Acid-Base Disorders
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Chemical Buffering
Extracellular buffers, including plasma proteins, phosphates, and bicarbonate, are the earliest defense against acidosis. The most prominent extracellular buffer is bicarbonate, which is highly abundant and acts as a dynamic buffer by independently regulating $P_{CO_2}$ through changes in alveolar ventilation. This feature increases buffering capacity by more than 10-fold. Buffering also occurs within the intracellular compartment but is delayed as $H^+$ equilibrates over a period of hours. Intracellular buffers, including bone, inorganic phosphates, proteins, and hemoglobin, are eventually responsible for more than 50% of the overall chemical buffering capacity.

Alterations in Alveolar Ventilation
Alterations in alveolar ventilation provide compensation for acute acid-base disturbances. According to the Henderson-Hasselbalch equation, serum pH can be determined as follows:

$$pH = pK_a + \log\frac{[HCO_3^-]}{[H_2CO_3]} + 0.03\left(P_{CO_2}\right)$$

Stimulation of peripheral chemoreceptors triggers changes in ventilation within minutes. By altering $P_{CO_2}$ through variations in minute ventilation, the $HCO_3^-/P_{CO_2}$ ratio remains relatively constant, and alterations in pH are thereby mitigated. The effectiveness of the ventilatory response is acutely limited by differences in the solubility of $CO_2$ and $H^+$ within the central nervous system (CNS). The hyperventilation induced by systemic acidosis is incomplete as a result of local alkalosis sensed by the central chemoreceptors as $CO_2$ diffuses more rapidly across the blood-brain barrier.

Alterations in Renal Hydrogen Ion Excretion
Because of the inability of $HCO_3^-$ to effectively buffer $H_2CO_3$ produced through acute $CO_2$ retention as described, renal compensation is centrally important in the response to primary respiratory disorders. Renal compensatory mechanisms include enhanced proton excretion and increased $HCO_3^-$ resorption. Renal compensation for acute acid-base disorders begins immediately; however, the full effect is not appreciated for 5 or 6 days.

Nomenclature
The normal range of serum pH is 7.38 to 7.42. Acidemia is defined by serum pH below 7.38. Likewise, alkalemia is defined by serum pH above 7.42. These terms describe the absolute directional change of measured pH but say nothing about the processes that alter pH from normal. The processes that alter pH are termed acidosis and alkalosis.

**KEY POINTS**

- Normal pH or serum bicarbonate values can mask an important, underlying acidosis in the setting of a mixed disorder.
- An elevated anion gap is a sign of metabolic acidosis and should be calculated on each chemistry sample.
- Arterial and venous blood gas sampling is a useful emergency department test because of the strong association between arterial and venous $HCO_3^-$ and pH.
- Correlation between venous $P_{CO_2}$ and arterial $P_{CO_2}$ is lacking, although venous $P_{CO_2}$ levels may be used as a screening tool for hypercapnia.
- Admission lactate level and standard base excess are markers of illness severity that correlate with patient morbidity and mortality in the hospital.
- The urine ketone dipstick test is highly sensitive for serum ketosis.
- Venous and arterial lactate samples are equivalent.
- Indiscriminate use of sodium bicarbonate for the treatment of undifferentiated metabolic acidosis should be avoided.

**REGULATION OF ACID-BASE BALANCE**
The normal hydrogen ion ($H^+$) concentration in serum is approximately 40 nanoequivalents per liter. This is approximately 1/1,000,000 the concentration of the other major serum ions, but the small size and high charge density of protons make them highly reactive and capable of inducing conformational and functional changes in body proteins. Rigid control of the free $H^+$ concentration is therefore essential to life.

Daily metabolism produces an acid load of 150 mmol of nonvolatile (fixed) acid and 12,000 mmol of volatile acid ($CO_2$). Physiologic, pathologic, and dysregulated endogenous production, as well as externally administered product, can all increase the systemic acid load.

Maintenance of systemic homeostasis in the setting of acid-base changes occurs via three main mechanisms:

1. Chemical buffering
2. Alterations in alveolar ventilation
3. Alterations in renal $H^+$ excretion
Acid-base disorders are often complex—pH may be normal in the setting of an obvious acid-base disorder because of the presence of a second or even a third coexisting acid-base process. For example, patients with a mixed disorder may have a normal or alkalamic pH during ketoacidosis if a concomitant alkalosis (metabolic or respiratory) is also present. It is therefore important to note that a normal pH does not exclude an important acid-base disorder.

