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Chapter 28

ACID-BASE INTERPRETATIONS

Life is a struggle, not against sin, noc against Money Power .. but against hydrogen ions.
H.L. MENCKEN

Seek simplicity, and distrust it.
Alfred North Whicehead

Disorders of acid-base balance can be found in as many as nine of every 10 patients in the ICU 0), which means that acid-base disorders may be the most common clinical problems you will encounter in the ICU. This chapter presents a structured approach to the identification of acid-base disorders based on a set of well-defined rules that can be applied to arterial blood gas (ABG) and serum electrolyte measurements (2-6).

BASIC CONCEPTS

The hydrogen ion concentration [H+) in extracellular fluid is determined by the balance between the partial pressure of carbon dioxide (PCO2) and the concentration of bicarbonate ($HC0_3$) in the fluid. This relationship is expressed as follows O):

$$[H+) (nEq/L) = 24 X (PCO2/HC0_3) \quad (28.1)$$

Using a normal arterial PCO2 of 40 mm Hg and a normal serum $HC0_3$ concentration of 24 mEq/L, the normal [H+) in arterial blood is 24 X (40/24) = 40 nEq/L.

Hydrogen Ion Concentration and pH

Note that the [H+) in extracellular fluid is expressed in nanoequivalents (nEq) per liter. A nanoequivalent is *one-millionth* of a milliequivalent, so there are millions more sodium, chloride, and other ions measured in mEq than there are hydrogen ions. Because nanoequivalents represent such a small amount, the [H+) is routinely expressed in pH units, which

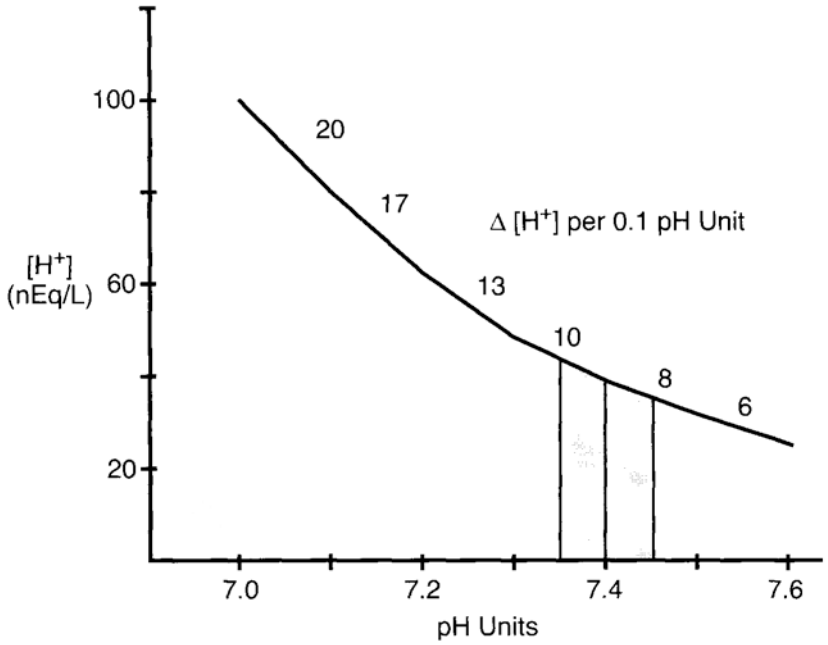

FIGURE 28.1 The relationship between hydrogen ion concentration [H^+] and pH. The numbers above the curve indicate the change in [H^+] associated with a change of 0.1 pH unit. The *shaded area* shows the normal pH range in extracellular fluid.

are derived by taking the negative logarithm (base 10) of the [H+) in nEq/L. The relationship between pH and [H+) is shown in Figure 28.1. A normal [H+) of 40 nEq/L corresponds to a pH of 7.40. Because the pH is a negative logarithm of the [H+], changes in pH are inversely related to changes in [H+) (e.g., a decrease in pH is associated with an increase in [H+]).

Inspection of the curve in Figure 28.1 reveals that, as the pH decreases from 7.60, the slope of the curve progressively increases, which means there is a progressively larger change in [H+] for a given change in pH. The numbers above the curve indicate the change in [H+] associated with each change of 0.1 pH units. At the acidotic end of the curve, the change in [H+] for a given change in pH is more than threefold greater than at the alkalotic end of the curve (20 nEq/L versus 6 nEq/L per 0.1 pH unit, respectively). Therefore, the acid-base consequences of a given change in pH depend on the baseline acid-base status of the patient.

Types of Acid-Base Disorders

The different types of acid-base disorders can be defined using the normal ranges for pH, PC02 and HCO3 concentration in extracellular fluid

as reference points. These normal ranges are shown below:

pH = 7.36-7.44
PCO2 = 36-44 mm Hg (28.2)
$HC0_3$ = 22-26 mEq/L

According to Equation 28.1, a change in either the PCO2 or the $HC0_3$ will cause a change in the pH of extracellular fluid. When the change involves the PCO2' the condition is called a *respiratory* acid-base disorder: an increase in PCO2 is a *respiratory acidosis,* and a decrease in PCO2 is a *respiratory alkalosis.* When the change involves the HC03' the condition is called a *metabolic* acid-base disorder: a decrease in $HC0_3$ is a *metabolic acidosis,* and an increase in $HC0_3$ is a *metabolic alkalosis.* if any of these changes causes the pH to change to a value outside the normal range, the suffix *emia* is used to describe the acid-base derangement: *acidemia* is the condition where the pH falls below 7.36, and *alkalemia* is the condition where the pH rises above 7.44.

Acid-Base Control

The [H+] in extracellular fluid normally varies less than 10 nEq/L (see the shaded area in Fig. 28.1). The determinants of extracellular fluid pH in Equation 28.1 indicate that tight control of the pH requires a fairly constant $PCO2/HC0_3$ ratio. Thus, a change in one of the determinants (PCO2 or $HC0_3$) must be accompanied by a proportional change in the other determinant to keep the $PCO2/HC0_3$ ratio (and the pH) constant. Thus, an increase in PCO2 (respiratory acidosis) must be accompanied by an increase in $HC0_3$ (metabolic alkalosis) to keep the pH constant. This is how the control system for acid-base balance operates. A respiratory disorder (change in PCO2) always initiates a complementary metabolic response (that alters the $HC0_3$), and vice-versa. These complementary changes in PaCO2 and $HC0_3$ are shown in Table 28.1. The initial change in PCO2 or $HC0_3$ is called the *primary* acid-base disorder, and the subsequent response is called the *compensatory* or *secondary* acid-base disorder.

TABLE 28.1 Primary Acid-Base Disorders and Associated Compensatory Changes

	***[H+]* = 24 X PCO2/$HC0_3$**	
Primary Disorder	**Primary Change**	**Compensatory Change***
Respiratory acidosis	Increased $PC0_2$	Increased $HC0_3$
Respiratory alkalosis	Decreased $PC0_2$	Decreased $HC0_3$
Metabolic acidosis	Decreased $HC0_3$	Decreased $PC0_2$
Metabolic alkalosis	Increased $HC0_3$	Increased $PC0_2$

'Compensatory changes are designed to keep the PCO2!HCO_s ratio constant.

Compensatory responses are not strong enough to keep the pH constant (they do not correct the acid-base derangement); they only to limit the change in pH that results from a primary change in PCO2 or HCO3.

Respiratory Compensation
Metabolic acid-base disorders elicit prompt ventilatory responses that are mediated by peripheral chemoreceptors located in the carotid body at the carotid bifurcation in the neck. A metabolic acidosis stimulates these chemoreceptors and initiates an increase in ventilation and a subsequent decrease in arterial PC02 (PaCO2)' A metabolic alkalosis silences the chemoreceptors and produces a prompt decrease in ventilation and increase in arterial PaCO2. The respiratory compensation for primary metabolic acid-base disturbances can be described quantitatively using the top two equations shown in Figure 28.2.

COMPENSATION FOR METABOLIC ACIDOSIS. The ventilatory response to a metabolic acidosis will reduce the PaCO2 to a level that is defined by Equation 28.3 (7). (The HCO3 in this equation is the measured bicarbonate concentration in plasma, expressed in mEq/L.)

Expected $PaCO_2$ = 1.5 X HCO) + (8 +/- 2) (28.3)

For example, if a metabolic acidosis results in a serum HCO3 of 15 mEq/L, the expected PaCO2 is 1.5 X 15) + (8 +/- 2) = 30.5 +/- 2 mm Hg. If the measured PaCO2 is equivalent to the expected PaCO2 then the respiratory compensation is adequate, and the condition is called a *compensated metabolic acidosis.* If the measured PaCO2 is higher than the expected PaCO2 (>32.5 mm Hg in this example), the respiratory compensation is not adequate, and there is a respiratory acidosis in addition to the metabolic acidosis. This acid-base disturbance is called a *primary metabolic acidosis with a superimposed respiratory acidosis.* If the PCO2 is lower than expected (lower than 28.5 mm Hg in the example), there is a respiratory alkalosis in addition to the compensated metabolic acidosis. This acid-base disturbance is called a *primary metabolic acidosis with a superimposed respiratory alkalosis.*

COMPENSATION FOR METABOLIC ALKALOSIS. The compensatory response to metabolic alkalosis has varied in different reports, but the equation shown below has proven reliable, at least up to a $HC0_3$levei of 40 mEq/L (8).

Expected PaCO2 = (0.7 X $HC0_3$) + (21 +/- 2) (28.4)

For example, if a metabolic alkalosis is associated with a plasma HCO3 of 40 mEq/L, the expected PC02 is (0.7 X 40) + (21 ±: 2) = 49 +/- 2 ffim Hg. If the measured PaCO2 is equivalent to the expected PaCO2 then the respiratory compensation is adequate, and the condition is called a *compensated metabolic alkalosis.* If the measured PaCO2 is higher than the expected PaCO2 (>51 mm Hg in this example), the respiratory compensation is not adequate, and there is a respiratory acidosis in addition to the metabolic alkalosis. This condition is called a *primary metabolic*

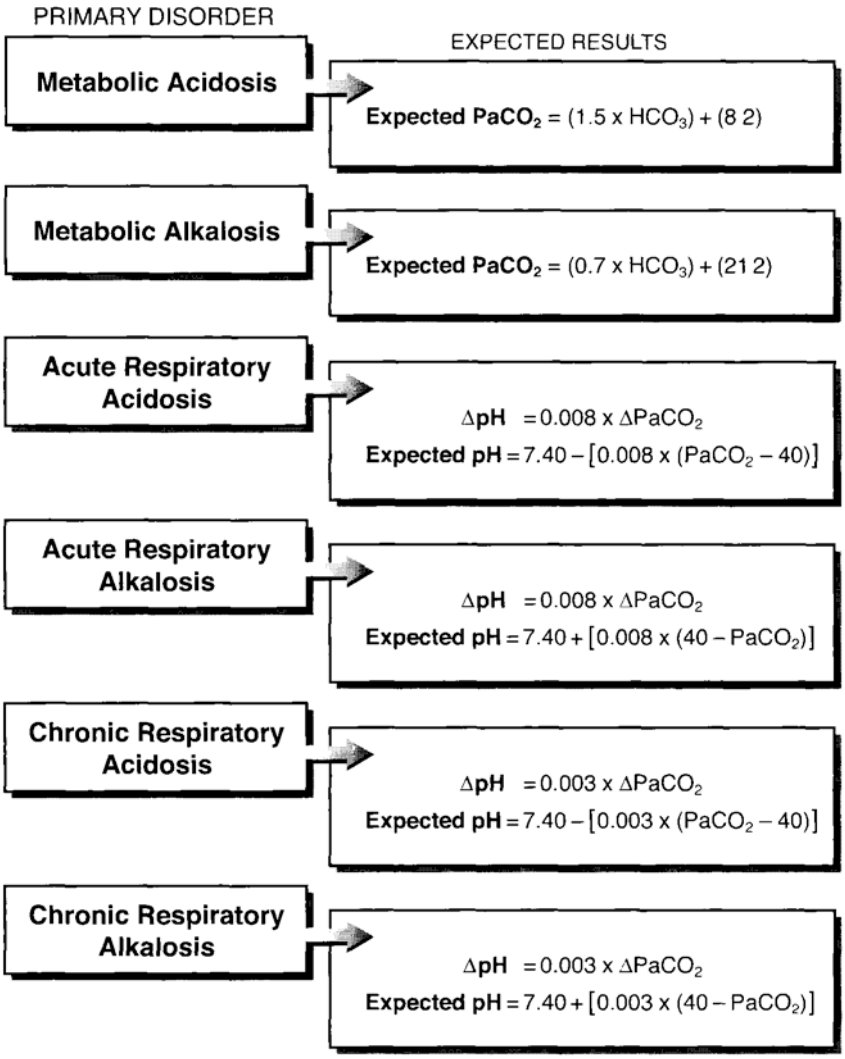

FIGURE 28.2 Useful formulas for acid-base interpretations.

