Acid-Base Disorders in the PICU

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Abstract

An appropriate acid-base milieu is essential for normal cellular function of the human organism. Disturbances of the pH balance frequently occur in critically ill or injured children. These pertubations most often serve as a marker of an underlying disorder responsible for their occurrence, but acid-base disturbances may in themselves require monitoring and treatment in the PICU. Proper assessment and treatment of acid-base imbalances therefore requires an understanding of terminology and measurement, insight into buffer systems, and recognition of the compensatory interactions involved in maintaining a homeostatic balance. The terms acidosis and alkalosis refer to the mechanisms which result in a given acid-base disturbance. Primary acid-base disorders are further classified as either metabolic or respiratory. Metabolic contribution to acid-base homeostasis is based on the presence of strong anions and cations. Ion strength is based on the tendency of an ion to dissociate in aqueous solutions and tendency to combine with other ions. The concentration difference between the sum of all strong anions and strong cations is defined as the strong ion difference (SID). The anion gap, determined by presence or absence of unmeasured anions, helps guide understanding of the etiology of metabolic acidosis, one of the most common disturbances in the critically ill child. Hypercapnic acidosis impacts pH balance, but could have potential therapeutic effects in children with acute lung injury. Specific therapies, such as intravenous fluids and cardiopulmonary bypass, intrinsically affect acid-base balance, and their impact should be considered.

Keywords

Acid-base disorder • Children • Critical illness • Buffer • Lactic acidosis • Metabolic acidosis • Respiratory acidosis • Hypercapnic acidosis • Metabolic alkalosis • Respiratory alkalosis • Strong ion difference • Anion gap • pH stat

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Introduction

An appropriate acid-base milieu is essential for normal cellular function of the human organism. Bronsted defined an acid as a substance that can donate H^+ ions and a base as a substance that can accept H^+ ions [1]. There are two classes of acids that are physiologically important – carbonic acid (H_2CO_3) and noncarbonic acids. During the course of a normal day, metabolism of carbohydrates and fats generates approximately 15,000 mmoles of CO_2, which combines with water to generate carbonic acid. The lung then plays an important role in acid-base regulation via removal of CO_2. Noncarbonic acids are derived from the metabolism of proteins (generally limited to approximately 50–100 mEq/day of acid) and are excreted by the kidney. The extracellular pH is tightly regulated between 7.35 and 7.45 under normal conditions by a combination of extracellular and intracellular chemical buffering, as well as by these respiratory and renal regulatory mechanisms. Disturbances of this balance frequently occur in critically ill or injured children. These disorders most often serve as a marker of an underlying disorder responsible for their occurrence, but acid-base disturbances may in themselves require monitoring and treatment in the PICU. Proper assessment and treatment of acid-base imbalances therefore requires an understanding of terminology and measurement, insight into buffer systems, and recognition of the compensatory interactions involved in maintaining a homeostatic balance.

The acidity of a particular solution may be expressed in terms of H^+, i.e., proton, concentration, or in terms of pH. The concentration of H^+ in the serum under normal conditions (0.00004 mEq/L) is relatively low compared to other ions, e.g., sodium ion (140 mEq/L). In order to avoid these cumbersome differences, the pH scale is used by convention to describe acid-base disturbances in the body. The pH of arterial blood is the negative logarithm of the H^+ concentration. Several important points deserve mention. First, pH and $[H^+]$ are inversely related – an increase in $[H^+]$ is defined by a decreasing pH (i.e., more acidic conditions), while a decrease in $[H^+]$ is defined by an increasing pH (i.e. less acidic conditions). Second, the normal arterial pH of 7.35–7.45 corresponds to a $[H^+]$ of 35–45 nEq/L. An *acidemia* refers to an arterial pH <7.35 (H^+ concentration below 35 nEq/L), while an *alkalemia* refers to an arterial pH >7.45 (H^+ concentration above 45 nEq/L). Third, the arterial $[H^+]$ can be estimated from the arterial pH with a reasonable degree of accuracy due to the linear relationship between pH and $[H^+]$ in the physiologic range – within this range, each 0.01 unit change in pH from 7.40 will either increase or decrease the $[H^+]$ by 1 nEq/L [2]. For example, a decrease in pH from 7.40 to 7.20 would require an increase in the $[H^+]$ from 40 to 60 nEq/L. By the same token, when pH changes by 0.3 log units, the $[H^+]$ either doubles or halves [2]. For example, if the pH falls from 7.40 to 7.10, the $[H^+]$ must double from 40 to 80 nEq/L.

The terms *acidosis* and *alkalosis* refer to the mechanisms which result in a given acid-base disturbance. Primary acid-base disorders are further classified as either metabolic or respiratory. For example, when the plasma bicarbonate concentration (HCO_3^-) deviates from the normal range, the resultant alteration in acid-base homeostasis is referred to as a metabolic acidosis or alkalosis. When a deviation in the arterial carbon dioxide tension ($PaCO_2$) is the primary event, the resulting disorder is referred to as a respiratory acidosis or alkalosis. Secondary compensatory mechanisms attempt to restore the extracellular pH back to normal. For example, the secondary respiratory compensation to a primary metabolic acid-base disturbance (i.e., an increase or decrease in minute ventilation to change the arterial $PaCO_2$) occurs within minutes and is usually complete within 12–24 h, though the arterial pH is never restored to a normal pH. Conversely, the secondary metabolic compensation (by the kidney) to a primary respiratory acid-base disturbance occurs more slowly, often requiring 3–5 days for compensation [3, 4]. Most acid-base disturbances are *simple acid-base disorders* in that a primary disruption produces a physiologic compensatory response. However, *mixed acid-base disorders* can also occur in which more than one primary disturbance can occur, particularly in the complex critically ill child.

Acid-Base Physiology

A *buffer* is defined as any substance which can absorb or donate H^+ ions and thereby diminish the effects on the pH of a solution. For example, in the following chemical equation, excess H^+ ions combine with the base, A^- to form the weak acid, HA:

$$H^+ + A^- \leftrightarrow HA$$

The weak acid HA buffers the excess H+ ions such that the effect of the increase in $[H^+]$ on pH is mitigated. The converse is true if there are not enough H^+ ions in solution, i.e., HA dissociates to form excess H^+ ions. Strong acids, e.g., HCl, H_2SO_4 are not effective buffers because, by definition, they dissociate at acidic pH. Conversely, weak acids are not effective buffers either, because by definition, they tightly bind H^+ even at alkalotic pH. Thus, the inherent tendency of a particular acid to dissociate or ionize determines the degree to which it can act as a buffer, denoted by the ionization constant, pK (note that the pK is inversely proportional to the strength of the acid). The most effective buffers have pKs that approximate the physiologic range of pH. The most important buffer pairs in the arterial blood are carbonic acid/

bicarbonate (H_2CO_3/HCO_3^-), phosphate ($H_2PO_4^-/HPO_4^{2-}$), and certain proteins, e.g. hemoglobin. By far the most important buffer system is the H_2CO_3/HCO_3^- system (see below):

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

Carbonic anydrase catalyzes the conversion of carbonic acid to CO_2 and H_2O and vice versa. The respiratory system therefore plays an important role in acid-base homeostasis through its effects on $PaCO_2$. The relationship of HCO_3^- and H_2CO_3 to pH is expressed by the Henderson-Hasselbach equation:

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

In the clinical setting, pH and $PaCO_2$ are measured, rather than HCO_3^- and H_2CO_3. The Henderson-Hasselbach equation can then be modified:

$$pH = pK' + \log\left(\left[HCO_3^-\right] / \left(0.03 \times PaCO_2\right)\right)$$

The modified Henderson-Hasselback equation can be rewritten without logarithms as the Henderson equation (Kassirer-Bleich modification) [2, 3]:

$$\left[H^+\right] = 24 \times PaCO_2 / \left[HCO_3^-\right]$$

Therefore, using the rules described above for estimating $[H^+]$, any one of the three values in the Henderson equation can be rapidly estimated when the other two are known (see more below).

When chemical buffering is not sufficient to prevent a change in pH, either metabolic or respiratory compensation occurs. Changes in pH, therefore, result entirely from changes in the respiratory response and the subsequent effect on volatile acids ($PaCO_2$), changes in the metabolic response and the subsequent effect on nonvolatile acids (hydrochloric, sulfuric, lactic acids), or changes in nonvolatile weak acid (chemical buffers). These are briefly discussed further below.

Respiratory Compensation: Volatile Acids (CO_2)

CO_2 and water are produced primarily from the combustion of glucose and fatty acids in the oxidative process of cellular respiration. CO_2 is transported through the arterial blood in one of three ways: (i) dissolved in physical solution in the plasma (approximately 5–10 %); (ii) complexed chemically with the terminal amine groups of proteins, e.g. hemoglobin (approximately 5–10 %); (iii) transported as bicarbonate (80–90 %). At the tissue level, CO_2 diffuses across the red blood cell (RBC) membrane and combines with water to form carbonic acid, in a reaction catalyzed by carbonic anhydrase.