**DIAGNOSTIC INTERPRETATION**

Primary acid-base processes are divided into respiratory or metabolic disorders by examining P\textsubscript{CO\textsubscript{2}} and serum bicarbonate. Primary elevations in P\textsubscript{CO\textsubscript{2}} signify respiratory acidosis, whereas decreased serum bicarbonate identifies metabolic acidosis. Diagnostic assessment of acid-base disorders requires accurate measurement of these plasma variables, in addition to calculated values, to unmask mixed disorders. Coupling the clinical history and physical assessment with these values reveals important clues about the causative illness.

Serum testing includes direct evaluation of pH, P\textsubscript{CO\textsubscript{2}}, and H\textsubscript{CO\textsubscript{3}}\textsuperscript{-} through arterial and venous blood sampling; calculation of the anion gap from serum chemistries; and additional measures (e.g., the standard base excess) in an attempt to quantify the metabolic component of acid-base disorders (see the “Facts and Formulas” box for basic formulas used in this chapter).

**FACTS AND FORMULAS**

\[
\text{pH} = 6.1 + \log[\text{HCO}_{3}^-] / 0.03 \times \text{P} \text{CO}_{2} \]

Anion gap = Unmeasured anions – Unmeasured cations = Na\textsuperscript{+} – [Cl\textsuperscript{-} + H\textsubscript{CO\textsubscript{3}}\textsuperscript{-}]

Delta gap = Δ Anion gap – Δ HCO\textsubscript{3} = [Calculated anion gap – 10] – [24 – Measured serum HCO\textsubscript{3}]

Calculated Sosm (mOsm/kg) = 2 (Na\textsuperscript{+}) + BUN/2.8 + Glucose/18 + Ethanol/4.8

Osmolal gap = Measured Sosm – Calculated Sosm

**Correction Formulas**

Corrected anion gap = Anion gap + 2.5 (Normal albumin – Measured albumin)

**Compensation Formulas**

Metabolic acidosis: P\textsubscript{CO\textsubscript{2}} = 1.5 (H\textsubscript{CO\textsubscript{3}}\textsuperscript{-}) + 8

Metabolic alkalosis: Increase in P\textsubscript{CO\textsubscript{2}} = 0.6 × Increase in H\textsubscript{CO\textsubscript{3}}\textsuperscript{-}

Respiratory acidosis

- Acute: [H\textsubscript{CO\textsubscript{3}}\textsuperscript{-}] increases by 1 mEq/L for each 10–mm Hg increase in P\textsubscript{CO\textsubscript{2}}
- Chronic: [H\textsubscript{CO\textsubscript{3}}\textsuperscript{-}] increases by 4 mEq/L for each 10–mm Hg increase in P\textsubscript{CO\textsubscript{2}}

Respiratory alkalosis

- Acute: [H\textsubscript{CO\textsubscript{3}}\textsuperscript{-}] decreases by 2 mEq/L for each 10–mm Hg decrease in P\textsubscript{CO\textsubscript{2}}
- Chronic: [H\textsubscript{CO\textsubscript{3}}\textsuperscript{-}] decreases by 5 mEq/L for each 10–mm Hg decrease in P\textsubscript{CO\textsubscript{2}}

**ARterial AND VENous BLOOD GASES**

The ability to substitute venous blood gas samples for arterial samples is appealing because of the pain, difficulty, and complications associated with arterial sampling. Arterial pH and venous pH vary by less 0.04 in most situations. Patients in clinical shock are an important exception, however, because arteriovenous P\textsubscript{CO\textsubscript{2}} (and therefore pH) can vary significantly.

Despite incomplete correlation between venous and arterial P\textsubscript{CO\textsubscript{2}}, venous P\textsubscript{CO\textsubscript{2}} may be used to screen for arterial hypercapnia. In hemodynamically normal patients, P\textsubscript{CO\textsubscript{2}} higher than 45 mm Hg is sensitive (but less than 50% specific) for the detection of arterial hypercapnia, which is defined as P\textsubscript{CO\textsubscript{2}} higher than 50 mm Hg. Venous blood gas screening led to a 29% reduction in arterial sampling in one study. Finally, arterial blood gas analysis enables precise interpretation of respiratory compensation when needed.

