

Disorders of the Acid–Base Status

2

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Core Messages

- › Essentially all pediatric disorders, if severe enough, can lead to acid–base disturbances directly, as a result of therapy, or both.
- › Acid–base disorders need to be anticipated in all critically ill patients. Proactive monitoring of the acid–base status will allow the early recognition of derangements and the prevention of what could become a life-threatening state.
- › Acidosis is the most common acid–base derangement in the intensive care unit (ICU), with metabolic acidosis potentially indicating a more severe course and worse outcome.
- › A pH of <7.2 merely indicates a primary acidosis-inducing disorder. Further assessment of the type of acidosis and the presence of a mixed acid–base disorder requires measurement of $p\text{CO}_2$, serum bicarbonate, albumin, and calculation of the anion gap.
- › The most commonly encountered causes of metabolic acidoses in the ICU are renal insufficiency, sepsis, and DKA, while acute respiratory distress syndrome (ARDS) and severe status asthmaticus are the *usual suspects* in respiratory acidoses.
- › Alkalosis, on the other hand, is less common in the ICU. Fluid status derangements and, especially, gastric fluid depletion are the usual underlying causes of metabolic alkaloses, whereas rapid respiration secondary to lung diseases, excessive mechanical ventilation, pain, or central nervous system processes are the common causes of respiratory alkaloses.
- › In the ICU, identification of acid–base derangements is followed by timely stabilization of the patient irrespective of the underlying cause. Depending on the severity of the derangement and the patient's response to the stabilizing interventions, the underlying cause might also need to be aggressively sought and emergently reversed.
- › Identification of the underlying cause(s) of the acid–base disorder at hand may be the final step in the management of these patients, but plays an important role both in the prevention of worsening of the derangement and other complications as well as in the determination of the patient's overall prognosis.

Case Vignette 1

An 11-year-old girl with a history of mild bronchial asthma presented with fever and increased work of breathing refractory to repeated albuterol treatments at her pediatrician's office. Status asthmaticus was diagnosed, and an ABG was obtained upon arrival to the emergency room, showing a pH of 7.22, a $p\text{CO}_2$ of 38 mmHg, and a serum bicarbonate level of 15 meq L^{-1} . Her serum sodium and chloride were 141 and 110 meq L^{-1} , respectively; her serum lactate concentration was 11 mmol L^{-1} , and her serum albumin level was 1 g dL^{-1} . What is your interpretation of her ABG?

The ABG is consistent with acidosis, given the low pH of 7.22. The bicarbonate level is low at 15 meq L^{-1} whereas $p\text{CO}_2$ is almost normal, rendering the primary disorder a metabolic acidosis. Following the rule of 1:1 compensation, $p\text{CO}_2$ would be expected to be 30–32. Thus, this patient also has an element of $p\text{CO}_2$ retention and thus a mixed acid–base disorder, namely primary metabolic acidosis and acute respiratory acidosis. The metabolic component is secondary to an AG acidosis, with the AG measuring 16 prior to the required adjustment as follows:

Corrected albumin (4 g dL^{-1} expected – 1 g dL^{-1} observed) of $3 \times 2.5 = 7.5$. Hence, adjusted AG 16 measured $+ 7.5 = 23$ with a Δ/Δ of 1, indicating no other underlying type of metabolic acidosis. Treatment to target lower airway obstruction with bronchodilators and steroids will assist in resolving both the respiratory and the metabolic defect. The latter will also be alleviated with judicious use of hydration. Lastly, the cause of severe hypoalbuminemia needs to be sought.

Case Vignette 2

A 2-year-old child was found unconscious and with increased work of breathing. An ABG showed a pH of 7.38, a $p\text{CO}_2$ of 28 mmHg, and a serum bicarbonate of 16 meq L^{-1} . What is your interpretation?

This is a typical ABG of a patient with salicylate poisoning. Depending on further clinical and laboratory evaluations, this patient might need intubation, gastric lavage, dialysis, or simple hydration and supportive care.

Acid–base disorders are among the most commonly encountered medical problems in critically ill patients. Departure of blood acidity from the normal range can result in a spectrum of adverse consequences and, when severe, can be life-threatening. Identifying acid–

base derangements, correcting the pH, and arriving at the correct underlying cause for each derangement are of paramount importance for caring for patients in the intensive care unit. This chapter will address physiology of acid–base status, interpretation of blood gas measurements, common causes of derangements, and approach to reestablishing normalcy.

2.1 Introduction

The human organs and tissues function under a tightly controlled pH in the range of 7.35–7.45. Depending on the degree of the deviation of pH outside this narrow range, several homeostatic responses are activated in an effort to restore normal acid–base status. Initially, reactions by chemical buffers will attempt to neutralize the derangement, followed by ventilatory adjustments by the lungs and, finally, alterations in acid excretion by the kidneys.

Several factors impact the prognosis of patients with acid–base disturbances:

1. Severity of acidemia or alkalemia.
2. Acuity and duration of the derangement.
3. Functional status of the lungs and kidneys.
4. Underlying cause: This factor is what ultimately defines the patient's outcome.

A plasma pH of 7.10 can be inconsequential when caused by diabetic ketoacidosis, but it portends a poorer outcome if it is secondary to septic shock and poor organ perfusion. Likewise, a plasma pH of 7.60 caused by anxiety-hyperventilation syndrome is inconsequential, whereas it signals a worse prognosis if it is secondary to a brain tumor.

To manage patients with serious acid–base disturbances appropriately, accurate history taking, precise interpretation of blood gas results, and arriving at the correct cause underlying the disorder are critical. Even though our management in the ICU is centered on stabilizing patients' cardiopulmonary status and correcting derangements, including acid–base disorders, knowing the underlying etiology of these disturbances and addressing it with the proper interventions, if deemed necessary, can expedite a patient's recovery and reverse the pathologic process.

2.2 Physiology of Acid–Base Balance

Hydrogen ion (H^+) is much more precisely regulated in the extracellular fluid in order to achieve a concentration

of $0.00004 \text{ meq L}^{-1}$ (40 neq L^{-1}) compared with sodium, for example, which is maintained at $135\text{--}145 \text{ meq L}^{-1}$. This precision with which H^+ is regulated emphasizes this ion's critical impact on cellular functions.

By definition, an acid is a substance that has at least one H^+ and can donate H^+ ions when in a solution, and a base is a substance that can accept H^+ ions [65]. A strong acid rapidly dissociates and releases large amounts of H^+ , such as hydrochloric acid, whereas a weak acid, such as carbonic acid, releases H^+ with less vigor. Similarly, hydroxides are strong bases, while bicarbonate (HCO_3^-), phosphate, and proteins are weak bases. Most acids and bases in the extracellular space are weak, but they constitute the body's principal buffers.