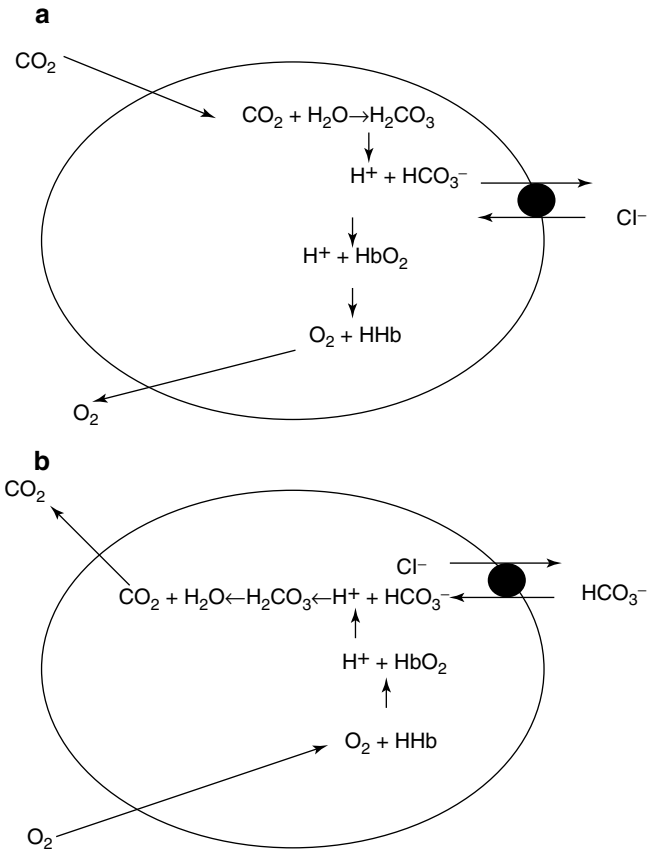

Fig. 14.1 CO_2 exchange at the tissue level (**a**) and alveolar level (**b**). See text for explanation

Carbonic acid then dissociates to bicarbonate (HCO_3^-) and H^+. The H^+ is buffered by hemoglobin (in exchange for O_2, which then is released to the tissues) and HCO_3^- leaves the RBC in exchange for chloride (Fig. 14.1a). CO_2 is then excreted in the lungs by a reversal of this process – bicarbonate re-enters the RBC to combine with protons (H+), forming carbonic acid. Carbonic acid then dissociates to water and CO_2, which diffuses freely into the alveolar space and is removed via the process of ventilation (Fig. 14.1b). Changes in the arterial or cerebrospinal fluid pH stimulate central medullary and carotid body chemoreceptors to regulate minute ventilation for altering CO_2 clearance. The maximum compensatory response (i.e., an increase in minute ventilation) to a severe metabolic acidosis can decrease $PaCO_2$ to a lower limit of 10–12 mmHg, though values less than 10mmHg may be achieved in rare instances (e.g., hyperventilation, or Kussmaul's respirations in diabetic ketoacidosis). Conversely, minute ventilation slows and $PaCO_2$ generally increases to approximately 50 mmHg to compensate for a metabolic alkalosis with plasma bicarbonate concentrations of 35 mEq/L or greater. $PaCO_2$ generally never exceeds 65 mmHg in a compensatory response, even in the face of a profound metabolic alkalosis.

Metabolic Compensation and Nonvolatile Acids/Strong Ion Difference (SID)

Nonvolatile acids are also produced by cellular metabolism, and their resultant effect on acid-base homeostasis is controlled by the kidney. The metabolism of sulfur-containing amino acids, such as cysteine and methionine, to sulfuric acid provides the major source of nonvolatile acids. Additional sources include oxidation of phospholipids to phosphoric acid, nucleoprotein degradation to uric acid, and incomplete combustion of carbohydrates and fatty acids to lactic and keto- acids. Efficient processing by the kidney is necessary to clear the approximately 1 mEq/kg of acids produced on a daily basis. Excretion occurs in tandem with the regeneration of HCO_3^-. In addition, the kidneys filter large amounts of circulating plasma HCO_3^- through almost complete reabsorption with sodium in the proximal tubule. Metabolic compensation for respiratory volatile acid effects occurs here; respiratory acidosis (i.e., high arterial $PaCO_2$) raises the rate of bicarbonate reabsorption, while respiratory alkalosis (i.e., low arterial $PaCO_2$) lowers it. Hypokalemia also increases the rate of bicarbonate reabsorption, probably by raising intracellular H^+ concentration. Volume contraction also increases proximal HCO_3^- reabsorption by resetting glomerulotubular balance upward and increasing the fractional rate of Na^+ and HCO_3^- reabsorption. Thus, correcting hypokalemia may be necessary to correct a metabolic alkalosis, particularly in children with volume contraction.

The actual excretion of nonvolatile acids occurs in the distal tubules with simultaneous regeneration of HCO_3^-. CO_2 is again hydrated to carbonic acid and dissociated into protons by tubular cells. HCO_3^- is reabsorbed and secreted protons titrate urinary buffers. The majority of acid excretion, however, takes place via ammonia (NH_3) secretion to bind protons released by CO_2 hydration.

Metabolic contribution to acid-base homeostasis is based on the presence of strong anions and cations. Ion strength is based on the tendency of an ion to dissociate in aqueous solutions. Strong ions are by nature always free and remain charged because they do not combine with other ions. Strong cations, which include sodium (Na^+), potassium (K^+), calcium (Ca^{++}), and magnesium (Mg^{++}), outnumber strong anions (predominantly chloride, Cl^- and lactate$^-$) in blood plasma. The concentration difference between the sum of all strong anions and strong cations is defined as the strong ion difference (SID). If other *unmeasured* anions are excluded, the apparent SID (SIDa) can be estimated by the following:

$$\text{SIDa} = \left(\text{Na}^+ + \text{K}^+ + \text{Ca}^{++} + \text{Mg}^{++}\right) - \left(\text{Cl}^- + \text{lactate}^-\right)$$

Because of electrical neutrality, plasma cannot be charged, and the SID difference is balanced by negative charges, primarily from CO_2 and from weak acids (A^-, described below). Thus, SID – (CO_2+ A^-) = 0 or SID = CO_2+ A^-. This measure is known as the effective SID (SIDe), where A^-can be estimated by the following formula:

$$\text{A}^- = 2 \times \left(\text{albumin,g/dL}\right) + 0.5 \times \left(\text{phosphorus,g/dL}\right)$$

SID drives water dissociation and with it the generation of H^+ ions; as SID increases, H^+ decreases and pH increases. SID in healthy humans is typically between 40 and 42 mEq/L, but can be significantly decreased with critical illness, resulting in a rapid decline in pH.

Nonvolatile Weak Acid Buffers

In contrast to strong ions, weak nonvolatile acids (or anions) exist as either charged (dissociated) or uncharged forms in vivo. Weak acids can be forced to combine with other ions and thus lose their charge. HCO_3^- is the most important weak acid in the buffer system, as it can readily combine with another weak ion, H^+, to form H_2CO_3, which dissociates into CO_2 and water. Weak acids serve as a buffer to take up protons within the human physiologic plasma pH range.

Quantification of Acid-Base Status

Three different methods are commonly employed to describe and quantify acid-base disorders, each differing only in assessment of the nonvolatile components. These methods quantify changes by assessing (i) HCO_3^- concentration in the context of $PaCO_2$; (ii) standard base excess (BE) supplemented by anion gap determination; or (iii) strong ion gap (SIG) based on the strong ion difference (SID). The first approach has been the most commonly accepted one, but conceptual differences bear discussion. As discussed above, the bicarbonate-carbonic acid pair provides the primary buffer system for extracellular fluid. The relationship between this buffer pair and $PaCO_2$ is defined by the Henderson-Hasselbach equation, in which pH = 6.1 + log [HCO_3^-]/ 0.03 × $PaCO_2$, where 6.1 is the dissociation constant (pK) for this buffer pair. This interaction tells us that an increase in $PaCO_2$ will lead to a decrease in pH and later a compensatory increase in [HCO_3^-]. Compensatory responses by the lungs and kidneys are essential to the physiologic response to primary acid-base disorders. These responses typically form a stereotypical pattern which can be described mathematically based in part on the Henderson-Hasselbach equation (compiled in Table 14.1). This relationship can be complicated by the possibility that an alteration in one element may directly impact another element in addition to its compensatory effect.