**Standard Base Excess**

Although the serum bicarbonate level may describe an acid-base disorder, the amount of acid or base added to the system cannot be calculated unless P\textsubscript{CO\textsubscript{2}} is held constant. The concept of the standard base excess (SBE) was introduced to address this problem and is defined as the quantity of strong acid or base required to restore plasma pH to 7.40 when P\textsubscript{CO\textsubscript{2}} is held constant at 40 mm Hg. A negative value indicates excess acid, whereas a positive value indicates excess base.

SBE has been studied extensively as a resuscitation endpoint in trauma and as a marker of tissue acidosis. Preresuscitation base excess values are reliably linked to the degree of tissue acidosis and serve as independent predictors of mortality in critically ill patients. Base excess has been shown to correlate with hypovolemia, length of hospital stay, and transfusion requirements, whereas the rate of normalization correlates with patient survival.

**Lactate**

Lactic acid is generated through the reduction of pyruvate with the reduced form of nicotinamide adenine dinucleotide (NADH) as follows:

Pyruvate + NADH ⇌ Lactate + NAD\textsuperscript{+}

Lactate is produced by skeletal muscle, brain, intestines, and kidneys, with normal blood lactate levels maintained below 2 mmol/L and the threshold for lactic acidosis defined by a serum level higher than 4 mmol/L.

Arterial lactate sampling is considered the most reliable measure for detecting hyperlactatemia; however, venous and capillary sampling is also used. Central venous sampling is highly correlated with arterial lactate measurements. Peripheral venous samples are sufficient to screen for hyperlactatemia but retain poor specificity (57%) when compared with arterial samples. Elevations in venous lactate should be confirmed with arterial sampling.

**ANion GAP**

Within serum, the requirement for electroneutrality dictates that the net serum cation charge equal the net total anion charge. The calculated difference in commonly measured serum ions is termed the anion gap (AG). It is important to note that the AG represents anions that are present but unmeasured (at least historically) and that an AG is present during health. Fortunately, the difference between unmeasured anions
and unmeasured cations may change (increased or decreased AG) and therefore provide a clue to disease states (Box 160.1).

The greatest utility of the AG is identification and discrimination of metabolic acidosis. The potential for a mixed acid-base disturbance to mask acidosis by normalizing pH and serum bicarbonate highlights the importance of calculating the AG on every chemistry sample. An increased AG almost always signifies a process causing a “wide-gap” metabolic acidosis. Furthermore, calculation of the AG assists in discriminating the cause of undifferentiated metabolic acidosis (e.g., AG versus non-AG processes carry different differential diagnoses).

When acids are added to the system, bicarbonate is replaced by the acid anion (X) as follows:

\[ \text{HX} + \text{NaHCO}_3 \rightarrow \text{NaX} + \text{H}_2\text{O} + \text{CO}_2 \]

Titration and replacement of bicarbonate by unmeasured organic acid produce a relative equimolar elevation in the AG. In contrast, bicarbonate loss (or addition of protons) can occur in the absence of an endogenous or exogenous anion contribution.

\[ \text{HCl} + \text{NaHCO}_3 \rightarrow \text{NaCl} + \text{H}_2\text{CO}_3 \rightarrow \text{CO}_2 + \text{H}_2\text{O} \]

Hyperchloremia maintains electroneutrality without altering the AG. Gastrointestinal and renal losses are the most common causes of non-AG metabolic acidosis (Box 160.2).

**Box 160.1 Causes of Measured Changes in the Anion Gap**

**Increased Anion Gap**
- Organic acids: lactate, ketones, phosphate, sulfate
- Toxins and metabolites: formate (methanol), oxalate (ethylene glycol), salicylates
- Severe volume depletion (hyperaluminaemia)
- IgA paraproteinaemia

**Decreased unmeasured cations**
- Calcium, magnesium, potassium
- Laboratory error
- Metabolic alkalosis
- Respiratory alkalosis

**Decreased Anion Gap**
- Laboratory error
  - Overestimation of chloride or bicarbonate
  - Underestimation of sodium
  - Bromide intoxication (overestimation of chloride)
  - Iodine intoxication (overestimation of chloride)

**Decreased unmeasured anions**
- Hypoalbuminaemia

**Increased unmeasured cations**
- Lithium
- Paraproteins (myeloma)
- Bromide intoxication
- Hypermagnesaemia
- Hypercalcaemia
- Hyperlipidaemia
- IgG gammopathy
- Polymyxin B

