method used matters less than the consistency of its application.

1. Look at the pH. If it is decreased, the primary or predominant disturbance is acidosis. If the pH is increased, the predominant disturbance is alkalosis.

2. If the pH indicates acidosis, the primary (or predominant) mechanism can be ascertained by examining the $[HCO_3^-]$ and Pco_2 (Figure 15–2A).

    1. If the $[HCO_3^-]$ is low (implying a primary metabolic acidosis), then the AG should be examined and, if possible, compared with a known steady-state value. Correct AG for abnormal albumin level [see Eq. (6) above].

    - If the AG is increased compared with the known steady-state value or is greater than 15 (or above institutional threshold), then by definition a wide AG metabolic acidosis is present, and the absolute change in the AG should be compared with the absolute change in the $[HCO_3^-]$ from normal to detect other disturbances.

    - If the AG is unchanged, then the disturbance is nonwidened or normal AG metabolic acidosis, typically with hyperchloremia.

- If the change in the AG is equal to the change in the [HCO_3^-] [see Eq. (7) above], then the wide AG acidosis is termed pure. If the AG has risen more than the [HCO_3^-] has decreased, then there is also likely to be a concomitant metabolic alkalosis. If the change in the AG is less than the change in the [HCO_3^-], then a normal AG acidosis is also present. (This is a difficult concept, but two separate physiologic mechanisms resulting in increased [H^+] can occur simultaneously.) Next examine whether the ventilatory response is appropriate.

- (1) If the decrease in the P_{CO_2} equals the decrease in the [HCO_3^-], there is appropriate respiratory compensation. Note that the pH will not return to normal.

- (2) If the decrease in the P_{CO_2} is greater than the decrease in the [HCO_3^-], there is a concomitant respiratory alkalosis. Although there are other formulas for this comparison, this is the simplest, as explained earlier in the text.

- (3) If the decrease in the P_{CO_2} is less than the decrease in [HCO_3^-], there is also a concomitant respiratory acidosis.

2. If the P_{CO_2} is elevated (rather than the [HCO_3^-] being decreased), the primary disturbance is respiratory acidosis (Figure 15–2A) The next step is to determine which type it is by examining the ratio of (i.e., the change in) [H^+] to (the upward change in) P_{CO_2}.

- If the ratio is 0.8, it is considered acute.

- If the ratio is 0.33, it is considered chronic.

- If the ratio is between 0.8 and 0.33, it is probably an acute exacerbation of the chronic condition.

- If the ratio is greater than 0.8, there must be a metabolic explanation for the excess [H^+].

- If the ratio is less than 0.33, a metabolic alkalosis must also be present.

3. If the pH is greater than 7.45, the primary or predominant disturbance is alkalosis (Figure 15–2B).

1. It is best to look at the [HCO_3^-] first. If it is elevated, there is a primary metabolic alkalosis. There is an expected ventilatory response, although it is quite varied. The ratio of the change upward in P_{CO_2} to the change upward in [HCO_3^-] can be examined. If the ratio is much less than 0.7, there is also a respiratory alkalosis (in addition to the metabolic alkalosis). If the ratio is more or less 0.7, this is likely to be a compensatory ventilatory response. If the ratio is well above 0.7, respiratory acidosis is concomitantly present.

2. If the P_{CO_2} is low, there is a primary respiratory alkalosis, and the ratio of the change in [H^+] to the change in P_{CO_2} should be examined. Acute respiratory alkalosis has a ratio of about 0.75. If the ratio is well above 0.75, there is probably also a concomitant metabolic alkalosis to explain the greater than expected decline in [H^+]. If the ratio is smaller, the condition is chronic or there may also be a metabolic acidosis component.

4. Every arterial blood gas that shows no or minimal pH derangement should still call for examination of the P_{CO_2}, [HCO_3^-], and AG, because there may well be a mixed acid-base disturbance (Figure 15–2C). It is quite possible for the pH, [HCO_3^-], and P_{CO_2} to be normal and yet have significant acid-base disturbances. The only evident abnormality may be the AG. Take the example of an [Na^+] of 145, [Cl^-] of 97, [K^+] of 4.5, and [HCO_3^-] of 25 and a normal arterial blood gas. All the numbers look reasonably normal. However, the AG is 23, so by definition there must be a wide AG metabolic acidosis. The explanation for the normal numbers is a concomitant metabolic alkalosis.

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