Table 14.1 Compensation for primary acid-base disorders

Disorder	Prediction of compensation	HCO_3^- (mEQ/L)	$PACO_2$ (mmHg)	SBE (mEQ/L)
Metabolic acidosis	$PaCO_2 = (1.5\times HCO_3^-)+8$ OR $PaCO_2$ will ↓ 1.25 mmHg PER mEQ/L ↓ $[HCO_3^-]$ OR $PaCO_2 = [HCO_3^-]+15$	<22	$= (1.5\times HCO_3^-)+8$	<–5
Metabolic alkalosis	$PaCO_2$ will ↑ 0.7 mmHg per mmol/L ↑ $[HCO_3^-]$ OR $PaCO_2 = [HCO_3^-]+15$	>26	$= (0.7\times HCO_3^-)+21$ $= 40+(0.6\times SBE)$	>5
Respiratory alkalosis				
Acute	pH will ↑ 0.08 per 10 mmHg ↓ $PaCO_2$ $[HCO_3^-]$ will ↓ 2 mEQ/L per 10 mmHg ↓ $PaCO_2$	$= [(40-PCO_2)/5]+24$	<35	= 0
Chronic	$[HCO_3^-]$ will ↓ 4 mEQ/L per 10 mmHg ↓ $PaCO_2$ pH will ↑ 0.03 per 10 mmHg ↓ $PaCO_2$	$= [(40-PCO_2)/2]+24$	<35	$= 0.4\times (PaCO_2-40)$
Respiratory acidosis				
Acute	$[HCO_3^-]$ will ↑ 1 mEQ/L per 10 mmHg ↑ in $PaCO_2$ pH will ↓ 0.08 per 10 mmHg ↑ in $PaCO_2$	$= [(PCO_2-40)10]+24$	>45	= 0
Chronic	$[HCO_3^-]$ will ↓ 4 mEQ/L per 10 mmHg ↓ in $PaCO_2$ pH will ↓ 0.03 per 10 mmHg ↑ in $PaCO_2$	$= [(PCO_2-40)/3]+24$	>45	$= 0.4\times (PaCO_2-40)$

The use of plasma bicarbonate concentrations does not provide a direct estimate of the total amount of fixed base in blood for clinical use. An alternative expression of buffering capacity in whole blood can be performed by calculation of the base excess (BE):

$$\mathrm{BE} = -1.2\times\left(24-\text{measured bicarbonate concentration}\right)$$

However, the plasma bicarbonate-carbon dioxide system only accounts for approximately 75 % of the buffer action of blood. Buffering is also provided byhemoglobin, phosphates, and plasma proteins, particularly albumin. Use of the Siggaard-Andersen nomogram utilizes pH, $PaCO_2$ and HCO_3^- to calculate a BE that takes into account the remaining buffer systems. Positive base excess signifies metabolic alkalosis, and negative BE implies metabolic acidosis. Standard base excess (SBE) represents the base excess of whole blood together with the surrounding interstitial fluid, comprising total extracellular fluid (ECF).

Calculation of BE and SBE does not allow discrimination between types of metabolic acidosis. The anion gap is more useful for this determination. The anion gap is based on the principle of electroneutrality; that is, the net ionic charge in a given solution is zero. In the case of extracellular fluid, sodium is the primary cation and is balanced primarily by the strong cations, chloride and the weak cation bicarbonate. The difference between these measured ions normally exists due to the presence of unmeasured anions, including sulfates, lactate, and ketoacids, but primarily due to phosphates and negatively charged proteins such as albumin. These are all balanced by sodium ions. The anion gap is the difference between measured cations and anions, represented by the equation:

$$\mathrm{AG} = \left[\mathrm{Na}^+ + \mathrm{K}^+\right] - \left[\mathrm{Cl}^- + \mathrm{HCO_3}^-\right]$$

Potassium is often omitted from the calculation because of its low extracellular concentration.

Under normal conditions, the normal anion gap is equal to 12 ± 4 mEq/L. Calculation of the anion gap is most useful for discerning the cause of metabolic acidosis as described in the section below. Strong ion gap (SIG) refers to the difference between the apparent SID (SIDa) and the effective SID (SIDe):

$$\mathrm{SIG} = \mathrm{SIDa} - \mathrm{SIDe}$$

In contrast to the anion gap, a normal SIG is zero. SIG does not change with changes in pH or in albumin concentration. The AG can be significantly altered by abnormal albumin or phosphate concentrations (see below). Thus, the AG is an estimate of the sum of SIG plus weak acids (A-), where A- can be

Table 14.2 Causes of respiratory acidosis in critically ill children

Acute or chronic lung disease
Upper airway obstruction (e.g., Croup, epiglottitis, foreign body aspiration)
Lower airway obstruction (e.g., Status asthmaticus, bronchiolitis)
Chronic obstructive lung disease (e.g., Cystic fibrosis, bronchopulmonary dysplasia)
Interstitial lung disease
Pneumonia
Pulmonary edema
Neuromuscular respiratory failure
Myasthenia gravis
Guillain-Barre syndrome
Hypokalemic periodic paralysis
Tick paralysis
Poliomyelitis
Muscular dystrophy
Spinal cord injury
Botulism
Chest wall disorders
Kyphoscoliosis
Morbid obesity
Flail chest
Inhibition of respiratory center
CNS depressant drugs
Cardiac arrest
CNS lesions (e.g., tumors)
CNS infection (e.g., meningoencephalitis)
Head trauma
Stroke

estimated as previously described. The SID and SIG concepts are helpful conceptually but AG is more commonly used in clinical practice for assessment and management.

Differential Diagnosis and Basic Management of Acid-Base Disorders

Respiratory Acidosis

A primary respiratory acidosis is defined by an arterial blood pH less than 7.35 due most commonly to a decreased CO_2 clearance (e.g., alveolar hypoventilation) or less commonly to increased CO_2 production. The differential diagnosis of an acute, primary respiratory acidosis is listed in Table 14.2. The acute increase in $PaCO_2$ is buffered by titration of non-bicarbonate intracellular buffers (e.g., hemoglobin, organic phosphates), resulting in an almost negligible rise in arterial HCO_3^- (generally only 0.1 mEq/L for every 1 mmHg increase in $PaCO_2$):

$$CO_2 + H_2O \leftrightarrow H_2CO_3$$

$$H_2CO_3 + Hb^- \leftrightarrow HHb + HCO_3^-$$

The maximal increase in HCO_3^- during acute compensation is 31–32 mEq/L [2, 3]. The arterial pH will decrease by 0.08 units for every 10 mmHg increase in $PaCO_2$. Chronic renal compensation (through proximal reabsorption of filtered HCO_3^- and excretion of H^+ as ammonia) generally occurs within 12–24 h, such that the [HCO_3^-] increases by 0.3 mEq/L for each 1 mmHg increase in $PaCO_2$ to a maximal increase of approximately 45 mEq/L [2–4]. Similarly, pH will decrease by 0.03 units for each 10 mmHg increase in $PaCO_2$. The bone provides additional buffering of chronic respiratory acidosis as calcium phosphates and carbonates (for this reason, osteoporosis is a common finding in children with chronic lung disease). Chronic respiratory acidosis also results in chloride depletion due to increased chloride excretion by the kidney and a shift of chloride ions into the RBC (in exchange for bicarbonate), which usually takes place over 3–5 days [5]. Interestingly, unless adequate chloride supplementation is provided during correction of the chronic respiratory acidosis, arterial bicarbonate may remain elevated, resulting in a post-hypercapnic alkalosis [5].

The clinical implications of respiratory acidosis depend to a great extent upon the acuity of the event as well as the degree of hypoxemia that is present. Even a profound degree of respiratory acidosis is surprisingly well-tolerated – e.g., elevations of $PaCO_2$ as high as 269 mmHg have been observed in some children with acute respiratory failure who ultimately survive [6]. Treatment of respiratory acidosis is directed at the underlying cause (e.g., mechanical ventilatory support for acute respiratory failure; bronchodilators, oxygen, corticosteroids for status asthmaticus; etc.). The role of $NaHCO_3$ in the treatment of acute respiratory acidosis is not well defined. For example, in a recent case series of 17 children with near-fatal status asthmaticus, administration of $NaHCO_3$ was associated with a significant decrease in $PaCO_2$ [7].

Conversely, the administration of $NaHCO_3$ has several theoretical disadvantages. Intracellular pH is probably more important for maintaining homeostasis than arterial pH (which is what is measured). CO_2 freely diffuses across the blood–brain barrier, while HCO_3^- does not. In addition, CO_2 diffuses across cell membranes at a much faster rate than HCO_3^-. Therefore, correction of arterial pH with the administration of $NaHCO_3$ could potentially result in worsening intracellular pH in the brain, cardiomyocytes, and other cells, leading to further cellular damage and dysfunction [8–12]. Additional concerns include (i) displacement of the oxyhemoglobin dissociation curve, (ii) acute intracellular shift of potassium leading to hypokalemia, (iii) calcium binding to serum proteins, leading to decreased ionized calcium, and (iv) sodium and/or water overload. Finally, $NaHCO_3$ administration can theoretically increase $PaCO_2$ transiently, especially in the face of inadequate alveolar ventilation [13–15]. However, in our experience this may be more of a theoretical concern. Given the absence of significant clinical benefit and the potential inherent risks, the routine administration of

Table 14.3 Causes of respiratory alkalosis in critically ill children

Anxiety
Agitation
Pain
Fever
Sepsis
Pneumonia
Hypoxemia
Pulmonary edema
Pulmonary thromboembolism
Central nervous system
Disorders (e.g., Trauma, tumor, infection, stroke)
Acute liver failure
Salicylate poisoning
Hyperthyroidism
Altitude

$NaHCO_3$ in the clinical setting of primary respiratory acidosis is probably not justified [16]. Finally, chronic respiratory acidosis can usually be managed much more conservatively, as metabolic compensation typically leads to adequate systemic pH for cellular function.