The historical range for the AG was 12 ± 4 (8 to 16 mEq/L). With the adoption of ion-specific electrodes, chloride is measured at a higher concentration such that the currently accepted range of AG is 7 ± 3 (4 to 10 mEq/L). More importantly, the AG must be corrected for individual patients. Albumin accounts for 80% of the AG in health. Consequently, large and important deviations may occur if serum albumin is assumed to be normal. AG is thus commonly corrected for serum albumin to improve sensitivity of the AG as a screening tool. The correction factor is calculated as follows:

\[ \text{Corrected AG} = \text{Calculated AG} + 2.5 \left[ \text{Normal} - \text{Measured albumin (g/dL)} \right] \]

**Delta-Delta Calculation**

The AG is also useful for investigating the presence of mixed metabolic disturbances. In simple AG acidosis, bicarbonate is presumably titrated in a one-to-one fashion by organic acid such that the following relationship is noted:

\[ \text{Increase in AG} = \text{Decrease in } \text{HCO}_3^- \]

The difference between the change in the AG and the change in serum bicarbonate is called the delta gap, or delta-delta calculation. Deviations from this stoichiometric relationship indicate a mixed metabolic disturbance. When the change (delta) in the AG is greater than the change in bicarbonate, a preexisting or concomitant metabolic alkalosis is present. Alternatively, a change in AG less than the change in bicarbonate identifies a coexisting non-AG acidosis. A delta gap higher than 6 is generally considered significant.

**Serum Osmolar Gap**

Osmolarity is defined as the number of particles within a volume of fluid (mmol/L), and osmolality is defined as the number of particles in a mass of fluid (mmol/kg). The terms are used interchangeably because the density of water is 1 kg/L. The size of the particle contributing to serum osmolality (Sosm) is unimportant; that is, small ions contribute equally with large proteins.

Sosm is elevated in the presence of osmotically active particles such as alcohols, glycols, and sugars. The difference in measured and calculated Sosm is termed the osmolar gap. An elevated osmolar gap confirms the presence of unmeasured osmotically active particles, which may be helpful

**Box 160.2 Causes of Non–Anion Gap Metabolic Acidosis**

**Gastrointestinal HCO₃⁻ Loss**
- Diarrhea

**Renal HCO₃⁻ Loss**
- Renal tubular acidosis (types 1, 2, and 4)
- Hyperaldosteronism
- Renal failure

**Ingestions**
- Ammonium chloride
- Hyperalimentation

**Other**
- Treatment phases of ketoacidosis
when investigating the cause of unexplained AG acidosis. Osmolar gaps greater than 10 mOsm/kg are considered abnormal and may reflect the presence of a toxic alcohol as the source of the acidosis. However, delayed evaluation after the ingestion of toxic alcohol will show little to no elevation in the osmolar gap as a result of metabolism of the offending alcohol. Likewise, normal osmolar gap values are imprecisely defined, with ranges of −13 to +14.0 mOsm/kg noted in healthy patients.¹⁰,¹¹ This wide variation in the normal range may lead to a normal osmolar gap in the presence of a significant ingestion.

**Evaluation of Mixed Acid-Base Disorders**

By applying the formulas for AG, delta gap, and expected physiologic compensation, a stepwise approach to the evaluation of simple and mixed acid-base problems can be developed.¹² This process is summarized in *Box 160.3*.

Additionally the clinical history is centrally important for proper interpretation of acid-base disorders (*Box 160.4*).

### SPECIFIC ACID-BASE DISORDERS

**Respiratory Acidosis**

Normal ventilatory control is regulated through central receptors that respond to elevated PCO₂ and through peripheral chemoreceptors in the carotid bodies that respond to hypoxia. Because the ventilatory response to hypercapnia is much stronger than that to hypoxemia, only minor elevations in PCO₂ are required to increase minute ventilation. As a result of this vigorous response and the ability to significantly increase minute ventilation, respiratory acidosis almost always develops as a consequence of impaired alveolar ventilation and not from increased production of CO₂.

Elevated PCO₂ causes a decrease in arterial pH and a variable, acute increase in plasma HCO₃⁻ as a result of shifts in equilibrium reactions and a similar, but chronic increase as a result of renal compensation through enhanced H⁺ excretion and HCO₃⁻ retention. CO₂ functions as a volatile acid:

\[
H^+ + HCO_3^- \rightarrow H_2CO_3 + H_2O + CO_2
\]

Under normal conditions, this acid load is immediately buffered by intracellular and extracellular nonbicarbonate buffers. The acute rise in PCO₂ elicits a similar elevation in HCO₃⁻ through a highly predictable relationship:

\[
[HCO_3^-] \text{ increases by } 1 \text{ mEq/L for each } 10-\text{mm Hg increase in PCO}_2
\]

In chronic respiratory acidosis, elevations in PCO₂ are partially protective, with larger amounts of CO₂ able to be excreted at lower minute ventilation. The system also adapts to chronically elevated CO₂ by enhancing renal H⁺ excretion and HCO₃⁻ retention, thereby attenuating the ventilatory response to hypercapnia. The result of chronic respiratory acidosis is that the ventilatory drive becomes dependent on a hypoxic stimulus.