alkalosis with a superimposed respiratory acidosis. If the PaCO2 is lower than expected (lower than 47 mm Hg in the example), there is an additional respiratory alkalosis, and this condition is called a *primary metabolic alkalosis with a superimposed respiratory alkalosis.*

Metabolic Compensation

The compensatory response to primary changes in PaCO2 takes place in the kidneys, and involves an adjustment in HCO3 reabsorption in the proximal tubules. An increase in PaCO2 (respiratory acidosis) results in an increased HCO3 reabsorption and a subsequent increase in serum

$HC0_3$ levels, while a decrease in PaCO2 (respiratory alkalosis) results in a decreased $HC0_3$ reabsorption and a subsequent decrease in plasma $HC0_3$ levels. These compensatory responses are slow to develop (unlike the ventilatory response to metabolic acid-base disorders, which is prompt). Compensation begins to appear in 6 to 12 hours and is fully developed after a few days. Because of this delay in renal compensation, respiratory acid-base disorders are classified as acute (before renal compensation begins) and chronic (after renal compensation is fully developed). The changes in pH that are expected in acute and chronic respiratory acidbase disorders are defined by the equations shown in Figure 28.2.

ACUTE RESPIRATORY ACID-BASE DISORDERS. Prior to the onset of renal compensation, a change in PaCO2 of 1 mm Hg will produce a change in xpH of 0.008 pH units: Delta pH = 0.008 X Delta PaCO2 (2,3). This relationship is incorporated into Equation 28.5 using 7.40 for the normal pH and 40 mm Hg for the normal $PaC0_2$• This equation then defines the expected pH for an *acute respiratory acidosis.*

Expected pH = 7.40 - [0.008 X (PaCO2 - 40)] (28.5)

The expected arterial pH for an *acute respiratory alkalosis* can be described in the same manner using Equation 28.6.

Expected pH = 7.40 + [0.008 X (40 - PaCO2)] (28.6)

For example, starting with a normal pH of 7.40, an acute increase in $PaC0_2$ from 40 to 60 mm Hg is expected to result in an arterial pH of [7.40 - (0.008 X 20)] 7.24 pH units, and a sudden drop in PaCO2 from 40 to 25 mm Hg is expected to result in an arterial pH of [7.40 + (0.008 X 15)] 7.56 pH units.

CHRONIC RESPIRATORY ACID-BASE DISORDERS. When the compensatory response in the kidneys is fully developed, the arterial pH changes only 0.003 pH units for every 1 mm Hg change in PaCO2: ApH = 0.003 X APaCO2 (3). This relationship is incorporated into Equation 28.7 using 7.40 as a normal arterial pH and 40 mm Hg as a normal PaCO2. This equation describes the expected change in pH for a *chronic (compensated) respiratory acidosis.*

Expected pH = 7.40 - [0.003 X (PaCO2 - 40)] (28.7)

The expected arterial pH for a *chronic (compensated) respiratory alkalosis* is described in a similar fashion in Equation 28.8.

Expected pH = 7.40 + [0.003 X (40 - $PaC0_2$)] (28.8)

For example, a patient with emphysema and chronic *COz* retention who usually has a PaCO2 of 60 mm Hg is expected to have the following arterial pH (from Equation 28.7): 7.40 - (0.003 X 20) = 7.34 pH units. The expected pH for an acute rise in $PaC0_2$ to 60 mm Hg (from Equation 28.5) is: 7.40 - (0.008 X 20) = 7.24 pH units. Therefore, the renal compensation

for an acute rise in PaCO2 to 60 mm Hg is expected to increase the arterial pH by 0.1 pH units.

A STEPWISE APPROACH TO ACID-BASE INTERPRETATION

The following is a structured approach to the diagnosis of acid-base disorders using rules of acid-base interpretation based on the material just presented. This approach has three distinct stages. The first two stages will allow you to identify major acid-base abnormalities using only three variables: pH, $PaC0_2$, and serum HCO3 concentration. The last stage allows you to further investigate cases of metabolic acidosis using commonly measured serum electrolytes. Several examples are provided along the way as instructional aids.

Stage I: Identify the Primary Acid-Base Disorder

In the first stage of the approach, the measured PaCO2 and pH are used to determine if an acid-base disturbance is present and, if so, to identify the primary acid-base disorder.

RULE 1: An acid-base abnormality is present if either the PaCO2 or the pH is outside the normal range. (A normal pH or $PaC0_2$ does not exclude the presence of an acid-base abnormality, as explained in Rule 3.)

RULE 2: If the pH and PaCO2 are both abnormal, compare the directional change. If both change in the same direction (both increase or decrease), the primary acid-base disorder is metabolic, and if both change in opposite directions, the primary acid-base disorder is respiratory.

EXAMPLE: consider a patient with an arterial pH of 7.23 and a PaCO2 of 23 mm Hg. The pH and PaCO? are both reduced (indicating a primary metabolic problem) and the pH is low (indicating acidemia), so the problem is a *primary metabolic acidosis.*

RULE 3: If either the pH or PaCO2 is normal, there is a mixed metabolic and respiratory acid-base disorder (one is an acidosis and the other is an alkalosis). If the pH is normal, the direction of change in PaCO2 identifies the respiratory disorder, and if the $PaC0_2$ is normal, the direction of change in the pH identifies the metabolic disorder.

EXAMPLE: Consider a patient with an arterial pH of 7.37 and a PaCO2 of 55 mm Hg. The pH is normal, so there is a mixed metabolic and respiratory acid-base disorder. The $PaC0_2$ is elevated, so the respiratory disorder is an acidosis, and thus the metabolic disorder must be an alkalosis. Therefore, this is a *combined respiratory acidosis and metabolic alkalosis.* There is no primary acid-base disorder in this situation; both disorders are equivalent in severity (which is why the pH is normal).

Remember that the compensatory responses to a primary acid-base disturbance are never strong enough to correct the pH, but act to reduce the severity of the change in pH. Therefore, a normal pH in the presence of an acid-base disorder always signifies a mixed respiratory and metabolic acid-base disorder. (It is sometimes easier to think of this situation as a condition of overcompensation for one of the acid-base disorders.)

Stage **II**: Evaluate Compensatory Responses

The second stage of the approach is for cases where a primary acid-base disorder has been identified in Stage **I**. (**If** a mixed acid-base disorder was identified in Stage I, go directly to Stage III.) The goal in Stage II is to determine if the compensatory responses are adequate and if there are additional acid-base derangements.

RULE 4: **If** there is a primary metabolic acidosis or alkalosis, use the measured serum bicarbonate concentration in Equation 28.3 or 28.4 to identify the expected $PaC0_2$• **If** the measured and expected $PaC0_2$ are equivalent, the condition is fully compensated. **If** the measured PaCO2 is higher than the expected $PaC0_2$, there is a superimposed respiratory acidosis. **If** the measured PCO2 is less than the expected *PCO2'* there is a superimposed respiratory alkalosis.

EXAMPLE: Consider a patient with a PaCO2 of 23 mm Hg, an arterial pH of 7.32, and a serum $HC0_3$ of 15 mEq/L. The pH is acidemic and the pH and PCO2 change in the same direction, so there is a primary metabolic acidosis. Equation 28.3 should be used to calculate the expected *PC02:* 0.5 X 15) + (8 :±:2) = 30.5 :±: 2 mm Hg. The measured PaCO2 (23 mm Hg) is lower than the expected $PaC0_2$, so there is an additional respiratory alkalosis. Therefore, this condition can be described as a *primary metabolic acidosis with a superimposed respiratory alkalosis.*

RULE 5: **If** there is a respiratory acidosis or alkalosis, use the PaCO2 to calculate the expected pH using Equations 28.5 and 28.7 (for respiratory acidosis) or Equations 28.6 and 28.8 (for respiratory alkalosis). Compare the measured pH to the expected pH to determine if the condition is acute, partially compensated, or fully compensated. For respiratory acidosis, if the measured pH is lower than the expected pH for the acute, uncompensated condition, there is a superimposed metabolic acidosis, and if the measured pH is higher than the expected pH for the chronic, compensated condition, there is a superimposed metabolic alkalosis. For respiratory alkalosis, if the measured pH is higher than the expected pH for the acute, uncompensated condition, there is a superimposed metabolic alkalosis, and **if** the measured pH is below the expected pH for the chronic, compensated condition, there is a superimposed metabolic acidosis. EXAMPLE: Consider a patient with a PaCO2 of 23 mm Hg and a pH of 7.54. The PaCO2 and pH change in opposite directions so the primary problem is respiratory and, since the pH is alkalemic, this is a primary respiratory alkalosis. The expected pH for an acute respiratory alkalosis is described in Equation 28.6, and is 7.40 + [0.008 X (40 - 23)] = 7.54. This is the same as the measured pH, so this is an *acute, uncompensated respiratory alkalosis.* **If** the measured pH was higher than 7.55, this would be evidence of a superimposed metabolic alkalosis.

Stage **III**: Use The "Gaps" to Evaluate Metabolic Acidosis

The final stage of this approach is for patients with a metabolic acidosis, and it involves two determinations known as *gaps.* The first is the *anion gap,* which is an estimate of unmeasured anions that helps to identify

the cause of a metabolic acidosis. The second gap is a comparison of the change in the anion gap and the change in the serum $HC0_3$ concentration: the gap between the two (known as the *gap-gap)* can uncover mixed metabolic disorders (e.g., a metabolic acidosis and alkalosis) that would otherwise go undetected. These two measurements are described in the next section.

THE ANION GAP

The anion gap is an estimate of the relative abundance of unmeasured anions, and is used to determine if a metabolic acidosis is due to an accumulation of non-volatile acids (e.g., lactic acid) or a net loss of bicarbonate (e.g., diarrhea) (5,9,10).

Measuring the Anion Gap
To achieve electrochemical balance, the concentration of negativelycharged anions must equal the concentration of positively-charged cations. All ions participate in this balance, including those that are routinely measured, such as sodium (Na), chloride (CL), and bicarbonate ($HC0_3$), and those that are not measured. The unmeasured cations (UC) and unmeasured anions (UA) are included in the electrochemical balance equation shown below:

$$Na + UC = (CL + HC0_3) + UA \qquad (28.9)$$

Rearranging the terms in this equation yields Equation 28.10.

$$Na - (CL + HC0_3) = UA - UC \qquad (28.10)$$

The difference (UA - UC) is a measure of the relative abundance of unmeasured anions and is called the *anion gap* (AG). The difference between the two groups reveals an anion excess (anion gap) of 12 mEq/L, and much of this difference is due to the albumin concentration.