Respiratory Alkalosis

A primary respiratory alkalosis is defined as an arterial pH >7.45 in the setting of hypocarbia secondary to hyperventilation. Respiratory alkalosis is one of the more common acid-base disturbances in critically ill children due to a variety of causes (Table 14.3). Most commonly, respiratory alkalosis results acutely via tachypnea secondary to anxiety, pain, agitation, or fever. Hypoxemia may induce a hyperventilatory response in association with parenchymal lung disease, congestive heart failure, pulmonary edema (of any etiology), or pulmonary thromboembolism. Neurogenic causes (increased intracranial pressure secondary to head trauma, infection, tumor, etc.) should also be considered in the differential diagnosis. Respiratory alkalosis may also arise from either deliberate or unintentional overventilation in an infant or child with respiratory failure. Salicylate poisoning causes respiratory alkalosis (in addition to the metabolic acidosis – see below) through stimulation of the respiratory centers in the CNS. Regardless of etiology, the initial fall in $PaCO_2$ is titrated by a mild decrease in arterial HCO_3^- (decrease by approximately 0.2 mEq/L for every 1 mmHg decrease in $PaCO_2$) which occurs within several minutes [2, 3, 17], and the pH will increase by 0.08 units for each 10 mmHg decrease in $PaCO_2$. The compensatory response to a chronic respiratory alkalosis by the kidneys usually occurs within 2–4 days via decreased tubular reabsorption of HCO_3^-, resulting in an increase in pH by 0.03 units for each 10 mmHg decrease in $PaCO_2$. Respiratory alkalosis leads to alterations in serum potassium (decreases), phosphate (decreases acutely, increases chronically), ionized calcium (decreases), and lactic acid (increases) [17]. Clinical manifestations include altered mental status, confusion, and seizures (due to the effects of hypercarbia on cerebral perfusion), tachycardia, arrhythmias, muscle cramping, and muscle spasms. Treatment is again directed towards the underlying cause.

Metabolic Acidosis

A primary metabolic acidosis is defined as an arterial pH <7.35 secondary to a decrease in arterial HCO_3^- (usually <22 mEq/L). Metabolic acidosis is generally caused by loss of HCO_3^- (from gastrointestinal or renal losses), an increase in endogenous acid production (such as lactate or ketoacids), decreased excretion of endogenous acids (as in acute renal failure), or accumulation of exogenous acids from toxins. The lungs respond to an acute metabolic acidosis with increased minute ventilation, leading to a decrease in $PaCO_2$. Maximal compensation occurs at a $PaCO_2$ 10 mmHg. The expected compensatory decrease in $PaCO_2$ may be determined using the Winters equation:

$$PaCO_2 = 1.5 \times \left[HCO_3^-\right] + 8 \pm 2$$

If the observed and calculated (i.e. expected) $PaCO_2$ differ, then a mixed acid-base disorder is present. In most cases of metabolic acidosis, respiratory compensation will be incomplete – even with maximal compensation, pH will never be in the normal range. Furthermore, respiratory compensation is only temporary – after several days, the kidneys will respond to the lower $PaCO_2$ with bicarbonate wasting (decreased tubular reabsorption) [18].

The etiology of metabolic acidosis can be generally characterized by the presence or absence of unmeasured anions – i.e., by the presence or absence of an anion gap (described above). Again, a normal anion gap is 12 ± 4 mEq/L. The anion gap has a few limitations that deserve mention. First and foremost, albumin is the major anion in the blood. Changes in albumin can therefore have a major impact on calculation of the anion gap (e.g., for every 1 g/dL decrease in serum albumin, the anion gap will decrease by approximately 2–3 mEq/L). Hypoalbuminemia is relatively common in critically ill children, and failure to account for this may grossly underestimate the true anion gap [19, 20]. Accordingly, Figge [21, 22] described a correction factor for albumin concentration in adults which has been subsequently validated in a cohort of critically ill children [20]:

$$AG_{corr} = AG + 0.25 \times (40\,g/L \quad \text{observed albumin})$$

Other conditions that may be associated with a falsely *low* anion gap include hyponatremia, profound hyperkalemia,

Table 14.4 Causes of high anion gap metabolic acidosis

M = Methanol
U = Uremia
D = Diabetic KetoAcidosis (DKA)
P = Paraldehyde
I = Iron, Isoniazid, or inborn errors of metabolism
L = Lactic acidosis
E = Ethylene glycol
S = Salicylate

hypercalcemia, hypermagnesemia, and hypophosphatemia. Finally, the arterial pH can affect measurement of the anion gap as well by affecting the anionic charge of serum proteins and by altering the quantity of organic acids – during acidemic states the AG will decrease by 1–3 mEq/L and increase by 3–5 mEq/L during alkalemic states.

Elevated Anion Gap Acidosis

Elevated anion gap acidosis is due to either the retention of endogenous acids (e.g., keto-acids, lactic acid, etc.) or the addition of exogenous acids (e.g., ingestion of ethylene glycol, salicylates) and has a variety of causes that are easily recalled by the classic mnemonic *MUDPILES* (Table 14.4). Lactic acidosis is by far the most common type of a high anion gap acidosis in the PICU and will be discussed in more detail below. Ketoacidosis may develop with starvation (i.e., free fatty acids are metabolized to keto-acids rather than being used for triglyceride formation) but more commonly develops during states of insulin deficiency, e.g., diabetic ketoacidosis (DKA). Starvation is usually associated with a mild metabolic acidosis, while DKA is commonly associated with profound metabolic acidosis. A wide variety of toxins and drugs can also cause an elevated anion gap acidosis, including methanol, ethylene glycol, salicylates (which are also associated with a respiratory alkalosis via direct stimulation of the respiratory centers), iron, isoniazid, and paraldehyde (paraldehyde was once commonly used for the treatment of refractory seizures and is used so infrequently now that this is rarely observed). Methanol and ethylene glycol are rapidly converted to the toxic metabolites, formic acid (via alcohol dehydrogenase) and glycolic acid (via aldehyde dehydrogenase) in the liver, respectively. These two metabolites are responsible for both the toxic effects and the elevated anion gap associated with the ingestion of these two alcohols. An important diagnostic clue to the presence of methanol or ethylene glycol as the etiology for an elevated anion gap is an increase in the osmolal gap:

$$\text{Osmolal gap} = \text{Measured serum osmolality} - \text{Calculated serum osmolality}$$

$$\text{Calculated osmolality} = 2\left[\text{Na}^+\right] + \text{BUN}/2.8 + \text{Glucose}/18$$

The normal osmolal gap is less than 10 mEq/L, though pseudohyponatremia secondary to either hyperlipidemia or hyperproteinemia can falsely elevate the osmolal gap [3]. Inborn errors of metabolism (i.e., endogenous organic acids) also are associated with an elevated anion gap. Finally, uremia (as with renal insufficiency or renal failure) causes an elevated anion gap.

Lactate is a byproduct of anaerobic metabolism. Aerobic metabolism provides 20 times more energy than anaerobic metabolism. For example, glucose is oxidized to pyruvate via glycolysis (also called the Embden-Meyerhof pathway), generating two molecules of ATP in the process (Fig. 14.2; Table 14.5). When oxygen supply is adequate, pyruvate enters the mitochondria and is converted to acetyl coenzyme A (acetyl CoA) by the pyruvate dehydrogenase enzyme complex, after which it is completely oxidized to CO_2 and H_2O via the Kreb's cycle (also known as the tricarboxylic acid or citric acid cycle) (Fig. 14.3) and oxidative phosphorylation (Fig. 14.4), generating a *net* total of 36–38 mol of ATP for every mole of glucose (Table 14.6). Conversely, when oxygen supply is inadequate, pyruvate is reduced by NADH and lactate dehydrogenase to lactate (lactic acid), a relatively inefficient process that generates considerably less ATP. Lactate can be converted back to pyruvate in the presence of oxygen via reduction of NAD^+ to NADH, which in turn enters the Kreb's cycle. Alternatively, lactate can be converted back to glucose via the Cori cycle (which requires 6 mol of ATP) and stored in the liver as glycogen.