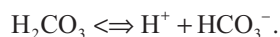
The two classes of physiologically produced acids are volatile acids, also known as carbonic acid (H_2CO_3), and fixed acids, also known as noncarbonic acids. The metabolism of carbohydrates and fats generates approximately $10,000\text{--}15,000 \text{ meq of CO}_2$ daily ($\sim 300 \text{ meq of CO}_2 \text{ kg}^{-1} \text{ day}^{-1}$), which in turn results in increased carbonic acid. The lung is the main organ charged with the elimination of volatile acids. The metabolism of proteins, on the other hand, generates fixed acids. Approximately $100 \text{ meq of fixed acids}$ are generated daily from ingestion and metabolism ($\sim 1\text{--}2 \text{ meq kg}^{-1} \text{ day}^{-1}$) [48]. The kidneys are the only organs capable of eliminating fixed acids through excretion in the urine. The resulting extracellular level of H^+ is approximately 40 neq L^{-1} ($30\text{--}60 \text{ neq L}^{-1}$). As a result of this disproportionate degree of production of volatile acids compared with fixed acids, the lung plays a profound role in acid–base status. Acute respiratory failure and inability to eliminate CO_2 as a result of airway obstruction or severe ARDS would result in a significant rise of pCO_2 and corresponding drop in pH that would overwhelm the cellular buffers and the kidneys' acute compensatory capabilities. On the other hand, acute renal failure and consequent inability to eliminate fixed acids, in the absence of pathological sources of noncarbonic acids, would result in a much milder and less acute derangement.

2.2.1 Henderson–Hasselbalch Equation

The pH of a solution is the negative logarithm of H^+ concentration as defined by

$$\text{pH} = -\log [\text{H}^+].$$

As CO_2 dissolves in a solution, it dissociates into carbonic acid following the Henderson–Hasselbalch equation:



The dissociation constant of carbonic acid follows the law of mass action and is as follows:

$$K_a = [\text{H}^+] \times [\text{HCO}_3^-] / [\text{H}_2\text{CO}_3]$$

Given that the concentration of H_2CO_3 is proportional to that of dissolved CO_2

$$K_a = [\text{H}^+] \times [\text{HCO}_3^-] / [\text{CO}_2]$$

After logarithmic transformation into $\log K_a = \log [\text{H}^+] + \log [\text{HCO}_3^-] / [\text{CO}_2]$ and rearrangement into $-\log [\text{H}^+] = -\log K_a + \log [\text{HCO}_3^-] / [\text{CO}_2]$, it follows that

$$\text{pH} = \text{p}K_a + \log [\text{base}] / [\text{acid}],$$

given that pH is the negative logarithm of H^+ concentration.

Normal acid–base status is maintained by the pulmonary excretion of carbonic acids and by the renal excretion of noncarbonic, fixed acids, and formation of bicarbonate. Hence, the last equation could be envisioned to be as follows: pH is proportionate to kidney $[\text{HCO}_3^-]$ over pulmonary $[\text{pCO}_2]$. Therefore, pH increases with increasing HCO_3^- , the numerator, and declines with increasing levels of pCO_2 , the denominator.

2.2.2 Homeostatic Responses

Once derangement occurs, H^+ concentration is corrected in a timely and stepwise approach starting with chemical buffers, followed by pulmonary ventilation and finally renal control of acid–base excretion.

2.2.2.1 Chemical Acid–Base Buffers

Chemical buffers are available in both extracellular and intracellular compartments. They respond within minutes to neutralize derangements. Chemical buffers are naturally occurring weak acids and bases. They impart their correction on systemic pH by converting strong acids or bases into weak acids or bases, thus minimizing alterations in pH.

There are three buffering systems that are recognized:

1. The bicarbonate system constituted of plasma sodium bicarbonate (NaHCO_3) and carbonic acid (H_2CO_3) and cellular H_2CO_3 and potassium bicarbonate (KHCO_3)
2. The phosphate system found in renal tubular fluid and intracellularly
3. Proteins

The bicarbonate buffer system is the most powerful of all the three systems in the extracellular space,

while proteins dominate the intracellular buffering compartment.

Depending on the severity of the derangement and its chronicity, the limited amount of chemical buffers may not be capable of completely ameliorating the derangements and correcting the pH.

2.2.2.2 Pulmonary Regulation

The lungs respond to deviations in pH by altering the rate and depth of ventilation. The lungs can only eliminate or retain CO_2 . Peripheral chemoreceptors in the carotid and aortic bodies respond within minutes to changes in pO_2 , pCO_2 , and pH. On the other hand, central chemoreceptors in the cerebral medulla are sensitive only to pCO_2 with a slower but stronger and more predominant response [74]. Arterial pCO_2 , therefore, is the most important factor in altering ventilation. These pulmonary responses typically begin in the first hour and are fully established by 24 h [61]. Pulmonary regulation, however, is only 50–75% effective in restoring H^+ concentration all the way back to normal when the primary process is metabolic, as the lung is only capable of eliminating CO_2 and not fixed acids. Nevertheless, the pulmonary buffering system is at least as effective as the chemical buffering system.

2.2.2.3 Renal Acid Regulation

The kidneys correct extracellular pH by controlling serum bicarbonate concentration through the regulation of H^+ excretion, bicarbonate reabsorption, and the production of new bicarbonate. The kidneys excrete H^+ in combination with phosphate ($\text{HPO}_4^{2-} + \text{H}^+ \rightarrow \text{H}_2\text{PO}_4^-$), other acids, or with ammonia to form ammonium [68]. When blood acidity is significantly increased, glutamine is proportionately metabolized into ammonia. Ammonia, in turn, serves as the recipient of H^+ . Whereas the lungs can eliminate or retain only volatile acid, namely pCO_2 , the kidneys can eliminate or retain both acids and bases and are the primary removal site for fixed acids. Renal compensation is the last process to join other buffering forces but insures complete correction over time. Renal compensation typically begins in the first day and is fully established in 3–5 days.

2.3 Acid–Base Monitoring

Acid–base status can be monitored intermittently or continuously. Arterial blood gas (ABG) analysis remains the gold standard in assessing for acid–base

disorders. In the ICU, ABGs can be obtained by arterial puncture or through an indwelling arterial catheter.