Reference Range
The normal value of the AG was originally set at 12 +/- 4 mEq/L (range = 8 to 16 mEq/L) (9). With the adoption of newer automated systems that more accurately measure serum electrolytes, the normal value of the AG has decreased to 7 ± 4 mEq/L (range = 3 to 11 mEq/L) (11). This newer reference range has not been universally adopted, and this is a source of error in the interpretation of the AG.

Influence oj Albumin
Another source of error in the interpretation of the AG occurs when the contribution of albumin is overlooked. As indicated in Table 28.2, albumin is major source of unmeasured anions, and a 50% reduction in

TABLE 28.2 Determinants of the Anion Gap

Unmeasured Anions	Unmeasured Cations
Albumin (15 mEq/L)'	Calcium (5 mEq/L)
Organic Acids (5 mEq/L)	Potassium (4.5 mEq/L)
Phosphate (2 mEq/L)	Magnesium (1.5 mEq/L)
Sulfate (1 mEq/L)	
Total UA: (23 mEq/L)	Total UC: (11 mEq/L)
Anion Gap = UA - UC = 12 mEq/L	

'If albumin is reduced by 50%, anion gap = 4 mEq/L

the albumin concentration will result in a 75% reduction in the anion gap. Since hypoalbuminemia is common in ICU patients, the influence of albumin on the AG must be considered in all ICU patients.

Two methods have been proposed to correct the AG for the influence of albumin in patients with a low serum albumin. One method is to calculate the expected AG using just the albumin and phosphate concentrations (6,12), since these variables are responsible for a majority of the normal anion gap.

Expected AG (mEq/L) = [2 x albumin (g/dL)]
+ [0.5 X $P0_4$ (mg/dL)] (28.11)

The calculated AG using the traditional method [Na - (CL + $HC0_3$)] is then compared to the expected AG. If the calculated AG is greater than the expected AG, the difference is attributed to unmeasured anions from non-volatile acids.

The second method of adjusting the AG in hypoalbuminemic patients involves the following equation (where the factor 4.5 is the normal albumin concentration in g/ dL) (3):

Adjusted AG = Observed AG + 2.5
X [4.5 - measured albumin (g/dL)] (28.12)

Thus, a patient with a calculated AG of 10 mEq/L and a serum albumin of 2 g/ dL would have an adjusted AG that is [10 + (2.5 X 2.5)] = 16 mEq/L. This represents a 60% increase in the AG, and this difference could transform a seemingly normal AG into an elevated AG.

The choice of method is up to you. The important issue is to use some method of adjusting the AG in patients with a low serum albumin.

Interpreting the Anion Gap

Metabolic acidoses are characterized as having an elevated AG or a normal AG (5,10). Those with an elevated AG are caused by the addition of a fixed (non-volatile) acid to the extracellular fluid, and those with

TABLE 28.3 Interpretation of the Anion Gap (AG)

High AG Acidoses	Normal AG Acidoses
Lactic acidosis	Diarrhea
Ketoacidosis	Isotonic saline infusion
End-stage renal failure	Early renal insufficiency
Methanol ingestion	Renal tubular acidosis
Ethylene glycol ingestion	Acetazolamide
Salicylate toxicity	Ureteroenterostomy

a normal AG are the result of a net increase in chloride concentration in the extracellular fluid. The conditions in each category are shown in Table 28.3.

High Anion Gap

When a fixed acid is added to the extracellular space, the acid dissociates to produce hydrogen ions and anions. The hydrogen ions combine with bicarbonate (HCO3) to form carbonic acid and, according to the relationship AG = Na - (CL + $HC0_3$), the decreased $HC0_3$ results in an increased AG. The usual causes of an elevated AG metabolic acidosis are lactic acidosis, ketoacidosis, and end-stage renal failure (where hydrogen ion secretion in the distal tubules is impaired) (9). Elevated AG acidosis can also be seen in certain toxic ingestions, including methanol (which forms formic acid), ethylene glycol (which forms oxalic acid), propylene glycol (which accelerates the formation of lactic acid and pyruvic acid), and salicylates (which form salicylic acid) **(O)**.

Normal Anion Gap

When a metabolic acidosis is caused by the loss of bicarbonate ions from the extracellular fluid, the bicarbonate loss is counterbalanced by a gain of chloride ions to maintain electrical charge neutrality. Some believe the increase in chloride comes first, and the loss of HCO3 is a secondary phenomenon to maintain electrical neutrality (6). Because the increase in chloride concentration is proportional to the decrease in bicarbonate concentration, the relationship AG = Na - (CL + $HC0_3$) remains unchanged. (In the high AG metabolic acidoses, the loss of $HC0_3$ is not accompanied by increased CL because the anions from the dissociated acids balance the loss of $HC0_3$.) Because normal AG metabolic acidoses are accompanied by increased chloride concentrations, they are often referred to as hyperchloremic metabolic acidoses.

The common causes of a normal AG metabolic acidosis include diarrhea (where there is loss of HCO3 in the stool), early renal insufficiency (which is accompanied by increased $HC0_3$ losses in the urine), and infusion of isotonic saline. The chloride concentration in isotonic saline is much higher than in extracellular fluid 154 mEq/L vs.

100 mEq/L, respectively), so infusion of isotonic saline raises the chloride concentration in extracellular fluid, and this is accompanied by increased HCO3 losses in urine to maintain electrical neutrality (4). This condition has been called "dilutional acidosis," but this is a misnomer because the decreased HCO3, in this condition is not a dilutional effect but is a specific response to the increased chloride concentration in the extracellular space. Other less common causes of a normal AG metabolic acidosis are renal tubular acidosis, acetazolamide (a carbonic anhydrase inhibitor that increases HC03, losses in urine), and fistulas between the ureters and GI tract (which promote HCO3 losses in stool).

Reliability

The reliability of the AG in detecting lactic acidosis has been questioned because there are numerous reports of lactic acidosis with a normal anion gap 05,16). However in most of the reported cases, the influence of hypoalbuminemia in reducing the AG was not considered. The general consensus at this time is that the AG is a reliable marker of conditions associated with fixed acid accumulation (e.g., lactic acidosis) as long as the confounding influence of hypoalbuminemia is considered 02,13).

The "Gap-Gap"

In the presence of a high AG metabolic acidosis, it is possible to detect another metabolic acid-base disorder (a normal AG metabolic acidosis or a metabolic alkalosis) by comparing the AG excess (the difference between the measured and normal AG) to the HCO3 deficit (the difference between the measured and normal HCO3 concentration in plasma). The ratio (AG excess/HCO3 deficit) is shown below using 12 mEq/L as the normal AG and 24 mEq/L as the normal plasma HCO3 concentration.

AG Excess/HCO3 deficit = (Measured AG - 12)/
(24 - Measured HCO3) (28.13)

This ratio is sometimes called the *gap-gap* because it is a measure of the difference (gap) between the increase in AG and the decrease in HCO3 concentration in extracellular fluid. This ratio can be used as follows.

Mixed Metabolic Acidoses

When a fixed acid accumulates in extracellular fluid (i.e., high AC metabolic acidosis), the decrease in serum HC03, is equivalent to the increase in AG, and the gap-gap (AG Excess/HC03; deficit) ratio is unity (= 1). However, when a hyperchloremic acidosis appears, the decrease in HCO3 is greater than the increase in the AG, and the ratio (AG excess/HCO3 deficit) falls below unity « 1). Therefore, in the presence of a high AG metabolic acidosis, a "gap-gap" (AG excess/$HC0_3$ deficit) ratio of less than 1 indicates the co-existence of a normal AG metabolic acidosis (2,17).

Diabetic ketoacidosis (DKA) is an example of a condition that can be associated with a high AG and a normal AG metabolic acidosis (8). DKA first presents with a high AG metabolic acidosis, but after therapy with isotonic saline begins, the high AG acidosis begins to resolve (as the keto-acids are cleared) and a normal AG acidosis begins to appear (due to the saline infusion). In this situation, the serum bicarbonate remains low, but the gap-gap (AG excess/HCO3 deficit) ratio begins to fall progressively below 1. Monitoring the serum $HC0_3$ alone will therefore create a false impression that the ketoacids are not being cleared. This is one example of the clinical utility of the gap-gap ratio.

Metabolic Acidosis and Alkalosis
When alkali is added in the presence of a high AG acidosis, the decrease in serum bicarbonate is less than the increase in AG, and the gap-gap (AG excess/$HC0_3$ deficit) ratio is greater than unity (>1). Therefore, in the presence of a high AG metabolic acidosis, a gap-gap (AG excess/HCO3 deficit) ratio of greater than 1 indicates the co-existence of a metabolic alkalosis. This is an important consideration because metabolic alkalosis is common in the ICU due to the frequent use of nasogastric suction and diuretics.

ARTERIAL vs. VENOUS BLOOD
The evaluation of acid-base disorders relies heavily on arterial blood gas (ABG) measurements, however the acid-base status in arterial blood is unlikely to reflect the acid-base status in peripheral tissues, particularly in hemodynamically unstable patients. Venous blood should be a more accurate representation of what is occurring in the tissues. The discrepancy between the acid-base status in arterial and venous blood during cardiopulmonary resuscitation is shown in Figure 28.3 (9). Note that the arterial blood has a normal pH, while the venous blood shows severe acidemia (pH = 7.15). Although these are extreme conditions, this serves to demonstrate that, in critically ill patients, the acid-base status of arterial blood may not be an accurate reflection of the acid-base conditions in peripheral tissues. At least remember this when you are performing CPR.

A FINAL WORD
The reliance on the PC02-HCO3 relationship to evaluate acid-base status has been criticized because the PaCO2 and HCO3 are both dependent variables (each depends on the other) and thus it is not possible to detect acid-base conditions that operate independently of these variables (6). There are alternate methods of acid-base analysis (see reference 6), but these involve complex equations and are not easily implemented

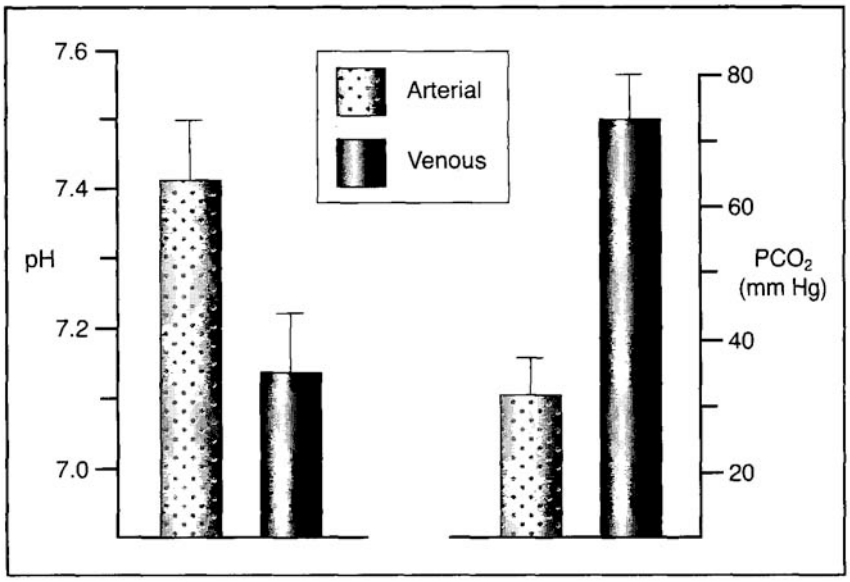

FIGURE 28.3 Acid-base parameters in arterial and venous blood during cardiopulmonary resuscitation. *Height of the vertical columns* indicates the mean; *cross-bars* indicate standard deviation. Study group: 16 adult patients. (From Weil MH, Rackow EC, Trevino R, et al. Difference in acid-base state between venous and arterial blood during cardiopulmonary resuscitation. N Engl J Med 1986;315:153–156.)

at the bedside. Furthermore, there is no convincing evidence that other systems of acid-base analysis provide any real clinical benefit over the traditional method presented in this chapter.