The renal compensatory response in patients with chronic respiratory acidosis requires 3 to 5 days to develop and may be predicted by the following equation:

\[
[HCO_3^-] \text{ increases by } 4 \text{ mEq/L for each } 10-\text{mm Hg increase in PCO}_2
\]

**Respiratory Alkalosis**

Respiratory alkalosis is produced through alveolar hyperventilation and results in a decrease in arterial PCO₂ and an increase in arterial pH. Plasma HCO₃⁻ is variably decreased, acutely because of shifts in equilibrium and later because of renal HCO₃⁻ wasting. The decreased PCO₂ causes a decreased volatile acid load with secondary release of H⁺ from nonbicarbonate buffers (Buf) as follows:

\[
[HCO_3^-] \text{ increases by } 4 \text{ mEq/L for each } 10-\text{mm Hg increase in PCO}_2
\]

**Rule 2: Determine whether there is a 1:1 relationship between the change in the anion gap and the change in serum bicarbonate**

- Each 1-point increase in the anion gap should be accompanied by a 1-mEq/L decrease in bicarbonate
- If bicarbonate is higher than predicted, a metabolic alkalosis is also present
- If bicarbonate is lower than predicted, a non-anion gap metabolic acidosis is present
BOX 160.4 Acid-Base Interpretation Based on Clinical History

Case 1
A 65-year-old man with a history of chronic obstructive pulmonary disease has had diarrhea for 1 week and his baseline PCO₂ is 65 mm Hg.

Based on his history, the patient’s HCO₃⁻ is lower than predicted, which represents acute metabolic acidosis in the presence of chronic respiratory acidosis.

Case 2
A 65-year-old man being treated long-term with diuretic therapy has an acute exacerbation of asthma.

His history indicates acute respiratory acidosis with an expected PCO₂ of 26.5 mm Hg. The elevated serum HCO₃⁻ indicates acute respiratory acidosis with concomitant metabolic alkalosis.

The renal compensatory response in chronic respiratory acidosis requires 3 to 5 days to develop and may be predicted by the following equation:

\[ [\text{HCO}_3^-] \text{ increases by } 4 \text{ mEq/L for each } 10^-\text{mm Hg increase in PCO}_2 \]

HCO₃⁻ + HBuf → H₂CO₃ + Buf → CO₂ + H₂O

The expected [HCO₃⁻] can be calculated from the following equation:

\[ [\text{HCO}_3^-] \text{ decreases by } 2 \text{ mEq/L for each } 10^-\text{mm Hg decrease in PCO}_2 \]

In chronic respiratory alkalosis, renal adaptive mechanisms result in diminished H⁺ secretion and enhanced HCO₃⁻ excretion. This combined response begins within hours and is completed within 2 to 3 days. The expected response may be calculated as follows:

[HCO₃⁻] decreases by 5 mEq/L for each 10^-mm Hg decrease in PCO₂

Ventilation is primarily controlled through peripheral, central, and pulmonary mechanical receptors. Peripheral chemoreceptors respond to changes in PCO₂ and O₂, so it is not surprising that many cases of hyperventilation stem from hypoxemia.

METABOLIC ACIDOSIS

Metabolic acidosis is induced by the addition of H⁺ ions or by the loss of HCO₃⁻. Addition of H⁺ may occur as a result of exogenous administration or endogenous production of acids associated with pathologic states. Loss of bicarbonate occurs primarily through gastrointestinal or renal wasting, with acidosis being produced by driving the equilibrium reaction to the left:

\[ \text{H}^+ + \text{HCO}_3^- \rightleftharpoons \text{H}_2\text{CO}_3 \rightleftharpoons \text{CO}_2 + \text{H}_2\text{O} \]

As discussed previously, the initial response to acidosis is extracellular and intracellular buffering, combined with respiratory compensation via increased alveolar ventilation. These protective mechanisms attempt to minimize free H⁺ within the system until a full renal response excretes the excess acid load.