2.3.1 Blood Gas Measurement

Blood gas measurements provide data on the acidity of the blood as reflected by pH, pCO_2 , and serum bicarbonate level, all at a single point in time. After sterilizing and subcutaneously anesthetizing the skin overlying a palpable arterial site, typically the radial artery, with 2% lidocaine, arterial blood is obtained by percutaneous needle puncture utilizing a 22- or 24-gauge needle. The brachial, axillary, posterior tibial, dorsalis pedis, and femoral arteries are all potential alternatives that are commonly used in the ICU. The umbilical artery is typically cannulated in neonates within the first week of life.

Several factors affect the accuracy of blood gas measurements. First, the type of syringe can introduce diffusion errors if the sample was left longer than 15 min prior to analyzing it. This error is most appreciated when utilizing plastic syringes as compared with glass syringes and can be minimized by placing the sample on ice [11, 24, 34]. Second, the presence of air bubbles in the blood sample, especially if they constituted more than 1–2% of the blood volume, could result in underestimation of pCO_2 [75]. This error is further magnified if the sample was agitated, increasing the surface area of the blood exposed to the air, especially the longer the sample was left before analysis [34, 57]. Third, the use of heparin as an anticoagulant would lower the measured pH slightly, but more importantly can result in lowering pCO_2 secondary to a dilutional effect [11, 33]. Given that most samples are now analyzed almost immediately, the utilization of heparin for the purpose of measuring ABGs has mostly dropped out of favor.

2.3.2 Sample Analysis

In a whole-blood ABG analysis, oxygen saturation and bicarbonate are calculated numbers based on the measured pH, pO_2 , and pCO_2 , respectively. A measured bicarbonate level is readily available from a serum sample instead, typically, as part of an electrolyte panel.

2.3.3 Temperature Correction

Even though the amount of carbon dioxide in the blood does not change, changes in temperature result in a predictable deviation pattern of the pH and pCO_2 .

Table 2.1 The effect of temperature on blood gas measurements

Temperature		pH	pCO ₂
°C	°F		
20	68	7.65	19
30	86	7.50	30
35	95	7.43	37
36	97	7.41	38
37	98	7.40	40
38	100	7.39	42
40	104	7.36	45

Adapted from [70]

As temperature drops, pCO₂ decreases while pH increases and vice versa (Table 2.1). Contemporary blood gas analyzers are capable of measuring all blood gas elements at either 37°C or any alternative temperature that is entered corresponding to the patient's body temperature. The current recommendation is to utilize uncorrected values measured at 37°C to guide management while keeping in mind the expected values that would correspond to the patient's temperature [64]. This becomes important when interpreting blood gas measurements in hypothermic patients.

2.4 Interpretation of Blood Gas Measurements

Interpretation of blood gas measurements is one of the easy mathematical exercises that, when done correctly and correlated with the patient's history and clinical presentation, yields immediate and rapid insight into the underlying process causing the acid–base status disturbance.

2.4.1 Definitions

Keeping in mind that CO₂ is an acid and the respiratory system is the main organ in charge of its homeostasis, while bicarbonate is an alkali with the kidneys being the organ in charge of its homeostasis, the following definitions would become easy to follow:

Acidosis is a disorder that predisposes to low systemic pH. Utilizing the Henderson–Hasselbalch equation, this can be caused by a fall in systemic bicarbonate concentration or by an elevation in the pCO₂. Acidosis can exist whether the pH became low or was

restored by compensatory mechanisms. It basically defines a process that continues to risk derangement and lower pH. *Acidemia*, on the other hand, is a state of low plasma pH.

Alkalosis is a disorder that predisposes to high systemic pH. This is usually caused either by an increase in systemic bicarbonate concentration or by a fall in the pCO₂.

Alkalemia, on the other hand, is the state of high plasma pH.

Metabolic acidosis is a disorder that predisposes to low pH and is induced by a low serum bicarbonate concentration.

Metabolic alkalosis is a disorder that predisposes to high pH and is induced by a high bicarbonate concentration.

Respiratory acidosis is a disorder that predisposes to low pH and is induced by high pCO₂.

Respiratory alkalosis is a disorder that predisposes to high pH and is induced by low pCO₂.

Respiratory derangements are either acute, reflecting a disorder of a few hours duration, or chronic, i.e., resulting from a process that is ongoing for longer than a few days.

2.4.2 Compensatory Responses

For every acid–base deviation, there is an appropriate compensatory response that follows a very predictable pattern. As was shown earlier, pH is determined by the ratio between the HCO₃[−] concentration and pCO₂ and not by either value in isolation. As such, processes that result in deviation in serum bicarbonate are compensated for by the lungs, which control pCO₂, and processes that result in deviation in pCO₂ are corrected by the kidneys, which regulate bicarbonate.

In metabolic acidosis, for example, a low HCO₃[−]/pCO₂ ratio causes a decline in pH, resulting in stimulation of peripheral chemoreceptors, which, in turn, increase ventilation to decrease pCO₂. Given that CO₂ is an acid, its fall causes the pH to increase back toward normal. In metabolic alkalosis, on the other hand, a high pH induces hypoventilation through peripheral chemoreceptors, resulting in a rise in pCO₂, which, in turn, lowers the pH. This latter response is limited by the degree of the resulting hypoxemia induced by hypoventilation, rendering pulmonary compensation for an increased pH not nearly as effective as for a reduced pH.

A very convenient approach to recall the appropriate compensatory mechanisms to the primary disorders is that bicarbonate and CO₂ vary in the *same direction*

(e.g., a fall in bicarbonate is compensated for by a fall in $p\text{CO}_2$ and vice versa), as one is an acid and the other is an alkali, each with biologically equivalent potential to neutralize the primary derangement.

In metabolic acidosis, the expected pulmonary compensation is a ~ 1 mmHg fall in $p\text{CO}_2$ for every 1 meq L^{-1} reduction in bicarbonate concentration [14].

In metabolic alkalosis, on the other hand, the pulmonary compensation raises $p\text{CO}_2$ by 7 mmHg for every 10 meq L^{-1} elevation in bicarbonate concentration [39, 40].

In *respiratory disorders*, the compensatory mechanisms are biphasic: The first phase is *acute* and dominated by chemical buffering mechanisms, while the second, *chronic* phase is dominated by renal responses. In *acute respiratory acidosis*, the serum bicarbonate concentration rises 1 meq L^{-1} for every 10 mmHg increase in $p\text{CO}_2$, whereas this ratio increases to 4 meq L^{-1} per 10 mmHg in *chronic respiratory acidosis*. This latter renal compensation is the result of neutralization of H^+ , initially by phosphate and subsequently by ammonium excretion [62, 73]. It is essential to recognize that the renal response is tightly regulated, in that the provision of medical bicarbonate results in the urinary excretion of the excess alkali with no change in the plasma HCO_3 or pH [62].