REFERENCES

Chapter 29

ORGANIC ACIDOSES

It is *incident* to *physicians, beyond all other men,* to *mistake subsequence for consequence.*
Samuel Johnson

This chapter describes the clinical disorders associated with the production of organic (carbon-based) acids. The characteristic feature of these disorders is a metabolic acidosis with a high anion gap (see Chapter 28 for a description of the anion gap) (1-3). The main focus of the chapter is lactic acidosis and ketoacidosis. The final section contains a brief description of the metabolic acidoses associated with toxic ingestions of ethylene glycol and methanol.

LACTIC ACIDOSIS

Lactate Metabolism

Lactate is the end product of anaerobic glycolysis, as shown below:

Glucose + 2ATP + 2H2P04 -> 2Lactate + 2ADP + 2H2O (29.1)

Note that this reaction produces lactate, a negatively charged ion, *not* lactic acid. The hydrogen ions needed to convert lactate to lactic acid must be generated by the hydrolysis of ATP (4-6). Therefore, lactate is not synonymous with lactic acid, and hyperlactatemia is not synonymous with lactic acidosis. Most of the lactate production occurs in skeletal muscle, bowel, brain, and erythrocytes. The lactate generated in these tissues can be taken up by the liver and converted to glucose (via gluconeogenesis) or can be used as a primary oxidative fuel.

The Lactate Shuttle

As described in Chapter II, lactate can serve as an alternate fuel source (see Table 11.3). This is demonstrated in Figure 29.1 The anaerobic metabolism

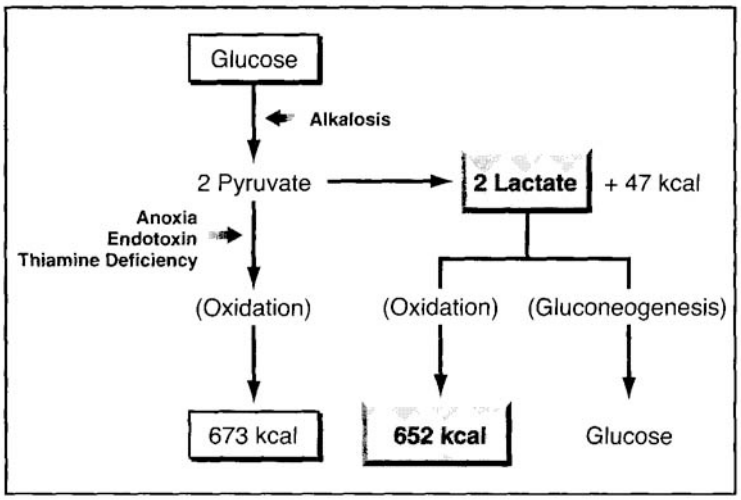

FIGURE 29.1 The salient features of glucose and lactate metabolism.

of one mole of glucose generates 47 kilocalories (kcal), which is only 7% of the energy yield from complete oxidation of glucose (673 kcal) (7). This energy difference can be erased by the oxidation of lactate, which generates 652 kcal per mole of glucose (326 kcal per mole of lactate) (7). The use of lactate as an oxidative fuel (called the *lactate shuttle)* has been described in exercise (8).

The lactate shuttle could also operate in critically ill patients. For example, there is evidence that the hyperlactatemia in sepsis is due to inhibition of glucose utilization by endotoxin (see Fig. 29.1). If the effects of endotoxin predominated in one organ (e.g., skeletal muscle), lactate that is generated could be used as a source of energy by other vital organs, such as the heart and central nervous system. In fact, both of these organs can use lactate as an energy source. This view of lactate is very different than the traditional view of lactate as a source of acidosis that can damage tissues.

Causes of Hyperlactatemia

Circulatory Shock

An increase in blood lactate levels in patients who are hemodynamically unstable is taken as evidence of impaired oxygen utilization by cells (cell dysoxia). This condition is generally known as *circulatory shock.* The degree of elevation in blood lactate levels is directly correlated with the mortality rate in circulatory shock, as shown in Figure 11.5 (9). It is important to emphasize that a decrease in systemic oxygen delivery, as occurs with anemia and hypoxemia, is not a cause of hyperlactatemia.

Sepsis
Systemic sepsis is often accompanied by hyperlactatemia. Some patients with sepsis have mild elevations of blood lactate (2 to 5 mEq/L) with a normallactate:pyruvate ratio and a normal blood pH. These patients have *stress hyperlactatemia,* which is considered a result of hypermetabolism without impaired cellular oxygen utilization (10). Patients with septic shock can have marked elevations in blood lactate with increased lactate:pyruvate ratios and a reduced blood pH. These patients have a defect in cellular oxygen utilization that has been called *cytopathic hypoxia* (11). This condition may not be associated with impaired tissue oxygenation, but may be due to a defect in oxygen utilization in mitochondria. One contributing factor could be endotoxin-mediated inhibition of pyruvate dehydrogenase, the enzyme that initiates pyruvate oxidation in the mitochondria (see Fig. 11.6) (11,12).

Thiamine Deficiency
Thiamine serves as a co-factor for the pyruvate dehydrogenase enzyme that initiates pyruvate oxidation in the mitochondria (see Fig. 29.1). Therefore, it is no surprise that thiamine deficiency can be accompanied by hyperlactatemia (13). Because thiamine deficiency may be common in critically **ill** patients, this diagnosis should be considered in all cases of unexplained hyperlactatemia in the ICU. (See Chapter 45 for information on the diagnosis of thiamine deficiency.)

Drugs
A variety of drugs can produce hyperlactatemia, including nucleoside reverse transcriptase inhibitors, acetaminophen, epinephrine, metformin, propofol, and nitroprusside (3,14). In most of these cases (except epinephrine), the lactic acidosis indicates a defect in oxygen utilization, and carries a poor prognosis.

Propylene Glycol
Propylene glycol is an alcohol used to enhance the water solubility of many hydrophobic intravenous medications, including lorazepam, diazepam, esmolol, nitroglycerin, and phenytoin. About 55-75% of propylene glycol is metabolized by the liver and the primary metabolites are lactate and pyruvate (15). Propylene glycol toxicity from solvent accumulation has been reported in 19% to 66% of ICU patients receiving high dose lorazepam or diazepam for more than 2 days (15,16). Signs of toxicity include agitation, coma, seizures, tachycardia, hypotension, and hyperlactatemia (which can exceed 10 mEq/L). The clinical presentation can mimic that of systemic sepsis.
Propylene glycol toxicity is probably much more common than suspected in patients receiving infusions of lorazepam and diazepam. (15). This condition should be suspected in any patient with unexplained hyperlactatemia who is on a continuous infusion of one of these drugs. **If** suspected, the drug infusion should be stopped and another sedative

agent selected. Midazolam does not have propylene glycol as a solvent, and could be used for short-term sedation. An assay for propylene glycol in blood is available, but the acceptable range has not been determined.

Lactic Alkalosis
Severe alkalosis (respiratory or metabolic) can raise blood lactate levels as a result of increased activity of pH dependent enzymes in the glycolytic pathway (17). When liver function is normal, the liver clears the extra lactate generated during alkalosis, and *lactic alkalosis* becomes evident only when the blood pH is 7.6 or higher. However, in patients with impaired liver function, hyperlactatemia can be seen with less severe degrees of alkalemia.

Other Causes
Other possible causes of hyperlactatemia in patients in the leu are seizures (from increased lactate production), hepatic insufficiency (from reduced lactate clearance), and acute asthma (possibly from enhanced lactate production by the respiratory muscles) (18-20). Hyperlactatemia associated with hepatic insufficiency is often mild and not accompanied by lactic acidosis (18). Hyperlactatemia that accompanies generalized seizures can be severe but is transient (19). Hyperlactatemia during nitroprusside infusions is a manifestation of cyanide intoxication and is an ominous sign (see Chapter 16).

Diagnosis

The Anion Gap
As described in Chapter 28, the anion gap should be elevated in lactic acidosis, but there are numerous reports of a normal anion gap in patients with lactic acidosis (19,21). As a result, the anion gap should not be used as a screening test for lactic acidosis. For more information on the anion gap, see Chapter 28.

Blood Lactate
Lactate concentrations can be measured in plasma or whole blood. If immediate measurements are unavailable, the blood sample should be placed on ice to retard lactate production by red blood cells in the sample. A lactate level above 2 mEq/L is abnormal, but in patients with sepsis, a blood lactate level above 4 mEq/L may have more prognostic value (as explained earlier).

D-Lactic Acidosis
The lactate produced by mammalian tissues is a levo-isomer (bends light to the left), whereas a dextro-isomer of lactate (bends light to the right) is produced by certain strains of bacteria that can populate the bowel (22). D-lactate generated by bacterial fermentation in the bowel can gain

access to the systemic circulation and produce a metabolic acidosis, often combined with a metabolic encephalopathy (23). Most cases of D-lactic acidosis have been reported after extensive small bowel resection or after jejunoileal bypass for morbid obesity (22-24).

Diagnosis

D-lactic acidosis can produce an elevated anion gap, but the standard laboratory assay for blood lactate measures only L-lactate. **If** D-lactic acidosis is suspected, you must request the laboratory to perform D-lactate assay.

ALKALI THERAPY FOR LACTIC ACIDOSIS

The primary goal of therapy in lactic acidosis is to correct the underlying metabolic abnormality. Alkali therapy aimed at correcting the pH is of questionable value (25). The following is a brief summary of the pertinent issues regarding alkali therapy for lactic acidosis.

Acidosis Is Not Harmful

The principal fear from acidosis is the risk of impaired myocardial contractility (26). However, in the intact organism, acidemia is often accompanied by an increase in cardiac output (27). This is explained by the ability of acidosis to stimulate catecholamine release from the adrenals and to produce vasodilation. Therefore, impaired contractility from acidosis is less of a concern in the intact organism. Furthermore, acidosis may have a protective rule in the setting of clinical shock. For example, extracellular acidosis has been shown to protect energy-depleted cells from cell death (27a).

Bicarbonate Is Not an Effective Buffer

Sodium bicarbonate is the standard buffer used for lactic acidosis, but has limited success in raising the serum pH (27b). This can be explained by the titration curve for the carbonic acid-bicarbonate buffer system, which is shown in Figure 29.2. The $HC0_3$ buffer pool is generated by the dissociation of carbonic acid (H_2C0_3):

$$CO_2 + H2O <-> H_2C0_3 <-> H+ + HC0_3- \qquad (29.2)$$

The dissociation constant (pK) for carbonic acid (i.e., the pH at which the acid is 50% dissociated) is 6.1, as indicated on the titration curve. Buffers are most effective within 1 pH unit on either side of the pK, so the effective range of the bicarbonate buffer system should be an extracellular pH between 5.1 and 7.1 pH units (indicated by the shaded area on the titration curve). Therefore, bicarbonate is not expected to be an effective buffer in the usual pH range of extracellular fluid. Bicarbonate is not

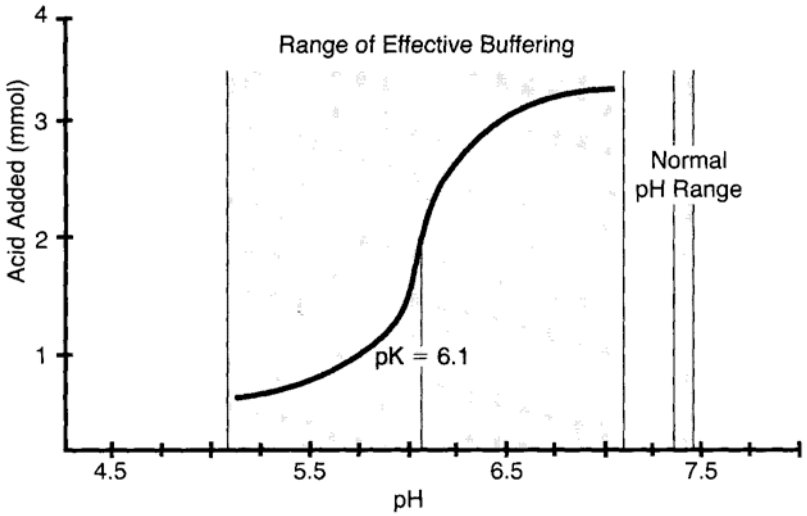

FIGURE 29.2 The titration curve for the carbonic acid-bicarbonate buffer system. The large, shaded area indicates the effective pH range for the bicarbonate buffer system, which does not coincide with the normal pH range for extracellular fluid. (Adapted from Comroe JH. Physiology of respiration. Chicago: Yearbook Medical Publishers, 1974;203.)

really a buffer (at least in the pH range we live in); rather, it is a transport form for carbon dioxide in blood (see Fig. 2.5).