It is important to remember that compensatory responses do not fully normalize pH. If a normal pH is seen in a patient with metabolic acidosis, a second acid-base disorder must be present. The typical laboratory pattern of metabolic acidosis is decreased pH and bicarbonate with a compensatory decrease in PCO₂ (Box 160.5).

Enhanced alveolar ventilation is triggered through pH-mediated stimulation of peripheral chemoreceptors. Minute
Metabolic Acidosis with Inadequate Respiratory Compensation

A 68-year-old woman exhibits dyspnea and coughing.

**Vital Signs:**
- Blood pressure, 100/50; heart rate, 120 beats/min; temperature, 101.3°F

**Laboratory Data:**
- Na⁺ = 142; Cl⁻ = 106; HCO₃⁻ = 6 mEq/L; lactate = 8.8 mEq/L; pH = 7.08; PCO₂ = 24 mm Hg; Po₂ = 70 mm Hg
- Review of the laboratory test results reveals an anion gap acidosis. Calculation of the expected respiratory compensation is as follows:

\[
\text{Expected } \text{HCO}_3^- = 1.5[\text{HCO}_3^-] + 8 = 1.5(6) + 8 = 17
\]

The expected PCO₂ is lower than the actual PCO₂, which is producing a relative respiratory acidosis and indicating a need for ventilatory assistance.

### BOX 160.6

This equation assesses the adequacy of respiratory compensation. A PCO₂ that is significantly higher or lower than this calculated value signals the presence of a secondary respiratory acidosis or alkalosis, which may have a profound impact on treatment decisions (Box 160.6).

This protective effect lasts only a few days, however, because the chronically diminished PCO₂ paradoxically signals renal bicarbonate wasting. The final effect is that arterial pH in chronic metabolic acidosis is the same, with or without respiratory compensation.

Causes of metabolic acidosis are classified according to the presence or absence of an elevated AG. However, even in the absence of an AG, there may be accumulation of unmeasured anions.

Non-AG acidoses are those that add HCl to the system. The acid anion in these cases is chloride; because of its inclusion in the AG equation, no change in the gap is noted. The most common causes of non-AG acidosis include renal and gastrointestinal bicarbonate wasting (Box 160.7).

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### BOX 160.7

**Four-Year-Old Boy with Diarrhea for 5 Days**

Physical examination reveals dry mucous membranes.

**Vital Signs:**
- Blood pressure, 80/50; heart rate, 170 beats/min; temperature, 99.1°F; respiratory rate, 44 breaths/min

**Laboratory Data:**
- Na⁺ = 134; K⁺ = 4.8; Cl⁻ = 114; HCO₃⁻ = 3; pH = 6.98; PCO₂ = 13 mm Hg; Po₂ = 110 mm Hg
- Step 1: The patient is found to be acidic on examination of arterial blood gases
- Step 2: Serum bicarbonate is less than 25 mEq, indicative of the presence of metabolic acidosis
- Step 3: The anion gap is elevated: 134 – 116 – 3 = 15
- Step 4: Respiratory compensation is appropriate: 1.5 × [HCO₃⁻] + 8 = [1.5 × 3] + 8 = 12.5
- Step 5: Calculation of the delta gap reveals that the change in HCO₃⁻ (24 – 3 = 21 units) is significantly greater than that the change in anion gap (15 = 10 = 5 units). This indicates the presence of a concomitant non–anion gap acidosis that is overshadowing the anion gap acidosis. The mixed acidosis can be clinically explained by the presence of diarrhea (non–anion gap acidosis) with dehydration (anion gap acidosis)

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**Metabolic Alkalosis**

Metabolic alkalosis is characterized by the net gain of base equivalent, as reflected by elevated plasma bicarbonate. Direct proton loss from extracellular fluid produces an elevation in serum bicarbonate by shifting the following equilibrium reaction to the right:

\[
\text{H}_2\text{CO}_3 \rightarrow \text{H}^+ + \text{HCO}_3^-
\]

The elevated plasma pH produces compensatory hypoventilation to increase PCO₂. Because serum pH is determined by the ratio of HCO₃⁻ to PCO₂ and not by the absolute HCO₃⁻ level, this compensatory response acts to minimize the change in serum pH.