In *acute respiratory alkalosis*, bicarbonate concentration falls by 2 meq L^{-1} for every 10 mmHg decrease in the $p\text{CO}_2$, whereas this ratio becomes 5 meq L^{-1} per 10 mmHg in *chronic respiratory alkalosis* [9, 45]. This serum bicarbonate decline is achieved by decreased urinary bicarbonate reabsorption and ammonium excretion [31]. The compensatory responses outlined earlier are summarized in mnemonic form in Table 2.2.

Table 2.2 Mnemonic version of expected compensatory responses to acid–base disturbances

	For every	Expect
Metabolic acidosis	$1 \downarrow \text{HCO}_3$	$1 \downarrow p\text{CO}_2$
Metabolic alkalosis	$10 \uparrow \text{HCO}_3$	$7 \uparrow p\text{CO}_2$
Respiratory acidosis, acute	$10 \uparrow p\text{CO}_2$	$1 \uparrow \text{HCO}_3$
Respiratory acidosis chronic	$10 \uparrow p\text{CO}_2$	$4 \uparrow \text{HCO}_3$
Respiratory alkalosis, acute	$10 \downarrow p\text{CO}_2$	$2 \downarrow \text{HCO}_3$
Respiratory alkalosis, chronic	$10 \downarrow p\text{CO}_2$	$5 \downarrow \text{HCO}_3$

Assuming a normal ABG of pH 7.4, $p\text{CO}_2$ 40, HCO_3^- 24, and utilizing meq L^{-1} or mmol L^{-1} for bicarbonate and mmHg for $p\text{CO}_2$, the mnemonic is 1 for 1, 10 for 7, 1, 4, 2, 5

2.4.3 Mixed Acid–Base Disorders

In the ICU, it is not infrequent to encounter patients with two or more acid–base disorders. This type of complex presentation is easily recognized whenever the measured compensatory values of either bicarbonate or $p\text{CO}_2$ differ significantly from what would be expected [21, 54]. For example, in a patient with primary metabolic acidosis, a bicarbonate level of 14 meq L^{-1} should be adequately compensated by hyperventilation that decreases $p\text{CO}_2$ to 30 mmHg (for every 1 meq decline of bicarbonate, $p\text{CO}_2$ declines by 1 mmHg in compensation).

2.4.4 Guidelines for Interpretation

There are several methods utilized to assess the acid–base status; they include the following:

1. Measurement of base deficit (or excess)
2. Comprehensive interpretation of the pH, $p\text{CO}_2$, and bicarbonate utilizing the Henderson–Hasselbalch principles
3. The recently developed Stewart–Fencl approach
4. Normograms

The simple measurement of serum bicarbonate and base deficit is the least accurate of the mentioned methods, because it depends on the presence of conditions that rarely exist in severely ill patients in the ICU, namely normal electrolyte, water, and albumin levels. The Stewart–Fencl method is a comprehensive method that employs the concepts of strong ions and weak acids in calculating *strong-ion difference (SID)* when assessing acid–base status [26]. Accuracy of this method is superior to the base deficit method and equivalent to the simple interpretation of pH, $p\text{CO}_2$, and bicarbonate utilizing the Henderson–Hasselbalch method, provided the latter is augmented by calculation of the anion gap (AG) and adjustment for the serum albumin level [12]. Blood gas measurements can also be directly assessed utilizing a Davenport diagram or an acid–base normogram in which the acid–base status of the patient is identified by plotting pH, $p\text{CO}_2$, and HCO_3^- measurements. Generally, however, these methods do not take into account AG, delta/delta, or any adjustment based on albumin level, rendering them less accurate than the methods described earlier. For the purpose of providing an accurate, comprehensive, and widely utilized method of ABG interpretation, the Henderson–Hasselbalch method will therefore be discussed in more detail later.

The first step in interpreting acid–base measurements accurately is the assessment of pH. Normal pH ranges between 7.35 and 7.45. For simplicity, in ICU patients with abnormal $p\text{CO}_2$ or bicarbonate levels, an arterial pH of less than 7.4 is indicative of acidosis while a pH higher than 7.4 indicates alkalosis.

The second step is to evaluate the primary type of derangement, whether respiratory or metabolic. In acidosis, low bicarbonate indicates a primary metabolic acidosis, while an elevated $p\text{CO}_2$ corresponds to a primary respiratory acidosis. Likewise, in alkalosis, high bicarbonate indicates a primary metabolic alkalosis, whereas a low $p\text{CO}_2$ is consistent with a primary respiratory alkalosis.

Once the primary change is established, the third step is to assess the extent of compensation. Metabolic derangements are corrected quickly; hence, any significant deviation from the expected compensation is indicative of a mixed acid–base disorder regardless of chronicity. Primary metabolic acidosis with superimposed respiratory acidosis is a common presentation in patients with severe status asthmaticus and respiratory failure. The goal of this third step is twofold: to identify mixed acid–base disorders, and to define the acuity of the disorder in the case of respiratory derangements.

If metabolic acidosis is noted, three additional steps are usually executed prior to determining whether the patient has a simple or a mixed acid–base derangement. A fourth step identifies the type of metabolic acidosis present, i.e., whether it is secondary to an anion that creates an AG on electrolyte measurement or not. The AG is a diagnostic tool to uncover the actual anions elevated in the blood but not routinely included in our measurements under normal conditions. It is calculated as follows:

$\text{AG} = \text{serum sodium} - \text{serum chloride} - \text{serum bicarbonate}.$

A normal anion gap is $<12 \text{ mmol L}^{-1}$.

The fifth step in interpreting metabolic acidosis is adjusting for factors that would falsely lower the anion gap if one existed, e.g., hypoalbuminemia and lithium or bromide ingestion [22]:

$\text{Adjusted AG in hypoalbuminemia} = \text{observed AG} + [2.5(\text{normal albumin} - \text{observed albumin})].$

The sixth step is the comparison of the degree of change in AG with the change in serum bicarbonate, aiming to assess the extent of contribution of the AG-producing process to the actual acidosis. This measurement is called delta/delta:

$\text{delta/delta} = \Delta\text{AG} / \Delta\text{HCO}_3^- = (\text{AG} - 12) / (24 - \text{HCO}_3^-).$

Obviously, clinical correlation is very important throughout this process. For example, a blood gas measurement indicating an acute primary respiratory acidosis mixed with metabolic alkalosis out of proportion to the expected compensation could be seen in severe asthma with vomiting caused by theophylline toxicity, or it could reflect acute respiratory failure superimposed on chronic respiratory insufficiency in a patient with advanced cystic fibrosis and chronic CO_2 retention (also see Tables 2.3 and 2.4).