The normal arterial lactate concentration is 1.0 ± 0.5 mmol/L, which represents the equilibrium between production and consumption during normal metabolism [23, 24]. The liver, kidneys, gastrointestinal tract, and muscle all have the capacity to remove lactate far in excess of what is normally produced during normal metabolism throughout the day. Therefore, lactate production (i.e., from anaerobic glycolysis) must increase substantially before it accumulates to any significant extent in the arterial blood. Cohen and Woods [25] divided lactic acidosis into two categories. Type A lactic acidosis results from an imbalance between oxygen delivery and oxygen consumption (e.g., shock), while type B lactic acidosis occurs without clinical evidence of tissue hypoxia. Type B lactic acidosis is more often associated with underlying diseases (e.g., diabetes mellitus, liver disease, malignancy, thiamine deficiency, pheochromocytoma), drugs or toxins (e.g., epinephrine, norepinephrine, alcohol, terbutaline, cyanide), or inborn errors of metabolism (e.g., glucose-6-phosphatase deficiency, fructose-1,6-diphosphatase deficiency, pyruvate dehydrogenase deficiency, defects in oxidative phosphorylation) [23, 25, 26]. In addition, hyperlactatemia may occur in critical illness (e.g., sepsis, burns, trauma) even in the absence of tissue hypoxia – in these cases, the increased lactate is secondary to increased glycolytic flux, down-regulation of pyruvate dehydrogenase, etc. [23, 24, 27]. In

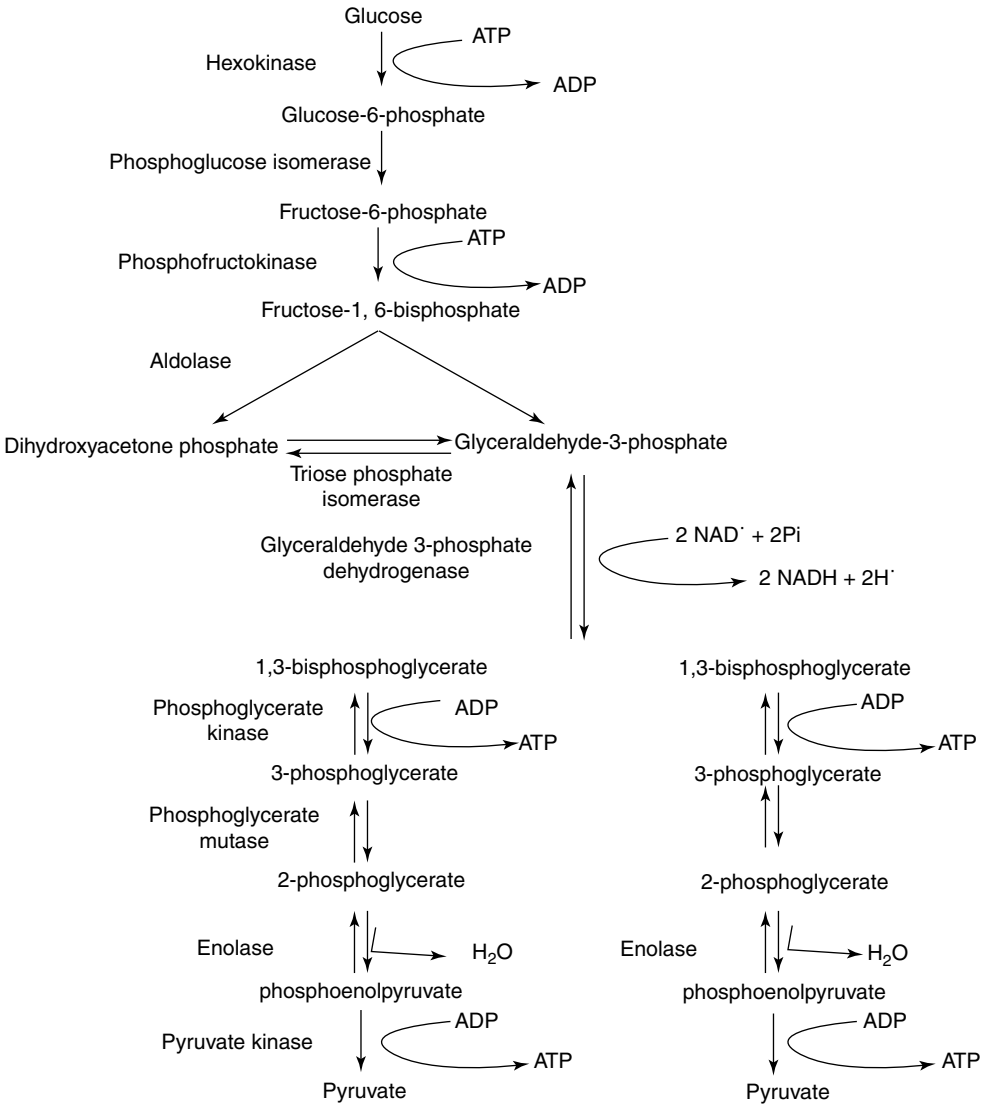

Fig. 14.2 Glycolysis (Embden-Meyerhof pathway): Glucose + 2 Pi + 2 ADP + 2 NAD^+ → 2 Pyruvate + 2 ATP + 2 NADH + 2H^+ + 2 H_2O

Table 14.5 Consumption and Generation of ATP in glycolysis

Reaction	ATP change per mole glucose
Glucose → glucose-6-phosphate	−1
Fructose 6-phosphate → fructose 1,6-bisphosphate	−1
2 1,3-Bisphosphoglycerate → 2 3-phosphoglycerate	+2
2 Phosphoenolpyruvate → 2 Pyruvate	+2
	Net +2

these cases, clinical exam, absence of other indicators of tissue hypoxia (i.e., low mixed venous saturation, worsening base deficit, organ dysfunction, etc.) is helpful in differentiating between increased production versus poor clearance. Alternatively, an elevated lactate/pyruvate ratio (defined as a lactate to pyruvate ratio greater than 18) is a useful indicator of lactate accumulation secondary to tissue hypoxia [28–30].

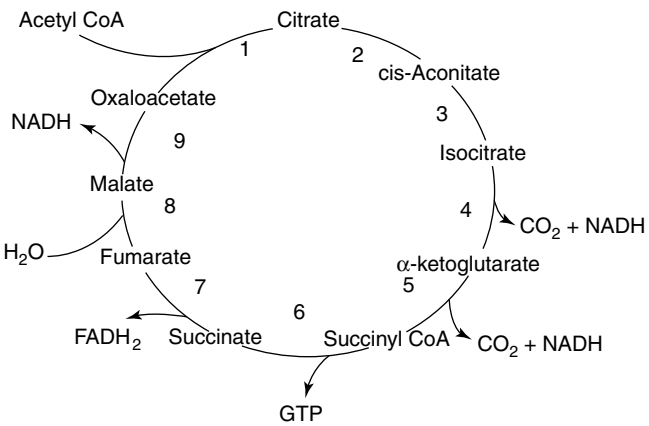

Fig. 14.3 Tricarboxylic acid (Kreb's) cycle: Pyruvate + CoA + NAD^+ → Acetyl CoA + CO_2 + NADH (via Pyruvate dehydrogenase complex) Acetyl CoA + 3 NAD^+ + FAD + GDP + Pi + 2 H_2O → 2 CO_2 + 3 NADH + $FADH_2$ + GTP + 2H^+ + CoA. *1* Citrate synthetase, *2* Aconitase, *3* Aconitase, *4* Isocitrate dehydrogenase, *5* α-ketoglutarate dehydrogenase complex, *6* Succinyl CoA synthetase, *7* Succinate dehydrogenase, *8* Fumarase, *9* Malate dehydrogenase

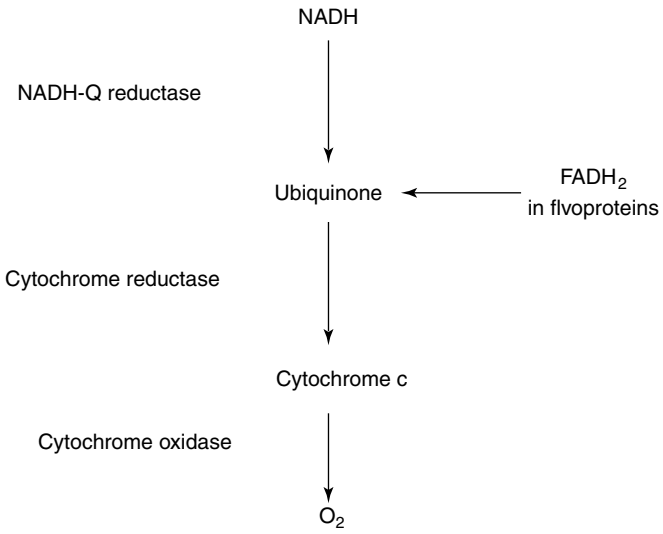

Fig. 14.4 Oxidative phosphorylation, the process by which ATP is formed as electrons are transferred from NADH or FADH $_2$ to O_2 by a series of electron carriers localized to the inner mitochondrial membrane. The oxidation of NADH yields three molecules of ATP, whereas oxidation of $FADH_2$ yields two molecules of ATP through the generation of a proton gradient across the inner mitochondrial membrane. Oxidation and ATP synthesis are coupled by transmembrane proton fluxes. As electrons are transferred from $FADH_2$ or NADH to O_2, H+ is pumped out of the mitochondrial matrix. ATP is synthesized when H+ flows back into the mitochondrial matrix