Bicarbonate Can Be Harmful

A number of undesirable effects are associated with sodium bicarbonate therapy. One of these is the ability to generate eo_2 and actually lower the intracellular pH and cerebrospinal fluid pH (28,29). In fact, considering that the PC02 is 200 mm Hg in standard bicarbonate solutions (see Table 29.1), bicarbonate is really a *CO2* burden (an acid load!) that must be removed by the lungs.

TABLE 29.1 Bicarbonate-Containing Buffer Solutions

	7.5% $NaHC0_3$	Carbicarb
Sodium	0.9 mEq/mL	0.9 mEq/mL
Bicarbonate	0.9 mEq/mL	0.3 mEq/mL
Dicarbonate	–	0.3 mEq/mL
$PC0_2$	>200 mm Hg	3 mm Hg
Osmolality	1461 mOsm/kg	1667 mOsm/kg
pH (25°C)	8.0	9.6

Finally, bicarbonate infusions have been associated with an increase in blood lactate levels (29). Although this effect is attributed to alkalosisinduced augmentation of lactate production, it is not a desirable effect for a therapy of lactic acidosis.

Carbicarb
Carbicarb is a commercially available buffer solution that is a 1:1 mixture of sodium bicarbonate and disodium carbonate. As shown in Table 29.1, Carbicarb has less bicarbonate and a much lower peo_z than the standard 7.5% sodium bicarbonate solution. As a result, Carbicarb does not produce the increase in PCO_z seen with sodium bicarbonate infusions (28).

Summary
Sodium bicarbonate has no role in the management of lactic acidosis. However, in the setting of severe acidosis (pH < 7.1) where the patient is deteriorating rapidly, a trial infusion of bicarbonate can be attempted by administering one-half of the estimated bicarbonate deficit (29).

$HC0_3$ deficit (mEq) = 0.6 X wt (kg) X (15 - measured $HC0_3$) (29.3)

(where 15 mEq/L is the end-point for the plasma $HC0_3$). If cardiovascular improvement occurs, bicarbonate therapy can be continued to maintain the plasma $HC0_3$ at 15 mEq/L. If no improvement or further deterioration occurs, further bicarbonate administration is not warranted.

KETOSIS
In conditions of reduced nutrient intake, adipose tissue releases free fatty acids, which are then taken up in the liver and metabolized to form the ketones acetoacetate and (3-hydroxybutyrate. These ketones are released from the liver and can be used as oxidative fuels by vital organs such as the heart and central nervous system. The oxidative metabolism of ketones yields 4 kcal/ g, which is a greater energy yield than the 3.4 kcal/ g produced by carbohydrate metabolism (see Chapter 45).
The normal concentration of ketones in the blood is negligible (less than 0.1 mmol/L), but blood ketone levels increase tenfold after just 3 days of starvation. Ketones are strong acids, and progressive ketosis eventually produces a metabolic acidosis. The prevalence of acetoacetate (AcAc) and (Beta-hydroxybutyrate (Beta-0HB) in blood is determined by the following redox reaction;

AcAc + NADH <–> Beta-0HB + NAD (29.4)

The balance of this reaction favors the formation of Beta-0HB. In conditions of enhanced ketone production, the Beta-0HB:AcAc ratio ranges from 3:1 in diabetic ketoacidosis, to as high as 8:1 in alcoholic ketoacidosis. The concentration of ketones in the blood in diabetic and alcoholic ketoacidosis is shown in Figure 29.3. Note the preponderance of beta-hydroxybutyrate

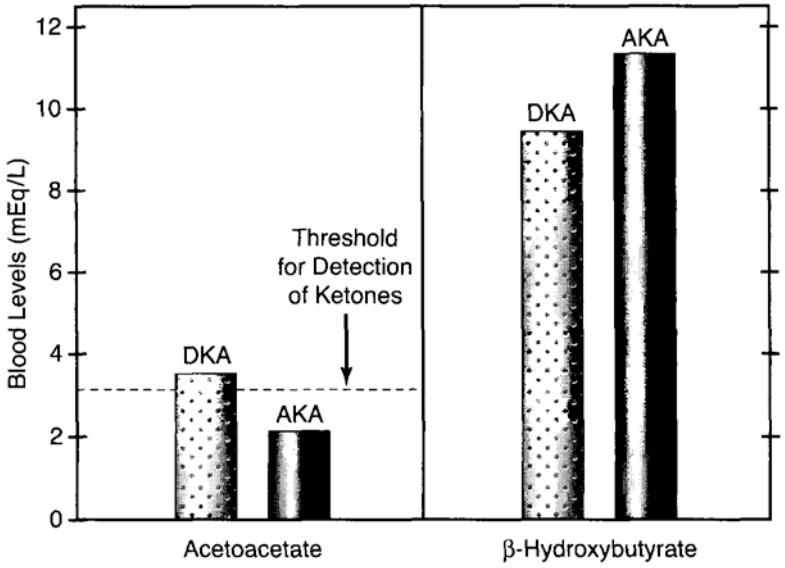

FIGURE 29.3 The concentrations of acetoacetate and β-hydroxybutyrate in the blood in diabetic ketoacidosis (DKA) and alcoholic ketoacidosis (AKA). The horizontal dashed line represents the minimum concentration of acetoacetate required to produce a positive nitroprusside reaction.

in both conditions. Because of this preponderance, ketoacidosis is more accurately called *beta-hydroxybutyrie acidosis.*

The Nitroprusside Reaction

The nitroprusside reaction is a colorimetric method for detecting acetoacetate and acetone in blood and urine. The test can be performed with tablets (Acetest) or reagent strips (Ketostix, Labstix, Multistix). A detectable reaction requires a minimum acetoacetate concentration of 3 mEq/L. Because this reaction does not detect the predominant ketoacid ll-hydroxybutyrate (30), it is an insensitive method for monitoring the severity of ketoacidosis. This is illustrated in Figure 29.3. In alcoholic ketoacidosis, the total concentration of ketoacids in blood is 13 mEq/L, which represents more than a hundredfold increase over the normal concentration of blood ketones, yet the nitroprusside reaction will be negative because the acetoacetate concentration is below 3 mEq/L.

DIABETIC KETOACIDOSIS

Diabetic ketoacidosis (DKA) is usually seen in insulin-dependent diabetic patients, but in 20% of cases, there is no previous history of diabetes mellitus. DKA is most often the result of inappropriate insulin dosing, but some patients have a concurrent illness, most commonly an infection (30).

Clinical Features

The hallmark of DKA is the combination of hyperglycemia, a serum bicarbonate below 20 mEq/L, and an elevated anion gap. The blood glucose is usually above 250 mg/ dL, but it may only be mildly elevated or even normal in about 20% of cases (30). There is no correlation between the severity of the hyperglycemia and the severity of the ketoacidosis (31). Semiquantitative methods for detecting ketones (acetoacetate) in blood and urine will be positive. However, as mentioned earlier, these methods will underestimate the severity of the ketonemia.

The Anion Gap

The increase in ketoacids should produce an elevated anion gap; however, this is variable, and the anion gap can be normal in DKA (32). The renal excretion of ketones is accompanied by an increase in chloride reabsorption in the renal tubules, and the resulting hyperchloremia limits the increase in the anion gap.

Management

The management of DKA is summarized in Table 29.2. The following are some of the details.

Insulin

Insulin therapy is given intravenously, starting with a bolus dose of 0.1 units per kilogram body weight (some do not feel this is necessary) and followed with a continuous infusion at 0.1 U /kg per hour. Because insulin adsorbs to intravenous tubing, the initial 50 mL of infusate should be run through the IV setup before the insulin drip is started. The blood glucose levels should be measured every 1 to 2 hours during intravenous

TABLE 29.2 Management of Diabetic Ketoacidosis

Insulin:	0.1 U/kg IV push, then 0.1 U/kg/hr by continuous infusion. Decrease dose rate 50% when serum $HC0_3$ rises above 16 mEq/L.	
Fluids:	Start with 0.9% saline, 1 L/hr for the first 2 hours. Follow with 0.45% saline at 250-500 mL/hr. Total fluid deficit is usually 50-100 m L/kg.	
Potassium:	If serum K = _ mEq/L, give _ mEq over next hour.	
	<3	40
	3-4	30
	4-5	20
	5-6	10
	>6	0
Phosphate:	If serum $P0_4$ is below 1.0 mg/dL, give 7.7 mg/kg over 4 hours.	

insulin therapy. The goal is to decrease the blood glucose by 50 to 75 *mg*/dL per hour (33). If this goal is not achieved, the insulin infusion rate should be doubled (33). Fingerstick glucose determinations can be performed if the blood glucose is below 500 mg/ dL.

Fluids
Volume deficits average 50 to 100 mL/kg (or 4 to 8 L for a 175 lb adult). If no evidence of hypovolemic shock exists, crystalloid fluids are appropriate for volume replacement. Fluid therapy begins with 0.9% (isotonic) saline infused at a rate of approximately 1 L/hour for the first 2 hours. This is followed by infusion of 0.45% (half normal) saline at 250 to 500 mL/hour. When the blood glucose falls to 250 *mg*/dL, dextrose can be used in the intravenous fluids and the infusion rate is dropped to 100 to 250 mL/hour.
If evidence of hypovolemic shock (e.g., hypotension, reduced urine output) does exist, fluid replacement should begin with colloid fluids until the blood pressure normalizes. The preferred colloid in this situation is 5% albumin because 6% hetastarch increases the serum amylase levels, and elevated amylase is a common finding in DKA (in up to 80% of cases) and may represent subclinical pancreatitis (30).

Potassium
Potassium depletion is almost universal in DKA, and the average deficit is 3 to 5 mEq/kg. However, the serum potassium is often normal (74% of patients) or elevated (22% of patients) at presentation. The serum potassium falls during insulin therapy (transcellular shift), and this fall can be dramatic. Therefore, potassium replacement should be started as soon as possible (Table 29.2), and the serum potassium should be monitored hourly for the first 4 to 6 hours of therapy.

Phosphate
Phosphorous depletion is also common in DKA and averages 1 to 1.5 mmol/kg. However, phosphorous replacement seems to have little impact on the outcome in DKA, and therefore phosphate replacement is not recommended routinely (30). The serum phosphate level should be measured 4 hours after the start of therapy. If the level is severely depressed (less than 1 *mg*/dL), phosphate replacement is advised (see Table 29.2 for the recommended replacement dose).

Bicarbonate
Bicarbonate therapy does not improve the outcome in DKA, and is not recommended, regardless of the severity of the acidemia (30).