2.5 Causes of Acidosis

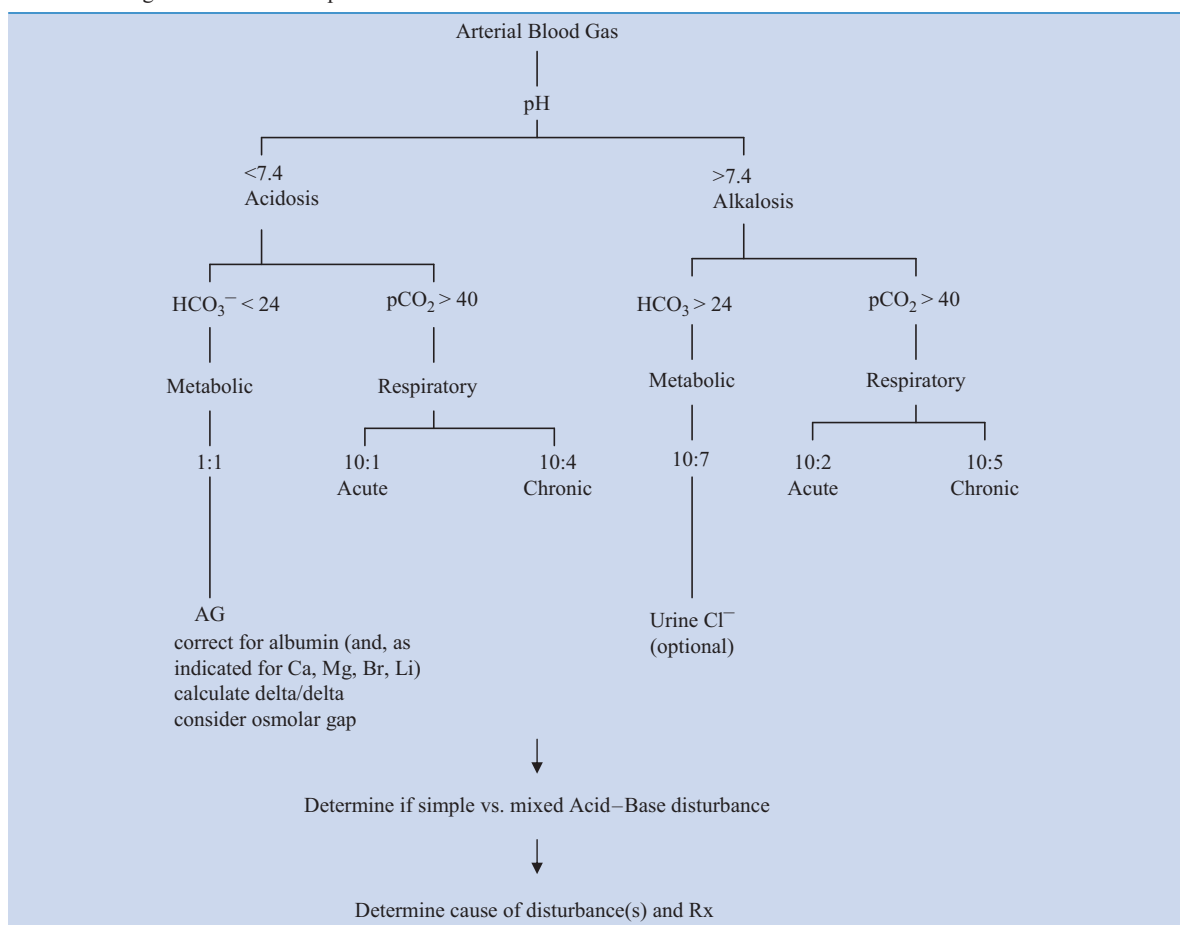
Acidosis is the predominant acid–base derangement encountered in critically ill pediatric ICU patients [37].

2.5.1 Respiratory Acidosis

Respiratory acidosis is caused by elevated $p\text{CO}_2$, whether acutely or over time [4]. This could be secondary to hypoventilation, airway obstruction, severe impairment of diffusion (e.g., pulmonary fibrosis), ventilation–perfusion mismatch (as observed in pneumonia, pulmonary edema, or ARDS), or excessive production of CO_2 to an extent that overwhelms even increased respiratory elimination. Common disorders causing hypoventilation in children are congenital central hypoventilation, drugs and toxins, for example, narcotic overdose, or severe restriction caused by either neuromuscular disorders or splinting secondary to rib fractures, e.g., in flail chest [10, 17]. The most common causes of airway obstruction in children include croup, foreign body aspiration, asthma, and bronchiolitis. In the ICU, ARDS is a frequent cause of respiratory failure secondary to ventilation–perfusion inequality

Table 2.3 Steps in interpreting blood gas measurements

Define whether the primary process is acidosis vs. alkalosis (pH)
Identify the source of the primary acid–base derangement (metabolic vs. respiratory)
Assess extent of compensation (acute vs. chronic respiratory disorders)
In metabolic acidosis: calculate anion gap
In metabolic acidosis: adjust for hypoalbuminemia
In anion gap metabolic acidosis: calculate delta/delta
Identify mixed acid–base disorders
Investigate possible underlying causes

Table 2.4 Algorithm for the interpretation of ABGs

leading to CO_2 retention. Disorders of increased CO_2 production are uncommon but can impart an ominous prognosis if not detected timely, for example, in malignant hyperthermia. CO_2 production can also be elevated by increased carbohydrate intake, especially in parenteral nutrition.

Chemical buffering mechanisms are promptly elicited with elevated pCO_2 , resulting in an acute rise in serum bicarbonate [2, 17, 50]. This process becomes further bolstered by the renal alkalization process [13, 20, 51]. The rise in pCO_2 corresponds to a decline in pO_2 as determined by the alveolar gas equation. In severe respiratory acidosis, hypoxemia becomes the principal determinant of mortality, and treating it with prompt and adequate provision of oxygen is critical for patients' survival. Diagnosing the underlying cause of the respiratory acidosis is usually the key in reversing the acidosis in these patients.