Table 14.6 Consumption and generation of ATP in aerobic glycolysis (complete oxidation of glucose to O_2 and H_2O)

Reaction	ATP change per mole glucose
Glucose → glucose-6-phosphate →	−1
Fructose 6-phosphate → fructose 1,6-bisphosphate	−1
2 1,3-Bisphosphoglycerate → 2 3-phosphoglycerate	+2
2 Phosphoenolpyruvate → 2 Pyruvate	+2
2 Glyceraldehyde 3-phosphate → 2 1,3-bisphosphoglycerate (yields 2 NADH → oxidation via respiratory chain 2–3 ATP:1 NADH[a])	+4 to +6
2 Pyruvate → 2 Acetyl CoA (yields NADH → oxidation via respiratory chain 3 ATP:1 NADH)	+6
2 Succinyl CoA → 2 Succinate	+2 (as GTP)
6 NADH from Kreb's cycle (oxidation via respiratory chain 3 ATP:1 NADH)	+18
2 $FADH_2$ from Kreb's cycle (oxidation via respiratory chain 2 ATP: 1 $FADH_2$)	+4
	Net +36 to +38

[a]NADH is formed by glycolysis (glycolytic enzymes are located in the cytosol). The inner mitochondrial membrane is impermeable to NAD^+ and NADH. One of two mechanisms is used to transport the electrons from cytoplasmic NADH across the inner mitochondrial membrane:
1 Glycerol phosphate shuttle: this shuttle mechanism transports the electrons from NADH rather than the NADH itself across the inner mitochondrial membrane in a process that generates $FADH_2$
2 Malate-aspartate shuttle: this shuttle mechanism transports the electrons from NADH rather than the NADH itself across the inner mitochondrial membrane in a process that regenerates NADH (dominant mechanism in the heart and liver)

Several studies have examined the correlation between lactic acidosis and subsequent outcome in both children and adults with critical illness from myriad causes [reviewed in [23, 24, 26, 31–34]]. For example, Vincent et al. [35] showed that the initial lactate level, as well as the change in lactate over time during resuscitation was predictive of outcome in adults with shock. These results have been replicated in other studies performed in adults with both hemorrhagic shock [36–39] and sepsis [40–44]. Similarly, the initial lactate level, as well as the change in lactate over time predict outcome in children with septic shock [30, 45–47] and low cardiac output syndrome following cardiopulmonary bypass [48–54]. In summary then, hyperlactatemia appears to be a useful indicator of poor tissue perfusion, though serial lactates are perhaps more useful than any one number. In addition, physicians at the bedside need to be cognizant of other causes of lactic acidosis (i.e. type B disorders – for example, sepsis) and exercise caution when interpreting serum lactate concentrations.

Acute metabolic acidosis can be tolerated in most healthy individuals, e.g. pH values as low as 7.15 may be generated in the exercising adult [55]. However, severe metabolic acidosis (usually pH <7.20) produces a variety of adverse hemodynamic consequences, including decreased cardiac output (via decreased cardiac contractility), decreased systemic vascular resistance (producing hypotension), increased susceptibility to ventricular arrhythmias, increased pulmonary vascular resistance, and decreased responsiveness to both endogenous and exogenous catecholamines [reviewed in [23, 24, 26]]. However, while generally accepted by most clinicians, the negative inotropic effects of acute metabolic acidosis have not been consistently demonstrated. Furthermore, there is evidence to suggest that acidosis may have protective effects in critical illness [reviewed in [26, 56, 57]]. Treatment of metabolic acidosis is therefore determined primarily by its etiology, and in general, the focus of treating an increased anion gap acidosis should be on treating the underlying cause of the increased acid accumulation. Sodium bicarbonate is rarely helpful and may be harmful in children with DKA and is therefore contraindicated in this population [58, 59]. There are several theoretical concerns to treating lactic acidosis with sodium bicarbonate as well (see discussion above). Importantly, acidosis shifts the oxyhemoglobin dissociation curve to the right (*the Bohr effect*), thereby improving oxygen delivery at the tissue level. Bicarbonate administration, by shifting the oxyhemoglobin dissociation curve back to the left could theoretically worsen oxygen delivery to hypoxic tissues. Alternative compounds for treating metabolic acidosis (e.g., Carbicarb, THAM, dichloroacetate) are available but have failed to show any significant improvements in either hemodynamics or outcome [review in [26, 56, 57]]. There are few randomized, controlled trials to suggest either a benefit or harmful effect of sodium bicarbonate in treating metabolic

Table 14.7 Causes of normal anion gap (hyperchloremic) metabolic acidosis

Gastrointestinal bicarbonate loss
Diarrhea
External pancreatic or small-bowel drainage
Ureterosigmoidostomy, jejunal loop, ileal loop
Drugs
Calcium chloride (acidifying agent)
Magnesium sulfate (diarrhea)
Cholestyramine (bile acid diarrhea)
Renal loss
Hypokalemia
Proximal RTA (type 2)
Distal (classic) RTA (type 1)
Hyperkalemia
Generalized distal nephron dysfunction (type 2 RTA)
(A) Mineralocorticoid deficiency
(B) Mineralcorticoid resistance
(C) ↓NA + delivery to distal nephron
(D) Tubulointerstitial disease
(E) Ammonium excretion defect
Drug-induced hyperkalemia (with renal insufficiency)
Potassium-sparing diuretics (Amiloride, Triamterene, Spironolactone)
Trimethoprim
Pentamidine
Angiotensin-converting enzyme inhibitors and AT-II receptor blockers
Nonsteroidal anti-inflammatory drugs
Cyclosporine
Other
Acid loads (ammonium chloride, hyperalimentation)
Loss of potential bicarbonate: ketosis with ketone excretion
Expansion acidosis (rapid saline administration)
Hippurate
Cation exchange resins

RTA renal tubular acidosis, *AT-II* angiotensin-II receptor blockers

acidosis in either children or adults with shock. Therefore, given the theoretical disadvantages of sodium bicarbonate administration and until more convincing evidence is available to support the argument either way, we would advocate the use of small, titrated doses of sodium bicarbonate to achieve a pH >7.15–7.20 in children with shock, while attempts to improve oxygen delivery (and minimize oxygen consumption) are continued [24].

Non-anion Gap Acidosis

A metabolic acidosis in the presence of a normal anion gap suggests that loss of HCO_3^- (usually via the kidneys or gastrointestinal tract) or rapid dilution of the extracellular fluid (ECF) has occurred. In either case, the concentration of chloride will be increased proportionately, resulting in hyperchloremia. Causes of a normal anion gap, hyperchloremic metabolic acidosis are listed in Table 14.7. One of the most common causes of a hyperchloremic metabolic acidosis in children is diarrhea (diarrheal fluid contains a high concentration of HCO_3^- relative to plasma). Large amounts of potassium are lost in diarrheal fluid as well, frequently resulting in hypokalemia. The small bowel and pancreatic fluids are also high in HCO_3^- and low in Cl^- such that tube or fistula drainage (e.g., ureteral diversion procedures using colon or small bowel) from these sites can also precipitate a hyperchloremic metabolic acidosis.

Renal tubular acidosis (RTA) is also characterized by a hyperchloremic metabolic acidosis, resulting from failure of bicarbonate reabsorption/regeneration (i.e. decreased H^+ secretion) in the distal tubule (type 1, or distal RTA), bicarbonate wasting in the proximal tubule (type 2, or proximal RTA), or aldosterone deficiency with decreased clearance of potassium (type 4, distal or hyperkalemic RTA). Certain diuretics can also induce the hyperchloremic acidotic state by inhibiting proximal sodium bicarbonate absorption (acetazolamide) or distal reabsorption (spironolactone). Another potentially significant disturbance in the critically ill children is dilutional acidosis. With large volume ECF expansion, as during resuscitation of shock with non-HCO_3^- -containing fluids such as 0.9 % normal saline, glomerulotubular balance is downregulated. The fractional rate of sodium reabsorption by the proximal tubule is thus decreased and with it, the reabsorption of bicarbonate, inducing hyperchloremic metabolic acidosis. Children with sepsis and trauma in particular may receive rapid volume resuscitation of significant multiples of their plasma volume. Normal saline contains equivalent amounts of sodium and chloride (154 mEq/L), and large volumes of normal saline can induce a hyperchloremic metabolic acidosis [60–64]. Approaches are discussed further later in this chapter.