Monitoring Acid-Base Status
The serum bicarbonate may not be a reliable parameter for following the acid-base changes in DKA. Fluid replacement therapy often produces a hyperchloremic acidosis by promoting ketoacid excretion in the urine,

which increases chloride reabsorption in the renal tubules. This can keep the bicarbonate from rising despite a resolving ketoacidosis. In this situation, the *pattern* of the acidosis is changing (i.e., changing from a high anion gap to a low anion gap acidosis). Therefore, monitoring the pattern of the acidosis as therapy proceeds can be more informative. This is accomplished by monitoring the gap gap: i.e., the anion gap excess: bicarbonate deficit ratio, as described in Chapter 28. This ratio is 1.0 in pure ketoacidosis, and decreases toward zero as the ketoacidosis resolves and is replaced by the hyperchloremic acidosis. When the ketones have been cleared from the bloodstream, the ratio approaches zero.

ALCOHOLIC KETOACIDOSIS

Alcoholic ketoacidosis (AKA) is a complex acid-base disorder that occurs in chronic alcoholics and usually appears 1 to 3 days after a period of heavy binge drinking (34). Several mechanisms seem to be involved in the ketosis, including reduced nutrient intake (which initiates enhanced ketone production), hepatic oxidation of ethanol (which generates NADH and enhances beta-hydroxybutyrate formation), and dehydration (which impairs ketone excretion in the urine).

Clinical Features

Patients with AKA tend to be chronically **iII** and have several comorbid conditions. The presentation usually includes nausea, vomiting, and abdominal pain (34). Electrolyte abnormalities are common, particularly the *hypos* (e.g., hyponatremia, hypokalemia, hypophosphatemia, hypomagnesemia, hypoglycemia). Mixed acid-base disorders are also common in AKA. More than half the patients can have lactic acidosis (caused by other conditions), and metabolic alkalosis occurs in patients with protracted vomiting.

Diagnosis

The diagnosis of AKA is suggested by the clinical setting (i.e., after a period of binge drinking), an elevated anion gap, and the presence of ketones in the blood or urine. However, the nitroprusside reaction for detecting ketones can be negative in AKA. This is shown in Figure 29.3. The oxidation of ethanol in the liver generates NADH, and' this favors the conversion of acetoacetate to l3-hydroxybutyrate and results in a low concentration of acetoacetate in blood and urine. Even though most cases of AKA have a positive nitroprusside reaction for ketones (34), the severity of the ketoacidosis is significantly underestimated.

Management

The management of AKA is notable for its simplicity. Infusion of dextrose-containing saline solutions is all that is required. The glucose helps retard hepatic ketone production, while the infused volume promotes the renal

clearance of ketones. The ketoacidosis usually resolves within 24 hours. Other electrolyte deficiencies are corrected as needed. Bicarbonate therapy is unnecessary (34).

TOXIC ALCOHOLS

Two alcohols are noted for their ability to generate organic acids: ethylene glycol and methanol. These are called toxic alcohols, but this is not meant to imply that ethanol is nontoxic.

Ethylene Glycol

Ethylene glycol is an alcohol solvent used primarily in antifreeze and deicing solutions. Toxic exposure to ethylene glycol is the leading cause of death from chemical agents in the United States (35). About 70% of toxic exposures are unintentional, but only 15% of life-threatening exposures are unintentional (36).

Pathophysiology

Ethylene glycol can be ingested, inhaled, or absorbed through the skin. Most life-threatening exposures involve ingestion. Absorption from the GI tract is rapid, and 80% of the ingested dose is metabolized in the liver. Metabolism by alcohol dehyrogenase in the liver produces glycolic acid, as shown in Figure 29.4. This is the major metabolite of ethylene glycol,

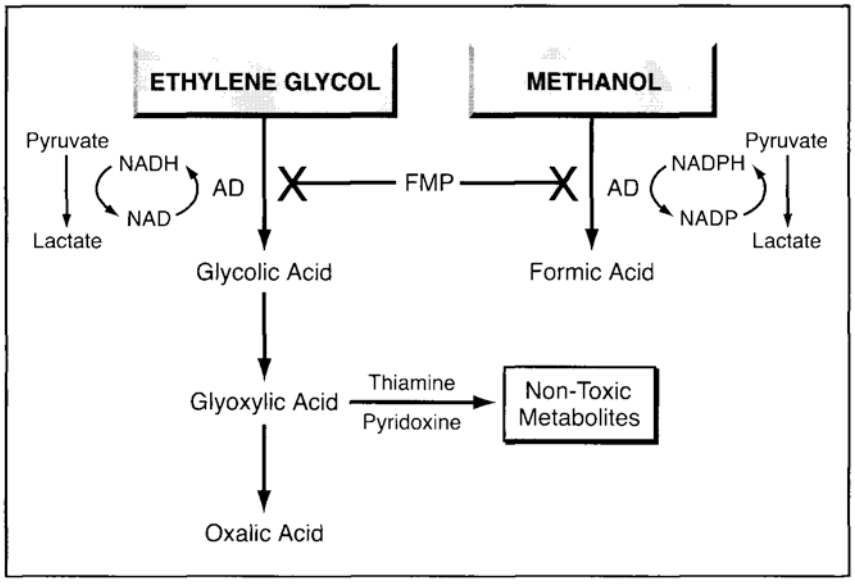

FIGURE 29.4 The metabolism of ethylene glycol and methanol. AD = alcohol dehydrogenase. FMP = fomepizole

and it produces a metabolic acidosis with an elevated anion gap (37). The formation of glycolic acid also involves the conversion of NAD to NADH, and this promotes the conversion of pyruvate to lactate. As a result, serum lactate levels are also elevated in ethylene glycol poisoning (37,38).
The final metabolite of ethylene glycol is oxalic acid, which can combine with calcium to form a calcium oxalate complex that precipitates in the renal tubules. The calcium oxalate crystals (which are recognizable on microscopic examination of the urine) can damage the renal tubules and produce acute renal failure.

Clinical Presentation
Early signs of ethylene glycol intoxication include nausea, vomiting, and apparent inebriation (altered mental status, slurred speech, and ataxia). Because ethylene glycol is odorless, there is no odor of alcohol on the breath. Severe cases are accompanied by depressed consciousness, coma, generalized seizures, renal failure, pulmonary edema, and cardiovascular collapse (37). Renal failure can be a late finding (i.e., 24 hours after ingestion).
Laboratory studies show a metabolic acidosis with an elevated anion gap and an elevated osmolal gap (see ehapter 32 for a description of the osmolal gap). Serum lactate levels can be elevated (usually 5 to 6 mEq/L) (37,38). Hypocalcemia can be present, and calcium oxalate crystals are visualized in the urine in about 50% of cases (39). A plasma assay for ethylene glycol is available, and a level> 25 mg/ dL is considered toxic, and deserving of immediate therapy (36,37). Plasma levels can be misleading because metabolism of the parent compound can result in negligible plasma levels in patients who present late after ingestion.

Treatment
The results of the ethylene glycol assay are often not available immediately, and therapy is started based on a high clinical suspicion of ethylene glycol intoxication (e.g., metabolic acidosis with elevated anion gap, elevated osmolal gap, and oxaluria). Treatment involves inhibition of alcohol dehydrogenase, and hemodialysis if necessary.

FOMEPIZOLE. The traditional use of ethanol to inhibit alcohol dehydrogenase has been replaced by the drug fomepizole, which inhibits alcohol dehydrogenase (see Figure 29.4) without the side effects that accompany ethanol. The best results are obtained when therapy begins within 4 hours of ingestion. The recommended dosage is: 15 mg/kg IV as an initial dose, then 10 mg/kg every 12 hours for 48 hours, then 15 mg/kg every 12 hours until the plasma ethylene glycol level is 25 mEq/L or lower (37,40). The increased dose at 48 hours compensates for a selfinduced increase in fomepizole metabolism.

HEMODIALYSIS. The clearance of ethylene glycol and all its metabolites is enhanced by hemodialysis. The indications for immediate hemodialysis include severe acidemia (pH < 7.1), and evidence of significant end-organ damage (e.g., coma, seizures, and renal insufficiency) (37,40).

Multiple courses of hemodialysis may be necessary. Fomepizole should be dosed every 4 hours if hemodialysis is continued (37).

ADJUNCTS. Thiamine (100 mg IV daily) and pyridoxine 000 mg IV daily) can divert glyoxylic acid to non-toxic metabolites (see Figure 29.4). Despite evidence that these measures improve outcome, they are recommended based on theoretical benefit (37).

Methanol

Methanol (which is popularly known as *wood alcohol* because it was first distilled from wood) is a simple alcohol that is a common ingredient in shellac, varnish, windshield washer fluid, and solid cooking fuel (Sterno) (37,41).

Pathophysiology

Like ethylene glycol, methanol is rapidly absorbed from the GI tract and is metabolized by alcohol dehydrogenase in the liver (see Figure 29.4). The metabolite, formic acid, is a mitochondrial toxin that acts by inhibiting cytochrome oxidase. Tissues that are particularly susceptible to damage are the retina, optic nerve, and basal ganglia (41). Serum lactate levels can be elevated for the same reason as explained for ethylene glycol, but the added mitochondrial toxicity of formic acid can result in higher serum lactate levels.

Clinical Presentation

Early signs (within 6 hours of ingestion) include signs of apparent inebriation without the odor of ethanol (as in ethylene glycol intoxication). Later signs (6 to 24 hours after ingestion) include visual disturbances (e.g., scotoma, blurred vision, complete blindness), depressed consciousness, coma, and generalized seizures. Pancreatitis has also been described (37). Examination of the retina can reveal papilledema and generalized retinal edema.

Laboratory studies show the same acid-base abnormalities and elevated osmolal gap as described for ethylene glycol intoxication (although lactate levels may be higher). Pancreatic enzymes can be also be elevated, and elevated CPK from rhabdomyolysis has been reported (37). A plasma assay for methanol is available, and a level above 25 mg/ dL is considered toxic (and deserving of treatment). As explained with ethylene glycol, plasma levels can be misleading in patients who present late after ingestion because the parent compound can be completely degraded by this time.

Treatment

Treatment is the same as described for ethylene glycol, except: visual impairment is an indication for dialysis, and adjunctive therapy with thiamine and pyridoxine is not indicated.

A FINAL WORD

The most important take-home message in this chapter is the fact that acidosis *per se* is not harmful, and does not require treatment. The problem with lactic acidosis and ketoacidosis is not the acidosis, but the underlying condition causing the acidosis. Lactic acidosis has a high mortality when it is caused by circulatory shock, but it is the shock that causes the high mortality, not the acidosis. The other point that deserves emphasis is the fact that bicarbonate is not much of a buffer in the pH range that we live with (see Figure 29.2), so even if alkali therapy was desirable, bicarbonate is not a good choice.

REFERENCES

Chapter 30

METABOLIC ALKALOSIS

Although the spotlight usually falls on metabolic acidosis, one of every three acid-base disorders in hospitalized patients is a metabolic *alkalosis 0).* In the ICU, the prevalence of metabolic alkalosis is determined by the popularity of diuretics and nasogastric decompression. However, the real culprit in ICU-related metabolic alkalosis is chloride depletion, aided by the inherent tendency of body fluids to remain electrically neutral 0-3).

ORIGINS OF METABOLIC ALKALOSIS

Metabolic alkalosis is characterized by an increase in extracellular bicarbonate ($HC0_3$) concentration without an associated decrease in arterial $PC0_2$ (see Table 28.1 in Chapter 28). The inciting event can be loss of fixed (nonvolatile) acid or gain in bicarbonate in the extracellular fluid. The kidneys have a prominent role in the development and maintenance of metabolic alkalosis, and the mechanisms involved are described next.

Renal Mechanisms of Acid-Base Control

The participation of the kidneys in acid-base control is illustrated in Figure 30.1. There are two principal mechanisms: bicarbonate reabsorption in the proximal tubules, and hydrogen ion secretion in the distal tubules.