Treatment: Depending on the severity of acidosis, endotracheal intubation, mechanical ventilation (whether noninvasive through a mask or invasive through an endotracheal tube or tracheostomy cannula), or in very severe cases, extracorporeal membrane CO_2 removal with or without oxygenation (ECOR vs ECMO, respectively) might be needed [3, 10, 17].

In patients with chronic pCO_2 retention, acute decompensation from infection, cardiopulmonary edema, narcotics, or excessive oxygen therapy can all result in exacerbations, given these patients' limited reserve. Antibiotics, bronchodilator therapy, diuretics, and removal of secretions are important interventions to implement timely. Naloxone therapy should be considered in suspected narcotic overdose (titrating $1\text{--}5\ \mu\text{g}\ \text{kg}^{-1}\ \text{dose}^{-1}$ until recovery of adequate respiratory effort). Treatment of a superimposed metabolic alkalosis with carbonic anhydrase inhibitors can also be helpful in restoring ventilatory drive.

Conservative institution of mechanical ventilatory assistance in chronic respiratory failure is driven by the concern about the difficulty in weaning affected patients off the ventilator.

Increasing minute ventilation by increasing the respiratory rate is the mainstay in ventilatory treatment of severe respiratory acidosis secondary to parenchymal lung disease. In obstructive pulmonary disease, decreasing the respiratory rate will likely allow for adequate exhalation of CO_2 and is usually implemented in patients with status asthmaticus or severe bronchiolitis. The current standard of care utilizes *lung protective strategy* in mechanical ventilation in which the tidal volume is limited to $\sim 5\text{--}7\text{ mL kg}^{-1}$ ideal body weight while maintaining a plateau pressure below $35\text{ cm of H}_2\text{O}$ in order to avert large swings in alveolar volume that in turn results in increased microvascular permeability and ventilator-induced lung injury [25, 78]. Such a lung-protective strategy was found to impart better survival rates on patients mechanically ventilated for parenchymal lung disease. Additionally, current practice employs *permissive hypercapnia* in which there is no therapeutic pCO_2 target level but, rather, a pH goal that should be maintained above 7.25 in order to ensure adequate myocardial and cellular function. The combination of low tidal volume ventilation with permissive hypercapnia results in patient discomfort and necessitates judicious use of sedation and, at times, neuromuscular paralysis. It is prudent to provide patients with an adequate respiratory rate to achieve the intended gas exchange, especially if paralyzed or oversedated. As CO_2 decreases, excess bicarbonate is excreted by the kidneys (assuming the serum chloride level has normalized, as patients with respiratory acidosis are usually hypochloremic) [3, 10].

Of note, alkali therapy has a very limited role in the treatment of respiratory acidosis. Mixed metabolic and respiratory acidosis or severe respiratory acidosis are potential indications of alkali therapy. Alkali therapy can be of special benefit in patients with severe bronchospasm by directly resulting in smooth muscle relaxation and by indirectly restoring their responsiveness to beta-adrenergic agonists [3, 10]. Moreover, alkali use to raise pH is especially beneficial in patients with severe component of pulmonary hypertension resulting in pulmonary smooth muscle relaxation. In general, however, alkali therapy can also result in pH-mediated ventilatory failure, in a further increase in pCO_2 from bicarbonate decomposition, and in volume expansion from sodium provision.

2.5.2 Metabolic Acidosis

Causes of metabolic acidosis are categorized into two groups: AG acidoses and non-AG acidoses.

2.5.2.1 AG Acidoses

Causes of AG acidosis can be summarized by the acronym KUSMALE: ketones, uremia, salicylates, methanol, alcohols, lactate, and ethylene glycol. Lactic acid and the ketoacids are organic acids generated from incomplete metabolism of carbohydrate or fat. When accumulating in large quantities, they result in severe acidosis that can be life-threatening. Under normal conditions and when these organic acids are only mildly elevated, the kidneys increase the excretion rate of these organic acids and restore homeostasis. As the amount of organic acids increases and exceeds the renal excretion capacity, lactic acidosis or ketoacidosis develops.

1. Diabetic Ketoacidosis

Diabetic ketoacidosis is not uncommon in pediatric patients. It occurs in patients with insulin-dependent diabetes mellitus and is the result of severe insulin deficiency in the setting of increased metabolic demand, as would occur in the setting of a concurrent infection. As a result of insulin deficiency and depletion of glycogen stores, lipolysis ensues with increased production of ketoacids. Insulin is integral to the metabolism of ketoacids, and its relative or complete deficiency in the setting of increased ketoacid production results in severe keto-, i.e., AG acidosis.

Treatment: Intravenous insulin is the most important therapy for patients with diabetic ketoacidosis [47]. Fluid, potassium, and phosphorous should be judiciously replaced. Insulin therapy induces the metabolism of ketones and results in the generation of alkali, hence obviating the need for sodium bicarbonate administration [43]. Indeed, sodium bicarbonate treatment that can delay the metabolic recovery by stimulating ketogenesis [56, 58] was found to be of no benefit for patients with severe DKA (as defined by a pH of 6.9–7.14), and was associated with an increased risk of cerebral edema in children [32, 56]. Therefore, sodium bicarbonate therapy is currently reserved for severe acidemia (pH < 6.9 in our practice) in order to avoid myocardial and cellular functional impairment at such an extremely low pH.

2. Uremia

While mild chronic renal failure can be associated with a non-AG, i.e., renal tubular acidosis (RTA) (see later), more advanced renal failure also results in an

AG metabolic acidosis secondary to the accumulation of sulfates and other ions. Dialysis is the cornerstone intervention in treating this type of acidosis.

3. Salicylate

Aspirin intoxication is becoming uncommon since aspirin use has been discouraged in febrile children because of concerns about Reye syndrome. Nonetheless, it continues to occur, and prompt recognition is a key in recovering these patients. The anions in salicylate intoxication include salicylate as well as lactic acid and ketoacids [28]. These organic acids are likely to be excessively produced as a result of respiratory alkalosis, as it has been shown that salicylate-induced acidosis can be ameliorated by controlling hypocapnia in animals [28].

Therefore, aspirin toxicity typically results in mixed respiratory alkalosis and metabolic acidosis. Initially, central hyperventilation results in early respiratory alkalosis. As time progresses and as lactic acid and ketoacids accumulate, metabolic acidosis ensues. Prognosis in aspirin toxicity is highly dependent on aspirin concentration; hence, limiting further drug absorption is a key in treating these patients. Activated charcoal and blood and urinary alkalinization are two common practices that aid in eliminating aspirin from the CNS and the blood, respectively [35]. Sodium bicarbonate can be administered in order to reach a pH of 7.45–7.50 [16]. In severe cases, and when the presentation is complicated by renal insufficiency, hemodialysis is used [30]. Finally, hydration typically aids in aspirin excretion and lactate and ketone clearance.