Calculation of the urinary anion gap can also be helpful in differentiating renal from GI causes of hyperchloremic metabolic acidosis. The urinary anion gap is defined as:

$$\text{Urinary anion gap} = \left[Na^+ + K^+\right] - \left[Cl^-\right]$$

The urinary anion gap is normally negative, as *unmeasured* ammonium is excreted by the kidney to balance Cl^- excretion, which is typically greater than urinary Na^+ and K^+ excretion. In the setting of hyperchloremic metabolic acidosis, a GI-induced bicarbonate loss will lead to normal renal compensation by increasing chloride excretion and balancing this with an increase in ammonium excretion, resulting in a greater negative urinary anion gap. A positive urinary anion gap reflects an impairment in ammonium excretion and suggests the presence of a RTA. The urine pH can then further differentiate between a proximal RTA (low urine pH) and a distal RTA (high urine pH). Patients with a hyperchloremic metabolic acidosis generally have wasting of endogenous bicarbonate buffer and generally benefit from sodium bicarbonate therapy.

Metabolic Alkalosis

A primary metabolic alkalosis is defined as an arterial pH >7.45 secondary to either loss of H^+ from the body or a net gain of HCO_3^-. Metabolic alkalosis is maintained when the kidneys fail to compensate by excreting excess HCO_3^- due to volume contraction, low glomerular filtration, or associated depletion of chloride or potassium. It is typically accompanied by an elevated $PaCO_2$ due to compensatory alveolar hypoventilation. The appropriate compensatory increase in $PaCO_2$ may be calculated by:

$$PaCO_2 = 0.7\Delta\left[HCO_3^-\right].$$

The maximal compensatory increase in measured $PaCO_2$ is approximately 65 mmHg. Conditions of bicarbonate loss can either be temporary and corrected by chloride replacement (so-called *chloride responsive*) or those in which hormonal mechanisms produce ongoing acid and chloride losses that are not effectively corrected by chloride (so-called *chloride resistant*) [2–4, 64]. Chloride responsive causes are characterized by a urine chloride concentration less than 10 mmol/L and include gastrointestinal losses from vomiting or excessive nasogastric suction, renal losses from diuretic use (loop diuretics), and as compensation for chronic hypercarbia. These states are exacerbated by volume contraction and/or hypokalemia, which augment distal H^+ secretion. In these cases, the metabolic alkalosis is corrected by chloride administration. Chloride resistant causes are characterized by a urine chloride greater than 20mmol/L and are generally less common in critically ill children. The chloride resistant causes are related to mineralocorticoid excess from hyperaldosteronism, either in a primary or secondary state. Notably, diuretic therapy produces both states by inducing chloride and potassium depletion but also by stimulating aldosterone secretion. Finally, exogenous alkali loads are relatively common in the PICU and are related to massive blood transfusions (blood products containing citrate), use of acetate in parenteral nutrition, or with citrated sodium as used in replacement solutions for continuous renal replacement therapies (Table 14.8).

Treatment of metabolic alkalosis is based on etiology. Chloride responsive disorders obviously benefit from replacement of chloride through saline infusion (NaCl), though KCl may also provide dual replacement benefit. In more severe states, dilute (0.1 N) intravenous hydrochloric acid can provide more rapid replacement, or oral ammonium chloride can be helpful (avoid in the presence of liver disease). Discontinuation of diuretics may also be necessary. If

Table 14.8 Causes of metabolic alkalosis

Exogenous HCO_3^- loads
Acute alkali administration
Milk-alkali syndrome
Effective ECFV contraction, normotension, hypokalemia, and secondary hyperreninemic Hyperaldosteronism
Gastrointestinal origin
Vomiting
Gastric aspiration
Congenital chlorodorrhea
Villous adenoma
Combined administration of sodium polystyrene sulfonate (Kayexalate) and aluminum hydroxide
Renal origin
Diuretics
Edematous states
Posthypercapnic state
Hypercalcemia/hypoparathyroidism
Recovery from lactic acidosis or ketoacidosis
Nonreabsorbable anions including penicillin, carbenicillin
MG2+ deficiency
K + depletion
Bartter's syndrome (loss of function mutations in TALH)
Gitelman's syndrome (loss of function mutation in NA + -CL- cotransporter in DCT)
ECFV expansion, hypertension, K ± deficiency, and mineralcorticoid excess
High renin
Renal artery stenosis
Accelerated hypertension
Renin-secreting tumor
Estrogen therapy
Low renin
Primary aldosteronism
Adenoma
Hyperplasia
Carcinoma
Adrenal enzyme defects
11 B-hydroxylase deficiency
17 A-hydroxylase deficiency
Cushings syndrome or disease
Other
Licorice
Carbenoxolone
Chewer's tobacco
Lydia Pincham tablets
Gain of function mutation or renal sodium channel with ECFV expansion, hypertension, K+ deficiency, and hyporeninemic-hypoaldosteronism
Liddle's syndrome

ECFV extracellular fluid volume, *TALH* thick ascending limb of Henle's loop, *DCT* distal convoluted tubule

ongoing diuresis is desired, the carbonic anhydrase inhibitor acetazolamide may be effective. Treatment of chloride resistant states is directed at treating mineralocorticoid excess. Use of agents blocking distal tubular sodium reabsorption, restriction of sodium intake, and potassium supplementation are used to treat primary hyperaldosteronism. Angiotensin-converting enzyme inhibitors are typically effective for secondary aldosteronism as well as discontinuation of exogenous corticosteroids.

Mixed Acid-Base Disorders

A mixed acid-base disorder occurs when there is more than one acid-base disorder occurring at the same time. For example, salicylate ingestions classically produce both a respiratory alkalosis (via direct stimulation of the respiratory centers in the brain) and a metabolic acidosis (elevated anion gap). The normal compensation to a primary acid-base disorder is NOT considered a mixed acid-base disorder. Proper analysis and interpretation of acid-base disorders requires a systematic approach [2–4, 65, 66] (Table 14.9).

Table 14.9 Systematic approach to analysis of acid-base disorders

1. *Interpret the arterial pH to determine whether there is an academia or alkalemia present*:
If pH >7.45, an alkalemia is present
If pH <7.35, an acidemia is present
2. *Determine whether the primary disturbance is respiratory or metabolic in origin*
Respiratory acidosis: ↓ pH, ↑ $PaCO_2$
Respiratory alkalosis: ↑ pH, ↓ $PaCO_2$
Metabolic acidosis: ↓ pH, ↑ $[HCO_3^-]$
Metabolic alkalosis: ↑ pH, ↓ $[HCO_3^-]$
3. *Calculate the anion gap (AG)* ($AG = [NA^+] - [HCO_3^- + CL^-]$). *Correct for hypoalbuminemia if indicated*!
Generally, AG >10 mEQ/L suggests the presence of a metabolic acidosis, while AG >20 mEQ/L is always associated with a metabolic acidosis
4. *Using the formulas listed in Table 14.1, determine whether the degree of compensation is appropriate. If it is not, then a mixed acid-base disorder is likely.*
5. *Calculate the delta AG: delta GAP = (calculated anion GAP – normal AG), i.e. (AG_{CALC} – 12). in other words, for every 1 mEQ/L increase in the calculated AG, there should be a 1 mEQ/L decrease in* $[HCO_3^-]$*:*
If the $[HCO_3^-]$ is lower than predicted by this relationship, a normal AG (hyperchloremia)
Metabolic acidosis is also present
If the $[HCO_3^-]$ is higher than predicted by this relationship, a metabolic alkalosis is also present
6. *Measure urine pH and urine electrolytes if a metabolic alkalosis is present*

Special Acid-Base Situations

Cardiopulmonary Bypass and Hypothermia: pH Stat and Alpha Stat Concepts

Hypothermia is a key element in creating optimal surgical conditions and end organ protection, particularly in the brain, during cardiopulmonary bypass (CPB). Two approaches to management of acid-base status during hypothermia (either iatrogenic, as with cardiopulmonary bypass or accidental) have been described – pH-stat versus alpha-stat. Alpha-stat and pH-stat are two divergent blood gas management strategies utilized during cardiopulmonary bypass (CPB) and are a topic of debate among cardiac anesthesiologists. The primary difference centers on the anesthesiologist's response to $PaCO_2$ and the change in its solubility during hypothermia and CPB. The differences between the two approaches is quite complex and deserve some explanation here.

The law of mass action states that the velocity of a reaction is proportional to the product of the concentrations of the reactants. For example, water dissociates into H^+ and OH^-:

$$H_2O \leftrightarrow H^+ + OH^-$$

Recall that the inherent tendency of a particular acid to dissociate or ionize is determined by the ionization constant, pK. Note that the pK is inversely proportional to the strength of the acid to dissociate – in other words, a strong acid (HA) would exist mostly as H^+ and A^- (the pK of this acid would be relatively high). Similarly then, the relative concentration of H+ is determined by the dissociation constant of water (pKw), which decreases as temperature decreases (i.e., water is less likely to dissociate), such that as the H^+ ions and OH^-decrease – the pH then increases [67]. Stated in another way, electroneutrality occurs at a neutral pH when $[H^+] = [OH^-]$. As temperature decreases, the pH at which water is *neutral* increases 0.017 units for each °C decrease in temperature – at 37 °C, the pH of neutral water (i.e. when $[H^+] = [OH^-]$) is 6.8, while at 25 °C, the pH of neutral water is 7.40. Since human plasma is mostly water, the same principles apply. Human blood has $[OH^-]$: $[H^+]$ ratio of 16: 1, resulting in a pH of 7.4 at 37°C (normal body temperature). This relationship remains constant despite changes in

temperature, so that the pH of blood also increases 0.017 units for each °C decrease in temperature [68].