Metabolic alkalosis is the second most common acid-base disorder and is found in approximately one third of hospitalized patients. It can be caused by several processes: increased H⁺ loss, typically through renal or gastrointestinal wasting; increased bicarbonate resorption; ingestion or infusion of bicarbonate; intracellular shifts in H⁺; or contraction of extracellular fluid around a stable HCO₃⁻ pool (Box 160.8).

Because of the kidneys’ ability to excrete excess HCO₃⁻, maintenance of metabolic alkalosis requires impairment of this process. The majority of the filtered bicarbonate is reclaimed in the proximal tubule, with approximately 10% of HCO₃⁻ being reabsorbed in the distal segments. Type B cells in the cortical collecting tubule may also actively secrete excess bicarbonate. Maintenance of metabolic alkalosis requires failure of these mechanisms. This generally results from contraction of extracellular volume, which stimulates Na⁺ retention and enhanced activity of the Na⁺-H⁺ antiporter in the proximal tubule.

Hyperaldosteronism induced by extracellular fluid depletion also plays a role in maintaining alkalosis by increasing H⁺ secretion in the distal nephron through activation of H⁺-transporting adenosine triphosphatase (H⁺-ATPase). Hypokalemia and hyperaldosteronism maintain the alkalosis through stimulation of proximal and distal bicarbonate resorption, transcellular exchange of K⁺ and H⁺, and increased ammoniagenesis.

The most frequent causes of metabolic alkalosis are loss of gastric secretion and use of diuretics. Loss of gastric secretion generates an equimolar gain in HCO₃⁻ for the lost H⁺. Likewise, loss of gastric secretion is associated with a contracted...
volume of extracellular fluid, which maintains alkalosis through volume depletion and hyperaldosteronism. Diuretics also induce an alkalosis through secondary hyperaldosteronism associated with hypovolemia, hypokalemia, and enhanced distal H+ secretion.

The respiratory compensation for metabolic alkalosis is variable. On average, PCO₂ can be predicted as follows:

\[ \text{Increase in} \ P_{\text{CO}_2} = 0.6 \ \text{increase in} \ HCO_3^- \]

Compensation rarely results in a PCO₂ greater than 55 mm Hg. Significant deviations from this compensatory response indicate a superimposed respiratory acidosis or alkalosis.

The signs and symptoms of alkalosis are commonly related to the associated volume contraction. Weakness, fatigue, coma, seizure, carpopedal spasm, respiratory depression, and neuromuscular irritability are observed, probably related to decreased ionized calcium as a result of alkalemia. Neuromuscular signs and symptoms are uncommon in patients with metabolic alkalosis because of the slow movement of charged HCO_3^- into the CNS.

Urine chloride helps determine the cause and treatment of the metabolic alkalosis. Urine chloride levels less than 20 \( \text{mEq/L} \) indicate appropriate renal chloride avidity and imply that the source of the metabolic alkalosis is extrarenal. Accordingly, fluid and chloride repletion is the mainstay of therapy in these saline- or chloride-responsive conditions. In contrast, urine chloride levels higher than 40 \( \text{mEq/L} \) indicate renal chloride wasting and implicate altered renal function at a source of the metabolic alkalosis.

**TREATMENT**

**METABOLIC ACIDOSIS**

Initial treatment of metabolic acidosis includes reversing the source of the metabolic acidosis and treating with exogenous bicarbonate when indicated. A second priority is assessing the adequacy of respiratory compensation and providing ventilatory support as needed. Respiratory exhaustion with concomitant respiratory acidosis compounds the patient’s dilemma.

Alkali therapy is aimed at reversing the acid-induced organ dysfunction. However, the effects of bicarbonate therapy are complex. Indiscriminate use may be more deleterious than helpful. Sodium bicarbonate infusions introduce an additional volatile acid load because bicarbonate produces CO₂ on reaction with water (serum):

\[ \text{HBuf} + \text{HCO}_3^- \rightarrow \text{Buf}^- + \text{H}_2\text{CO}_3 \rightarrow \text{CO}_2 + \text{H}_2\text{O} \]

This additional CO₂ load must be excreted by the lungs to have an impact on pH. Additionally, CO₂ diffuses freely across cell membranes and paradoxically exacerbates intracellular and CNS acidemia. Sodium bicarbonate is associated with complications that include hypertonicity, hypernatremia, hypervolemia, increased organic acid (lactate) production, and impaired oxygen unloading.