4. Methanol, Alcohols, and Ethylene Glycol

Alcohol toxicity, with either methanol, ethanol, or ethylene glycol, can result in profound AG acidosis secondary to the accumulation of ketoacids and lactic acid [19, 27]. Ketoacidosis is very common in alcohol intoxication. It generally ensues after large ingestions, especially if combined with limited food intake or protracted vomiting. Hepatic ketogenesis can be enhanced by superimposed alkalosis induced by vomiting, dehydration (contraction alkalosis), or hyperventilation [19].

Treatment: Discontinuing alcohol intake and provision of hydration and dextrose typically result in prompt recovery unless the acidosis is very severe enough to cause complications, especially myocardial depression [76]. Dextrose stimulates insulin secretion, thereby promoting the generation of bicarbonate from ketoacid metabolism. Hydration, on the other hand, will correct fluid deficits and lactic acidosis.

Additional therapeutic measures include gastric lavage, oral charcoal, as well as, in the case of ethylene

glycol toxicity, intravenous or oral ethanol (which occupies alcohol dehydrogenase, rendering it unavailable for further metabolite production from the ingested ethylene glycol) and, when very severe, hemodialysis [30].

5. Lactate

Lactic acidosis is commonly encountered in the pediatric ICU. It is caused by either increased lactate production or decreased hepatic metabolism. Tissue hypoxia secondary to hypotension with or without sepsis is the main cause. In sepsis, similar to other causes of circulatory failure, severe lactic acidosis, sets of a vicious cycle of further circulatory failure, worsening tissue perfusion, more lactate production, and decreased consumption by the liver and kidneys [36, 49, 53]. Either lactate itself or the ensuing acidosis can result in myocardial depression and hypotension [46, 77]. In patients with severe status asthmaticus, lactic acidosis occurs secondary to increased work of breathing with elevated skeletal muscular oxygen demand.

Treatment: Management of lactic acidosis should center on reestablishing tissue perfusion while identifying and reversing the underlying disease [18, 36, 49, 53]. Restoring intravascular volume and effective circulation is the cornerstone in treating patients with lactic acidosis, and reversing the underlying cause promptly can be lifesaving. Specifically, management includes the provision of antibiotics in sepsis, operative repair of tissue ischemia or intestinal perforation, insulin for patients with diabetic ketoacidosis, and dextrose infusion (and possibly dialysis) in alcohol toxicity and congenital lactic acidosis [49, 52, 53].

Alkali therapy is not considered a standard intervention in lactic acidosis and carries a real risk of increased lactate production [18, 71, 72]. Nevertheless, it is our practice to utilize sodium bicarbonate in lactic acidosis when blood pH falls below 7.1, predominantly for concerns about hemodynamic compromise.

6. Other

Sniffing hydrocarbon (toluene in glue) is increasingly recognized as a cause of rapidly developing, profound AG acidosis secondary to the production of benzoic acid and hippuric acid during toluene metabolism. With normal renal function, this acidosis is typically transformed to a non-AG acidosis following the rapid renal excretion of hippurate anion [15].

2.5.2.2 Non-AG Acidoses

Non-AG acidosis, also described as *hyperchloremic metabolic acidosis* results from a decrease in serum

bicarbonate secondary to its either absolute or relative extracellular depletion (Table 2.5).

1. Decline in extracellular bicarbonate content (bicarbonate loss)

Whereas hydrochloric acid is the major chemical lost in vomiting (resulting in metabolic alkalosis), bicarbonate is the main chemical lost from the digestive tract distal to the stomach, whether secondary to diarrhea or any form to enterocutaneous or uroenteric fistula. If profuse diarrhea results in dehydration serious enough to decrease tissue perfusion, a picture of mixed metabolic acidosis ensues with non-AG acidosis (secondary to the bicarbonate loss) as well as an AG acidosis (secondary to lactic acidosis, acute renal failure, or hyperproteinemia) [6, 44].

Treatment: Even though the kidneys are capable of generating bicarbonate through ammonium production, severe losses require timely provision of exogenous bicarbonate to correct acid–base status. Restoring hydration and electrolyte homeostasis is also an essential part of treatment.

2. Saline

Aggressive resuscitation and generous intraoperative hydration are the two most common causes of saline-induced, dilutional acidosis.

Treatment: Provision of sodium bicarbonate in cases of severe acidosis corrects the derangement promptly.

3. Early renal insufficiency and RTA

Patients with RTA can maintain a stable acid–base status by decreasing production of endogenous fixed acids [41], but more severe renal insufficiency or RTA can lead to profound hypobicarbonatemia.

Treatment: Severe cases necessitate treatment with sodium bicarbonate (e.g., RTA type I) [69]. Mixed acidosis can occur in these patients as a result of hypokalemia-induced muscle weakness and consequent

hypoventilation-related respiratory acidosis; hence, correcting electrolyte levels is especially important in these patients.

4. Other

Carbonic anhydrase inhibitors (e.g., acetazolamide and topiramate) are known to cause a non-AG acidosis that is typically mild and does not require aggressive intervention. Total parenteral nutrition and excessive arginine supplementation are additional causes of non-AG acidosis.

2.6 Causes of Alkalosis

2.6.1 Respiratory Alkalosis

Respiratory alkalosis is caused by increased elimination of CO₂ or decreased production [5]. The latter can occur in moderate to severe hypothermic states. Increased CO₂ elimination, on the other hand, can occur under any of the circumstances listed in Table 2.6.

2.6.2 Metabolic Alkalosis

There are very few conditions that can lead to metabolic alkalosis, and a careful assessment of the clinical presentation is typically most helpful in their recognition. Additionally, the urinary chloride level is a useful discriminating marker, with a low level suggesting either vomiting, diuretic therapy, or a posthypercapnic state as likely underlying causes and a high urinary chloride level pointing toward steroid excess.