The function of proteins is critically dependent upon their tertiary and quarternary structures, which in turn depend to a great extent upon the ionic charges of the individual amino acid constituents. Thus, intracellular proteins need a buffer to maintain a constant ionization state despite changes in pH [69]. Reeves [70] suggested that the imidazole moiety of histidine could serve this role, as it undergoes a pK change with a temperature that parallels that of pKw (the so-called *alpha-stat hypothesis*). The portion of the histidine imidazole group that loses a proton (H^+) in its dissociation to maintain electrical neutrality (thereby acting as a buffer) is designated alpha-imidazole. Thus, while changes in temperature will affect the pH of water, the ionization state of proteins remains the same relative to this pH – this allows proteins to maintain their structure, and thus function, regardless of the temperature. The *alpha-stat hypothesis* contends that the alpha imidazole histidine ionization state is a primary determinant of the charge state and the pH-dependent functions of most of the body's proteins. With alpha stat management (as observed in poikilotherms whose tissues must function over a wide range of temperatures), changing temperature does not alter histidine ionization and, hence, pH of neutrality, protein charge state, structure, and function are better preserved.

Other factors are important as well. During hypothermia, the solubility of CO_2 in blood increases such that for a given concentration of carbon dioxide in blood, the $PaCO_2$ decreases as total CO2 remains constant. Keeping CO_2 constant is essential because it guarantees that the OH^-/H^+ ratio, alpha-imidazole, and protein charge state remains stable, thereby maintaining biologic neutrality as tissues cool. With regards to CPB, *alpha-stat management* means to measure the arterial blood gases at 37 °C (i.e., the arterial blood is warmed prior to 37 °C prior to analysis) and any necessary adjustments to maintain arterial pH 7.4 and $PaCO_2$ 40 mmHg at 37 °C are then made, regardless of the core body temperature. In theory, the primary advantages to alpha-stat management are preserving the Gibbs-Donnan equilibrium and maintaining a normal cerebral blood flow/metabolism relationship [71–76].

The other commonly used approach to pH management is known as *pH stat management*. Here, arterial pH is maintained constant over varying temperatures – in other words, management is directed towards maintaining pH 7.4 and $PaCO_2$ 40 mmHg, irrespective of core body temperature. Generally, in order to maintain $PaCO_2$ 40 mmHg, CO_2 must be added to the sweep gas as the patient is cooled, owing to the increased solubility of CO_2 with decreasing temperature. Extracellular and intracellular OH^-:H^+ ratios are altered and total CO_2 stores become elevated. This type of pH management is observed in hibernating animals – these animals hypoventilate to generate a respiratory acidosis. Importantly, the goal during hibernation is to minimize oxygen consumption and energy expenditure while preserving blood flow to the vital organs (especially the brain). Many experts argue then that the pH-stat management is more appropriate to the human undergoing CPB [71–76].

The debate surrounding alpha-stat versus pH-stat blood gas management revolves around CO_2 and hypothermia and their effect on cerebral blood flow, cerebral oxygen consumption, intracellular pH, and extracellular pH in the setting of CPB and deep hypothermic circulatory arrest (DHCA). The discrepancy in $PaCO_2$ and pH between the two strategies is significant and approaches 80 mmHg and 0.24 respectively [71–76] (Table 14.10). The main concern of the debate is to minimize poor neurodevelopmental and neuropsychometric outcomes [72, 77, 78]. Studies evaluating both methods present conflicting data and have not resolved the debate as to the ideal acid-base strategy. A prospective, randomized study comparing alpha stat and pH stat in two similar groups demonstrated shorter duration of intubation, ICU stay, and post-operative seizures in pH stat managed patients, however without any statistical significance [79]. The study also looked at 1 year follow up in 111 of 182 patients enrolled and found no difference in neurologic evaluation, EEG, or psychomotor or mental development indices [80].

Table 14.10 Alpha-stat vs pH-stat management

	Measured and reported at 37 °C				Actual (at in vivo temperature)			
Core body temperature	pH alpha-stat	pH pH-stat	$PaCO_2$ alpha-stat	$PaCO_2$ pH-stat	pH alpha-Stat	pH pH-stat	$PaCO_2$ alpha-stat	$PaCO_2$ pH-stat
37 °C	7.40	7.40	40	40	7.40	7.40	40	40
33 °C	7.40	7.34	40	47	7.44	7.40	35	40
30 °C	7.40	7.30	40	54	7.50	7.40	29	40
27 °C	7.40	7.26	40	62	7.55	7.40	26	40
23 °C	7.40	7.21	40	74	7.60	7.40	22	40
20 °C	7.40	7.18	40	84	7.65	7.40	19	40

Hypercapnic Acidosis and Permissive Hypercapnia in Ventilatory Management

Lung protective ventilator strategies utilizing low tidal volumes and permissive hypercapnia are currently standard practice in managing patients with acute respiratory distress syndrome (ARDS). Hypercapnic acidosis (HCA) is regarded as an acceptable side effect of permissive hypercapnia. HCA has a myriad of effects on many physiological processes, mostly demonstrated in animal models. Animal models have suggested that acidosis attenuates hypoxic pulmonary vasoconstriction, maintain nitric oxide, reduction in oxidative stress, attenuates pulmonary endothelial wound repair, and overall dampening the inflammatory response [81]. The recognition of these effects is important as it will affect the decision whether or not to allow the development of HCA on a case by case basis. The resultant effect of HCA on physiological functions depends on a myriad of factors including the level of hypercapnia and patients prior medical illnesses.

Experimental studies have demonstrated therapeutic benefits of HCA in a number of lung injury models [82–90]. However, it is unclear if it is the respiratory acidosis per se rather than the elevated carbon dioxide milieu that is responsible for this beneficial effect. HCA can enhance oxygenation through several mechanisms. Respiratory acidosis resulting in a decreased pH causes a shift of the oxyhemoglobin dissociation curve to the right during acute respiratory acidosis, which causes the release of oxygen to the tissues (the Bohr effect). Additionally HCA causes microvascular vasodilatation, promoting oxygen delivery and tissue perfusion [91, 92]. However, pCO_2 levels of greater than 100 mmHg will result in vasoconstriction. Additional potential benefits include enhancement of lung ventilation-perfusion (V/Q) matching by potentiating hypoxic pulmonary vasoconstriction and increases in CO_2-mediated augmentation of cardiac output and peripheral oxygen delivery. Alternatively, the impact could be harmful by increasing intrapulmonary shunting and worsening pulmonary vasoconstriction [93]. Avoidance of HCA is recommended in patients with intracranial processes or with significant cardiac disease. Hypercapnia increases cerebral blood flow which can have significant deleterious effects in head injury. In children with cardiac disease, the direct effect of myocardial depression may or may not be outweighed the positive effects on coronary blood flow, afterload reduction, and improved cardiac output.

Choice of Intravenous Fluid Composition and Acid-Base Balance

Increasing literature has questioned the use of normal saline solutions (0.9 % NaCl) as the standard fluid for resuscitation, maintenance in intensive care units, or intraoperative surgery [94]. Numerous studies have shown the generation of hyperchloremic metabolic acidosis induced by routine use of 0.9 % NaCl for maintenance and resuscitation in postoperative patients and trauma models [60–64, 94, 95]. Adult studies have demonstrated, however, that the alternative use of lactated Ringers solutions instead of normal saline could also demonstrate acidosis secondary to lactemia. The use of a calcium-free balanced crystalloid (Plasmalyte) for replacement of fluid losses on the day of major surgery, however, was associated with less postoperative morbidity than use of 0.9 % NaCl [96]. Use of 0.9 % NaCl was associated with hyperchloremia, reduced bicarbonate levels, acidosis, and increased base deficit in patients compared to patients receiving Plasmalyte [97]. Patients with diabetic ketoacidosis (DKA) could also potentially have worsening acidosis from 0.9 % NaCl. Resuscitation of DKA patients with Plasmalyte resulted in lower serum chloride and higher bicarbonate levels than patients receiving 0.9 % NaCl, due to decreased generation of hyperchloremic metabolic acidosis [98]. Current evidence is insufficient, particularly in children, to recommend a specific change in practice to completely avoid use of 0.9 % NaCl. However, in patients in whom metabolic acidosis is a concern prior to fluid resuscitation, alternative fluid choices to 0.9 % NaCl could be considered to decrease iatrogenic worsening of acidosis. Use of Ringer's lactate (Na^+ 130 Eq/L, Cl^- 109 mEq/L, K^+ 4 mEq/L, and lactate 28mEq/L) has been recommended by some authors over normal saline for preferential use during resuscitation. The lactate is generally metabolized by the liver and does not usually contribute to lactic acidosis.

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