Use of bicarbonate infusions is appropriate for bicarbonate-wasting acidoses or toxic acidosis because systemic alkalization facilitates removal of toxin through ion trapping. However, supplemental bicarbonate in patients with organic acidoses (lactic acidosis and ketoacidosis) has not been shown to affect outcome. In these states, therapy should be aimed at addressing the underlying cause of the acidosis and promoting regeneration of bicarbonate through metabolism of the accumulated anions. In hyperchloremic acidosis, no anions exist for the regeneration of bicarbonate, and therefore infusions can promptly reverse the acidemia and restore serum bicarbonate.

When used, the goal of bicarbonate infusion is to increase pH to 7.1 to 7.2 and restore buffering capacity (>12 \( \text{mEq/L} \) HCO_3^-). Overzealous administration risks paradoxic alkalemia on metabolism of organ acids. The bicarbonate deficit may be calculated with the Henderson-Hasselbalch equation or by estimating the deficit at 1 \( \text{mEq/kg} \) and infusing one half the amount over a period of 20 to 30 minutes, with the remainder being infused over the next 2 to 4 hours. Bicarbonate also makes an excellent resuscitation or maintenance fluid. Isotonic bicarbonate is prepared by combining three ampules of sodium bicarbonate (50 \( \text{mEq} \)) with 1 L of sterile water, which creates an isotonic solution of 130 to 150 \( \text{mEq/L} \) NaHCO_3 (depending on removal of water before instillation). During this time, acid-base and volume status must be carefully monitored to avoid overshooting the pH correction.

**METABOLIC ALKALOSIS**

Metabolic alkalosis is best treated by correcting the underlying cause of the alkalosis. Examination of urine chloride allows causes to be classified as saline responsive or saline resistant.

The majority of cases of metabolic alkalosis are saline responsive. Volume depletion is reversed with 0.9% normal saline. Concomitant hypokalemia is an important

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**BOX 160.8 Causes of Metabolic Alkalosis**

<table>
<thead>
<tr>
<th>Loss of Hydrogen</th>
<th>Gastrointestinal</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Vomiting, nasogastric suction</td>
<td>• Antacid therapy</td>
</tr>
<tr>
<td>• Antacids</td>
<td>• Bulimia</td>
</tr>
<tr>
<td>• Chloride-losing diarrhea (villous adenoma)</td>
<td><strong>Renal</strong></td>
</tr>
<tr>
<td>• Loop and thiazide diuretics</td>
<td>• Mineralocorticoid excess (hyperaldosteronism, drug or medication)</td>
</tr>
<tr>
<td>• Cushing disease</td>
<td>• Bartter syndrome</td>
</tr>
<tr>
<td>• Gitelman syndrome</td>
<td>• Chronic hypercapnia</td>
</tr>
<tr>
<td>• Low chloride intake</td>
<td>• High-dose carbenicillin</td>
</tr>
<tr>
<td>• Hypercalcemia, milk-alkali syndrome</td>
<td><strong>Intracellular H+ Shift</strong></td>
</tr>
<tr>
<td><strong>Contraction Alkalosis</strong></td>
<td>Massive blood transfusion</td>
</tr>
<tr>
<td>Loop or thiazide diuretics</td>
<td>NaHCO_3 administration</td>
</tr>
<tr>
<td>Gastric loss</td>
<td>Milk-alkali syndrome</td>
</tr>
<tr>
<td>Sweat loss (cystic fibrosis)</td>
<td><strong>Contraction Alkalosis</strong></td>
</tr>
</tbody>
</table>

**Causes of Metabolic Alkalosis**

- Gastric loss
- Loop or thiazide diuretics
- Contraction alkalosis
- Milk-alkali syndrome
- Massive blood transfusion
- NaHCO_3 administration
- Intracellular H+ shift
- Contraction alkalosis

**CHAPTER 160 ACID-BASE DISORDERS**
maintenance factor that should be reversed with potassium chloride. The total body potassium deficit may be profound and is often underappreciated.

Saline-resistant alkaloses display excessive mineralocorticoid activity, such as hyperaldosteronism, Cushing syndrome, and renal artery stenosis. Treatment of saline-resistant causes (urine chloride >20 mEq/L) is directed at the other causes of the metabolic alkalosis. Potassium deficits should be corrected by supplementation or direct antagonism of aldosterone with agents such as spironolactone. In patients with metabolic alkalosis and concomitant edematous states (e.g., congestive heart failure, cirrhosis, nephrotic syndrome), acetazolamide enables bicarbonate and volume excretion.

REFERENCES

References can be found on Expert Consult @ www.expertconsult.com.
REFERENCES