Table 2.5 Causes of non-AG acidosis

Ureterosigmoidostomy/fistulae
Saline
Early renal insufficiency
Diarrhea
Carbonic anhydrase inhibitors
Amino acids
Renal tubular acidosis
Supplements

Mnemonic: USED CARS

Table 2.6 Clinical scenarios predisposing to respiratory alkalosis

Primary pulmonary disease
Early asthma
Pneumonia
Central nervous system disease
Pain
Infection
Tumors
Metabolic acidosis
Psychogenic hyperventilation
Iatrogenic causes
Excessive mechanical ventilatory rate or tidal volume (high minute ventilation)
Swift CO ₂ removal through an extracorporeal circuit

2.7 Complications of Severe Acidemia

While the prognosis of acidosis as a process is largely driven by its underlying cause as long as blood pH is maintained within the normal range through adequate compensation, acidemia (defined as $\text{pH} < 7.2$), on the other hand, has a set of detrimental effects warranting corrective intervention (also see Table 2.7). Acid–base homeostasis affects cellular and tissue performance through its influence on protein structure and function: Hydrogen ions, for example, are highly reactive when they interact with proteins [29, 66]. Upon either net gain or loss of H^+ , proteins accordingly undergo major changes in their charge distribution, structural configuration, and, ultimately, their function.

Even though metabolic acidemia is generally more deleterious than respiratory acidemia, either type of acidosis will result in severe tissue injury if the pH continues to decline. Cardiovascular consequences of acidemia are the most significant complications in critically ill patients and include dysrhythmias and catecholamine-refractory shock, causing systemic hypoperfusion and ultimately multiorgan-system failure [42, 49, 59, 60]. Of note, hyperkalemia resulting

from acidosis-induced potassium shifts out of cells is most prominent in nonorganic acidoses and carries the risk of fatal dysrhythmia [1, 7].

Acidemia is characteristically associated with a significant mismatch between the increased metabolic demands caused by the concomitant sympathetic surge and the decreased tissue uptake and anaerobic utilization of glucose induced by insulin resistance [8, 38]. Patients, consequently, enter a hypercatabolic state with significant protein breakdown [23, 55, 63]. Additionally, hepatic lactate uptake is impaired, resulting in lactic acidosis that further aggravates acidemia [49]. These metabolic complications are proportionate to the severity of acidosis and are further compounded by hypoxemia.

2.8 Complications of Severe Alkalemia

Alkalemia is defined as a blood pH above 7.60 and is seldom encountered in the ICU (also see Table 2.7). However, in its most severe forms, respiratory alkalemia can impair cerebral and coronary perfusion and result in fatal infarctions [17, 67]. This is partly the result of the decline of CO_2 , a potent cerebral and coronary vasodilator.

Table 2.7 Consequences of acid–base disturbance by organ system

Organ	Acidosis	Alkalosis
Cardiac	Impaired myocardial contractility with decreased cardiac output and hypotension Reentrant dysrhythmias and ventricular fibrillation Catecholamine insensitivity	Reduction in ischemia threshold Refractory dysrhythmias
Peripheral vasculature	Arteriolar dilation Venoconstriction Centralization of blood volume Increased pulmonary vascular resistance (PVR)	Arteriolar constriction Reduction in coronary blood flow Reduction in PVR
Respiratory	Hyperventilation Skeletal muscle weakness Shift of the oxygen–hemoglobin dissociation curve to the right (resulting in desaturation)	Hypoventilation Impaired hypoxic pulmonary vasoconstriction and worsened ventilation–perfusion mismatch Increased hemoglobin affinity for oxygen
Metabolic	Increased metabolic demands Insulin resistance Hyperkalemia Increased protein degradation	Stimulation of organic acid production Decreased plasma electrolyte levels: hypokalemia, hypocalcemia (ionized), hypomagnesemia, and hypophosphatemia)
Central nervous system	Altered mental status and depressed level of consciousness	Reduction in cerebral blood flow if respiratory in origin Reduced seizure threshold Altered mental status and depressed level of consciousness

Hypokalemia is another characteristic complication of alkalemic disorders, more prominently those of metabolic origin. Shift into the cells at least partly account for the decline in extracellular potassium. The remainder of potassium deficit is attributable to renal and extrarenal losses [17, 67]. Hypokalemia can result in weakness, dysrhythmias, polyuria, and increased ammonia production. Other electrolyte abnormalities occurring during alkalemia can also result in severe complications commensurate to the severity of the particular electrolyte derangement: hypocalcemia and hypomagnesemia can lead to tetany, seizures, and altered mental status. As mentioned previously in this chapter, alkalemia stimulates the generation of lactic acid and ketoacids through the induction of anaerobic glycolysis. Additionally, acute alkalemia shifts the oxygen–hemoglobin dissociation curve to the left, resulting in increased oxygen affinity of hemoglobin and consequent relative tissue hypoxia. This effect is eventually ameliorated in persistent alkalemic states by the induction of 2,3-diphosphoglyceric acid production in red cells.

- › Alkalosis, on the other hand, is less encountered in the ICU. Fluid status and gastric fluid depletion are the common underlying causes of metabolic alkaloses. Whereas rapid respiration secondary to lung diseases, excessive mechanical ventilation, pain or central nervous system process are the common causes of respiratory alkaloses.
- › When caring for critically ill patients, identifying derangements are followed by timely stabilization of the patient irrespective of the underlying cause of the derangement. Depending on the severity of the derangement and the patient's response to the stabilizing interventions, the underlying cause might need to be aggressively sought and emergently reversed.
- › Identifying the underlying cause(s) of the acid-base disorder at hand is the final step in the management of these patients and plays an important in preventing further derangement, worsening of the derangement and defining the patient's overall prognosis.

2.9 Summary

Acid–base derangements are encountered in almost every critically ill patient. A stepwise approach of recognizing the derangements, accurately defining their type and severity, actively intervening to restore cardiopulmonary and hemodynamic stability, and, whenever possible, reversing the underlying cause can be lifesaving.

Take-Home Pearls

- › Any pediatric disease when severe can result in an acid–base disturbance, directly, as a result of therapy or both.
- › Acid–base disorders should be anticipated in all critically ill patients and proactively monitored. This will allow the early recognition of derangements and the prevention of what could become a life-threatening state.
- › Acidosis is the most common acid–base derangement in the ICU with metabolic acidosis signaling a more severe course and worse outcome.
- › A pH of < 7.2 merely indicates a primary acidosis-inducing disorder. Further assessment of the type of acidosis and the presence of a mixed acid–base disorders requires measurement of PCO_2 , serum bicarbonate, albumin and calculation of the anion gap.
- › The most commonly encountered causes of metabolic acidoses in the ICU are renal insufficiency, sepsis and DKA, while ARDS and severe status asthmaticus are the usual suspects in respiratory acidoses.

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