Bicarbonate Reabsorption

Bicarbonate is readily filtered at the glomerulus, and most (80%) of the filtered $HC0_3$ is returned to the bloodstream in the proximal tubules. The mechanism of $HC0_3$ reabsorption in the proximal tubules is shown in the left panel of Figure 30.1. Hydrogen ions (H+) are released into the lumen of the proximal tubules by a sodium-hydrogen (Na+-H+) transporter protein on the luminal surface of the tubular epithelial cells. The H+ reacts with $HC0_3$ to form carbonic acid, which dissociates immediately to form CO_2 and H_20. The CO_2 moves across the wall of the renal

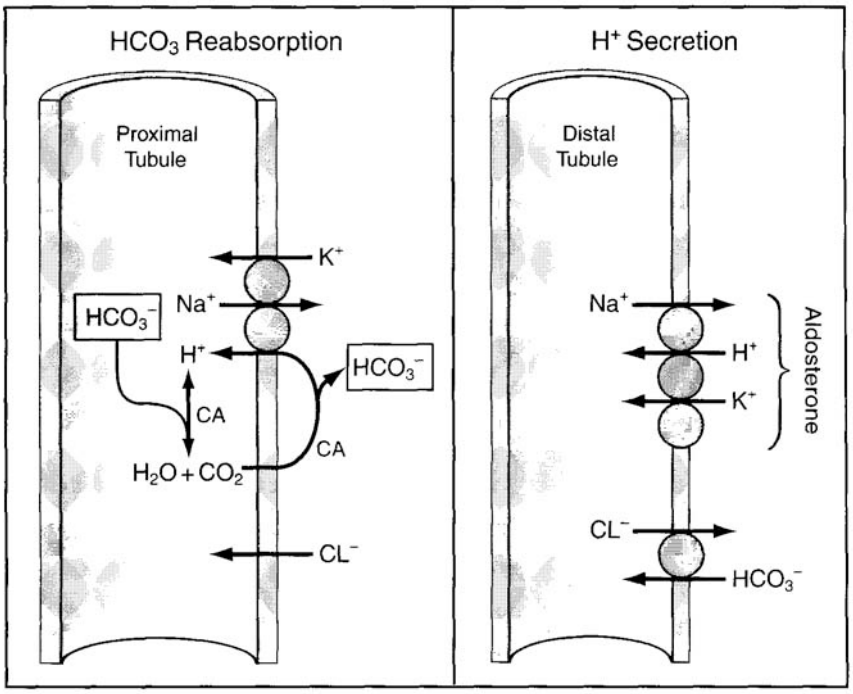

FIGURE 30.1 Mechanisms of acid-base control in the kidneys. CA = carbonic anhydrase.

tubule and is hydrated in the process to regenerate the $HC0_3$ and H+. The $HC0_3$ moves into the bloodstream and the H+ is transported back into the lumen of the renal tubule for another go-round. The reactions in this sequence are facilitated by the enzyme carbonic anhydrase (the importance of this will surface later in the chapter).

For every molecule of $HC0_3$ that is reabsorbed and added back to the extracellular fluid, one molecule of chloride moves in the opposite direction (from extracellular fluid to the lumen of the renal tubules). This maintains electrical neutrality in the extracellular fluid. The reciprocating relationship between chloride and bicarbonate plays a pivotal role in the development of metabolic alkalosis, as will be explained.

Hydrogen Ion Secretion

The kidneys are responsible for removing fixed (nonvolatile) acids from the body, and this occurs in the distal tubules, where H+ is secreted into the lumen of the tubules and excreted in the urine (see the panel on the right in Figure 30.1). The secretion of H+ is accomplished by a Na+-H+ transport protein (like the one in the proximal tubule) and a membrane pump that can move potassium as well as H+ into the renal tubules.

The Na + -H+ -K+ transport system in the distal tubules is responsive to aldosterone, which promotes the reabsorption of Na + and the secretion of H+ and K+.
The renal mechanisms of acid-base control are the major determinants of bicarbonate concentration in extracellular fluid. As such, the kidneys are involved in most cases of metabolic alkalosis in the ICU.

Predisposing Conditions
The following conditions are responsible for most cases of metabolic alkalosis in ICUs.

Loss of Gastric Secretions
Gastric secretions are rich in hydrogen and chloride ions (concentration of each is 50 to 100 mEq/L), and loss of these secretions from vomiting or nasogastric suction can produce a profound metabolic alkalosis. Despite the loss of gastric acid, chloride depletion is the major factor responsible for the metabolic alkalosis that accompanies vomiting and nasogastric suctioning. Chloride depletion stimulates HCO reabsorption in the kidneys, and the resulting increase in extracellular huid $HC0_3$ creates a metabolic alkalosis. The $HC0_3$ that is added to the extracellular fluid must match the chloride that is lost to maintain electrical neutrality. Therefore, the severity of the alkalosis is determined (at least partly) by the magnitude of the chloride loss. Other factors that contribute to the alkalosis from loss of gastric secretions are hypovolemia and hypokalemia.

Diuretics
Thiazide diuretics and "loop" diuretics like furosemide promote metabolic alkalosis by increasing the urinary loss of electrolytes and free water. The following electrolytes are involved:

The principal action of these diuretics is to increase sodium loss in urine (natriuresis). However, an equivalent amount of chloride is also lost in urine because chloride excretion in the urine usually follows the sodium excretion. The increased urinary chloride excretion is known as *clzloruresis,* and diuretics that promote chloride loss in the urine are known as *clzloriuretic* diuretics (2).

Potassium loss in the urine is also increased by these diuretics because sodium delivery to the distal tubules is increased, and this promotes potassium secretion via the sodium-potassium exchange pump in the distal tubule (see Fig. 30.1).

Magnesium reabsorption in the kidneys usually mirrors sodium reabsorption, so these diuretics also promote magnesium loss in the urine. Magnesium depletion plays an important role in diuretic induced potassium depletion, as described in Chapter 34.

An additional mechanism for diuretic-induced metabolic alkalosis is volume depletion, as described next.

Volume Depletion

Volume depletion promotes metabolic alkalosis in two ways. Sodium and bicarbonate reabsorption are directly linked (by the Na+ -H+ transporter) so the increased sodium reabsorption in response to volume depletion is accompanied by an increase in bicarbonate reabsorption. Volume depletion also stimulates renin release and thereby promotes the formation of aldosterone, which will promote H+ secretion in the distal tubules.

Volume depletion has a longstanding relationship with metabolic alkalosis, as shown by the term *contraction alkalosis.* However, the importance of volume depletion as an independent source of metabolic alkalosis is being questioned because volume resuscitation does not correct metabolic alkalosis without chloride repletion (2). Because volume depletion is often associated with chloride depletion, the distinction may not be important, as long as isotonic saline is used to correct the volume deficits.

Hypokalemia

Hypokalemia is associated with a transcellular shift of H+ into cells, and an increase in H+ secretion in the distal tubules: both of these effects favor the development of a metabolic alkalosis. The enhanced secretion of H+ in the distal tubules involves a Na + -H+ transporter (see Figure 30.1) that requires adequate delivery of sodium to the distal tubules. In the setting of hypovolemia, most of the filtered sodium is reabsorbed in the proximal tubules, and the effects of hypokalemia on H+ secretion are minimal. The trans cellular shift of H+ is considered the most important mechanism favoring metabolic alkalosis from hypokalemia in ICU patients.

Organic Anions

The administration of organic anions such as lactate (in lactated Ringer's solution), acetate (in parenteral nutrition solutions), and citrate (in banked blood) could produce a metabolic alkalosis. However, only citrate administration in blood transfusions is capable of causing a metabolic alkalosis (4), and a minimum of 8 units of blood must be transfused before the plasma $HC0_3$ begins to rise (5).

Chronic CO2 Retention

The compensatory response to CO_2 retention is a metabolic alkalosis that results from an increased bicarbonate reabsorption in the kidneys. According to the scheme shown in Figure 30.1 (left panel), CO_2 can directly stimulate $HC0_3$ reabsorption. **I**f chronic hypercapnia is corrected suddenly (e.g., by overventilation during brief periods of mechanical ventilation), the compensatory metabolic alkalosis will become a primary acid-base disorder. The metabolic alkalosis in this case should not be a concern because it is an adaptive response to prevent severe acidosis from CO_2 retention.

CLINICAL CONSEQUENCES

Despite the potential for harm, metabolic alkalosis has no apparent deleterious effects in most patients. The following adverse effects are the ones most often mentioned.

Neurologic Manifestations

The neurologic manifestations attributed to alkalosis include depressed consciousness, generalized seizures, and carpopedal spasms. However, these manifestations are almost always associated with respiratory alkalosis, not metabolic alkalosis. This is explained by the greater tendency for respiratory alkalosis to influence the acid-base status of the central nervous system.

Hypoventilation

Unlike the ability of metabolic acidosis to stimulate ventilation, metabolic alkalosis does not cause significant respiratory depression or CO_2 retention in most patients. The magnitude of increase in serum bicarbonate that is needed to cause significant respiratory depression can be determined using the equation shown below.

$$\text{Expected } PaC0_2 = (0.7 \text{ X } HC0_3) + (21 \pm 2) \quad (30.1)$$

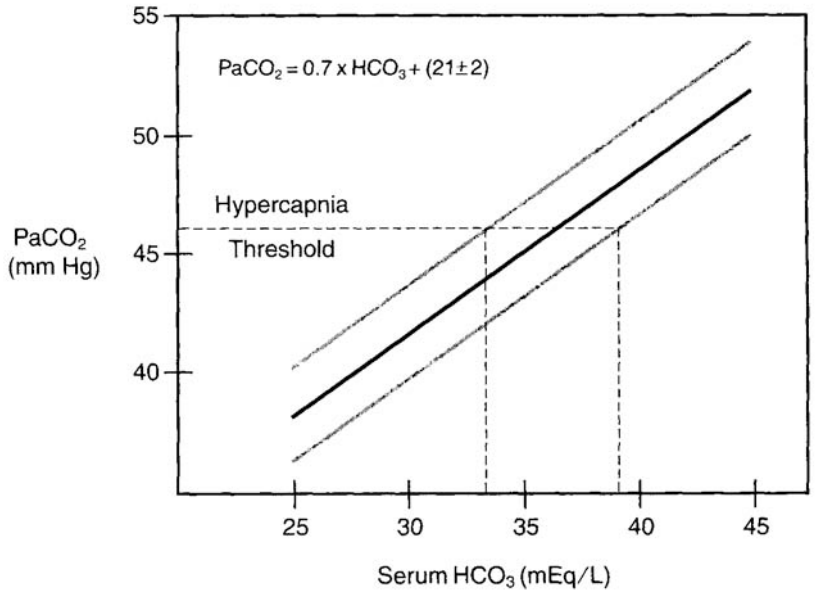

FIGURE 30.2 The relationship between serum bicarbonate (HCO_3) and arterial PCO_2 ($PaCO_2$) from the equation shown at the top of the graph. Note that the serum HCO_3 must rise above 30 to 35 mEq/L to produce hypercapnia (i.e., $PaCO_2$ above 46 mm Hg).

This equation was presented in Chapter 28 (Equation 28:4) as a means of identifying if the respiratory response to metabolic alkalosis is appropriate (6). This equation is used to plot the relationship between serum $HC0_3$ and arterial PCO_z shown in Figure 30.2. The threshold for hypercapnia (which is an arterial $PC0_2$ of 46 mm Hg in this graph) corresponds to a serum $HC0_3$ of 34 to 39 mEq/L. Therefore, significant hypoventilation is not expected in metabolic alkalosis until the serum $HC0_3$ reaches the mid-thirties range.

Systemic Oxygenation

Alkalosis has a number of effects that, in combination, can threaten tissue oxygen availability. These effects are indicated in Figure 30.3, and each is summarized below. Once again, these effects are more prominent with respiratory alkalosis.
Severe alkalemia (pH> 7.6) can produce widespread vasoconstriction. Alkalosis increases the fraction of serum calcium that is bound to albumin, and the resultant decrease in ionized (free) calcium can promote widespread vasoconstriction that compromises tissue perfusion. Myocardial contractility is often reduced, and cardiac output decreases.
Alkalosis shifts the oxyhemoglobin dissociation curve to the left (Bohr effect), so that hemoglobin is less willing to release oxygen into the tissues.

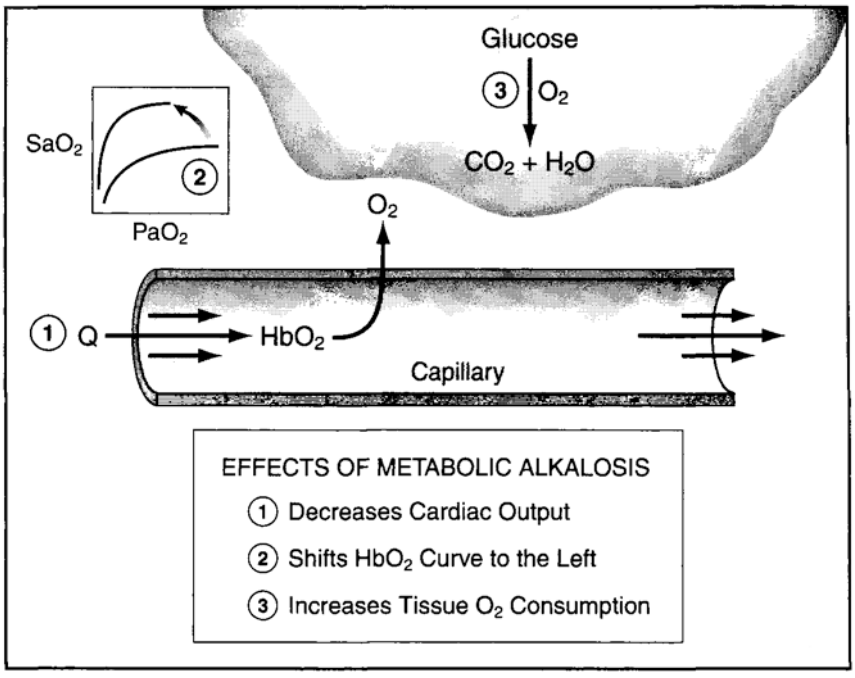

FIGURE 30.3 Effects of metabolic alkalosis on the determinants of tissue oxygenation.

Intracellular alkalosis increases the activity of enzymes in the glycolytic pathway, and the rate of glycolysis subsequently increases (7).

Therefore, metabolic alkalosis can decrease tissue oxygen availability while increasing tissue oxygen demands. The clinical significance of these effects is unclear, but they certainly deserve attention in patients with circulatory failure or circulatory shock.

THE EVALUATION

Metabolic alkaloses are traditionally classified as chloride-responsive or chloride-resistant, based on the urinary chloride concentration (see Table 30.1).

Chloride-Responsive Alkalosis

A *chloride-responsive* metabolic alkalosis is characterized by a low urinary chloride concentration (i.e., less than 15 mEq/L), indicating chloride depletion. This type of metabolic alkalosis is the result of gastric acid loss, diuretic therapy, volume depletion, or renal compensation for hypercapnia. As indicated by the inciting conditions, volume depletion is common in chloride responsive metabolic alkalosis. The majority of cases of metabolic alkalosis in hospitalized patients are the chloride-responsive variety.

Chloride-Resistant Alkalosis

A *chloride-resistant* metabolic alkalosis is characterized by an elevated urinary chloride concentration (i.e., above 25 mEq/L). Most cases of chloride resistant alkalosis are caused by primary mineralocorticoid excess (e.g., hyperadrenal conditions) or severe potassium depletion (these two conditions often co-exist). This type of metabolic alkalosis is usually associated with volume expansion rather than volume depletion. The disorders associated with chloride-resistant alkalosis are uncommon in the ICU, with the possible exception of aggressive corticosteroid therapy.

TABLE 30.1 Classification of Metabolic Alkalosis

Chloride-Responsive	Chloride-Resistant
Urinary chloride <15 mEq/L:	Urinary chloride >25 mEq/L:
1. Loss of gastric acid	1. Mineralocorticoid excess
2. Diuretics	2. Potassium depletion
3. Volume depletion	
4. Posthypercapnia	

Spot Urine Chloride
When the cause of a metabolic alkalosis is unclear, the concentration of chloride in a random (spot) urine sample can help identify the possible sources of the problem. One source of error occurs in thel early stages of diuretic therapy, when the urinary chloride concentratio is elevated in a chloride-responsive metabolic alkalosis. Another benefit of measuring the spot urinary chloride concentration is in selecting the appropriate therapy to correct the alkalosis. These are described next.

MANAGEMENT
Because most metabolic alkaloses in hospitalized patients are chloride-responsive, chloride replacement is the mainstay of therapy for metabolic alkalosis. The chloride can be replaced as sodium chloride, potassium chloride, or hydrochloric acid (HCl).

Saline Infusion
Because volume depletion is common in chloride-responsive metabolic alkalosis, infusion of isotonic saline (0.9% sodium chloride) is the most common method of chloride replacement in this condition. The volume of isotonic saline needed can be determined by estimating the chloride (Cl) deficit, as shown below:

Cl deficit (mEq) = 0.2 X wt (kg) X (normal Cl - actual Cl)

The factor 0.2 represents the extracellular volume as a fraction of body weight. Once the chloride deficit is determined, the volume of isotonic saline needed to correct the deficit is the ratio: Cl deficit/154, where 154 is the chloride concentration in isotonic saline. This method is summarized in

Table 30.2.
EXAMPLE. A patient who weighs 70 kg and has a metabolic alkalosis from repeated vomiting with a serum chloride of 80 mEq/L. Using a

TABLE 30.2 Saline Infusions for Metabolic Alkalosis

Step 1: *Catculate the chloride (Cl) deficit.*
Cl deficit (mEq) = 0.3 x wt (kg) x (100 - plasma [Cl])
Step 2: *Determine the volume of isotonic saline to correct the Ct deficit.*
Volume of saline (L) = Chloride Deficit/154

From References 2 and 3.

normal serum chloride of 100 mEq/L, the chloride deficit is 0.2 X 70 X 000 - 80) = 280 mEq. The volume of isotonic ~line needed to correct this deficit is 280/154 = 1.8 liters.

Potassium Chloride

The administration of potassium chloride is not an effective method of chloride repletion because the maximum rate of potassium infusion that is safe is 40 mEq/hour (see Chapter 33). Therefore, potassium chloride administration is indicated only for patients who are hypokalemic. However, because hypokalemia can promote metabolic alkalosis, correcting hypokalemia is an important measure for correcting a metabolic alkalosis. **It** is important to emphasize that the administration of potassium chloride will not replenish potassium stores **if** there is concurrent magnesium depletion (8). Therefore, it is important to identify and correct magnesium depletion before attempting to replace potassium deficits (see Chapter 34 for information on identifying and correcting magnesium deficiency).

Hydrochloric Acid Infusions

Infusions of dilute solutions of hydrochloric acid (HCl) produces the most rapid correction of metabolic alkalosis 0). However, because of the risks involved (see later), HCl infusions are reserved for patients with severe alkalemia (pH greater than 7.5) who are not candidates for saline infusions or potassium replacement, or have failed these therapies.

Method

The "dose" of HCl is determined by estimating the hydrogen ion (H+) deficit with the equation below (see Table 30.3).

H+ deficit (mEq) = 0.5 X wt (kg) X (actual $HC0_3$ - desired $HC0_3$)

TABLE 30.3 Infusions of Hydrochloric Acid for Severe or Refractory Metabolic Alkalosis

Step 1: *Calculate the hydrogen ion (W) deficit.*

H+ deficit (mEq) = 0.5 x wt (kg) x (actual $HC0_3$ - desired $HC0_3$)

Step 2: *Determine the volume of* O. 1 *N HCl needed to correct the H+ deficit.*

Volume of 0.1 N HCl (L) = H+ *deficit/100*

From References 2 and 3.

The factor 0.5 represents the volume of distribution for H+ (relative to body weight) and is larger than the chloride space because some of the H+ will end up inside cells. The desired $HC0_1$ should be above the normal range (the goal is not to correct the alkalosis, but to reduce the severity), and can be set halfway between the actual and normal HCO_T
The preferred HCl solution for intravenous use is O.lN HCI, which contains 100 mEq H+ per liter (similar to the H+ concentration of 50 to 100 mEq/L in gastric secretions). The volume of O.l N HCl needed to correct the H+ deficit is determined as the ratio (H+ deficit/100), as shown in Table 30.3. Because HCl solutions are sclerosing, they must be infused through a large, central vein (9), and the infusion rate should not exceed 0.2 mEq/kg/hr (3).

EXAMPLE. Consider a patient who weighs 70 kg and has a plasma $HC0_3$ of 45 mEq/L and an arterial pH of 7.59. Using a desired plasma $HC0_3$ of 35 mEq/L, the H+ deficit is 0.5 X 70 X 10 = 350 mEq. The corresponding volume of O.lN HCl is 350/100 = 3.5 L, and the maximum infusion rate is (0.2 X 70)/100 = 0.14 Llhour (2.3 ml/minute).

Adverse Effects
The major concern with HCl infusions is the corrosive effects of the ECl solutions. Extravasation of HCl solutions can produce severe tissue necrosis, even when the solution is infused through a central vein (0). Solutions more concentrated than 0.1N HCl can also corrode the intravascular catheters (11)!

Gastric Acid Suppression
Inhibition of gastric acid secretion (with histamine H_2 receptor antagonists or proton pump inhibitors) has been recommended for patients who require continued nasogastric suction. However, it is important to point out gastric acid suppression will substitute sodium chloride losses for hydrochloric acid losses, so chloride will continue to be lost. Considering that chloride depletion plays a major role in the metabolic alkalosis from upper GI losses, the rationale for gastric acid suppression in this setting needs to be reevaluated.

Chloride-Resistant Alkalosis
The management of chloride-resistant metabolic alkalosis is aimed at treating the underlying cause of the mineralocorticoid excess (e.g., hyperadrenalism, heart failure) and correcting potassium deficits. The carbonic anhydrase inhibitor, acetazolamide, can also be used to relieve the alkalosis in this condition (see below).

Acetazolamide
Acetazolamide (Diamox) blocks $HC0_3$ reabsorption in the kidneys by inhibiting the carbonic anhydrase enzyme involved in the CO_2 <-> $HC0_3$

reaction sequence (see Figure 30.1). The increase in $HC0_3$loss in urine is accompanied by an increase in sodium loss inturine, and this produces a diuretic effect. Therefore, acetazolamide has a dual benefit in patients with chloride-resistant metabolic alkalosis because most of these patients have an increased extracellular volume. The recommended dose is 5 to 10 mg/kg IV (or PO), and the maximum effect occurs after an average of 15 hours (2).
Acetazolamide promotes potassium depletion as well as volume depletion, and it should not be used in cases of chloride resistant metabolic alkalosis that are associated with hypokalemia or volume depletion.

A FINAL WORD

The final word for this chapter is *chloride:* i.e., most cases of metabolic alkalosis in the ICU are associated with (and probably caused by) chloride depletion, and most cases are corrected by giving chloride as NaCl, KCl, or HCl. Metabolic alkalosis seems to have very few deleterious effects that are apparent clinically, so treating the alkalosis is probably not as important as correcting the condition that produces the alkalosis.

REFERENCES