

Acid Base Balance in Critical Care Medicine

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Learning Objectives: after reading this issue, the participant should be able to:

1. *To describe acid base chemistry in terms of the physical chemistry of water.*
2. *Compare and contrast different approaches to acid base data interpretation*
3. *Use the physical-chemical approach to interpret most acid base abnormalities encountered in the ICU.*

For the past 100 years acid base chemistry has occupied a special corner of clinical medicine. Physicians generally agree that acid base balance is important, but struggle to understand the science, pathology and application. Undoubtedly, the body carefully controls the relative concentrations of hydrogen and hydroxyl ions in the extracellular and intracellular spaces. Alterations in this “balance” disrupts transcellular ion pumps leading to significant cardiovascular problems. Most acid-base abnormalities are easily explained, but some remain problematic. Moreover, traditional teaching emphasizes data interpretation rather than pathophysiology¹. Consequently much confusion exists regarding cause, effect and treatment of acid base abnormalities.

The “modern” physical-chemical approach, introduced by Peter Stewart² and subsequently refined³⁻⁶ has significantly enhanced our understanding of these problems, and simplified the clinical application^{4;7}.

Physical Chemistry of Water

The human body is composed principally of water. Water is a simple triatomic molecule with an unequal charge distribution resulting in a H-O-H bond angle of 105°. This leads to polarity, aggregation, a high surface tension, low vapor pressure, high specific heat capacity, high heat of vaporization and a high boiling point.

Water is a highly ionizing. Water is itself slightly ionized into a negatively charged hydroxylated (OH⁻) ion and a positively charged protonated (H_nO⁺) ion ⁸.

Conventionally, this self-ionization of water is written as follows:



The symbol H⁺ is convenient but metaphorical. While protons dissociating from water have many aliases (such as H₃O⁺, H₅O₂⁺ and H₉O₄⁺), most physicians and chemists refer to them as hydrogen ions. Water dissociation is constant (K_w), and is governed by changes in temperature, dissolved electrolytes and cellular components:

$$K_w = [\text{H}^+][\text{OH}^-].$$

In other words, if [H⁺] increases, then [OH⁻] decreases by the same magnitude.

The self ionization of water is miniscule. In pure water at 25°C, the [H⁺] and [OH⁻] are 1.0 x 10⁻⁷ mEq/L ⁹. Using the Sorenson negative logarithmic pH scale, this is a pH of 7.0. Water becomes alkaline with falling temperature (at 0°C, pH is 7.5) and acidic with increasing temperature (at 100°C, pH is 6.1). Physiologic pH, that at which the body resides, differs between the intracellular (pH 6.9) compartment (pH 7.4) and between venous (pH 7.5) and arterial (pH 7.4) blood. Conventionally, acid-base balance refers to changes in hydrogen ion concentration in arterial blood, which reflects extracellular fluid (ECF), from 7.4. This is reasonable as cells are relatively impervious to ionic materials,

and changes in fluids, electrolytes and carbon dioxide tension easily alter the ECF. Thus acidosis (an increase in hydrogen ion concentration) occurs when the pH is less than 7.3, and alkalosis (a decrease in hydrogen ion concentration) occurs when pH is greater than 7.5. An acid is a substance that increases hydrogen ion concentration when added to a solution. A base is a substance that decreases hydrogen ion (and increases hydroxyl ion) concentration when added to a solution ^{4;10}. All hydrogen and hydroxyl ions are derived from water dissociation ¹¹.

The extracellular fluid is an ionic soup containing uncharged cells and particles, dissolved gases (oxygen and carbon dioxide), and fully- and partially- dissociated ions. Many of these factors influence water dissociation depending on chemical charge, quantity and degree of dissociation, ⁹. In addition, ionized particles, particularly sodium and chloride, exert a significant osmotic effect. The particles dissolved in the ECF obey three distinct laws ⁷:

1. electrical neutrality – the net positive charge must equal the net negative charge.
2. Mass conservation – the total quantity of a substance in the extracellular space is constant unless added, removed, generated or destroyed.
3. Dissociation equilibria for all incompletely dissociated substances (albumin, phosphate and carbonate) must be obeyed. Thus, to determine the acid-base status of a fluid, it is essential to account for all substances governed by these rules.

Strong Ions

Strong ions are completely dissociated at physiologic pH. The most abundant strong ions in the extracellular space are Sodium (Na^+) and Chloride (Cl^-). Other important strong ions include K^+ , SO_4^{2-} , Mg^{2+} and Ca^{2+} . Each applies a direct electrochemical and osmotic effect.

The charge difference between strong cations and strong anions is calculated by:

$$\text{SID} = ([\text{Na}^+] + [\text{K}^+] + [\text{Ca}^{2+}] + [\text{Mg}^{2+}]) - ([\text{Cl}^-] + [\text{Other strong anions: A}^-]) = 40\text{-}44\text{mEq}$$

This excess positive charge, called the Strong Ion Difference (SID) by Peter Stewart², is always positive and is balanced by an equal amount of “buffer base”, principally phosphate, albumin and bicarbonate¹². SID independently influences water dissociation via electrical neutrality [i.e., $([\text{all} + \text{charged particles}]) - ([\text{all} - \text{charged particles}]) = 0$] and mass conservation [i.e., if all other factors such as PCO_2 , albumin and phosphate are kept constant]. Thus, an increase in SID will decrease hydrogen ion liberation from water (and increase hydroxyl ion liberation) and cause alkalosis. A decrease in SID increases hydrogen ion liberation causing acidosis.

Weak Acids

Albumin and phosphate are weak acids. Their degree of dissociation is related to temperature and pH. The independent effect of weak acids, symbolized as A_{TOT} , on acid base balance, depends on absolute quantity and dissociation equilibria^{2,13}. Failure to account for A_{TOT} limits the applicability of previous approaches to acid base balance to critically ill patients^{14,15}. Hypoalbuminemia results from hepatic reprioritization, administration of intravenous fluids and capillary leak¹⁵. Hypophosphatemia is associated with malnutrition, refeeding, diuresis and hemodilution. Hyperphosphatemia

occurs in renal failure. A reduction in serum albumin or phosphate leads to metabolic alkalosis⁵. Hyperphosphatemia leads to metabolic acidosis.

Carbon Dioxide

The major source of acid in the body is carbon dioxide, created as by-product of aerobic metabolism. The reaction of carbon dioxide with water produces 12,500mEq of H⁺ a day, most ultimately excreted by the lungs. Thus, [carbon dioxide]_{ECF} is determined by tissue production and alveolar ventilation. By contrast, only 20 – 70mEq of hydrogen ion promoting anions/day are eliminated by the kidney.

Dissolved carbon dioxide exists in four forms: carbon dioxide [denoted CO₂(d)], carbonic acid (H₂CO₃), bicarbonate ions (HCO₃⁻) and carbonate ions CO₃²⁻.

Prior to elimination, volatile acid is buffered principally by hemoglobin (Hb). DeoxyHb is a strong base, and there would be a huge rise in the pH of venous blood if Hb did not bind hydrogen ions produced by oxidative metabolism. Venous blood contains 1.68mmol/L extra CO₂ over arterial blood: 65% as HCO₃⁻ and H⁺ bound to hemoglobin, 27% as carbaminohemoglobin (CO₂ bound to hemoglobin) and 8% dissolved.

Carbon dioxide easily passes thru cell membranes. Within the erythrocyte CO₂ combines with H₂O, under the influence of carbonic anhydrase, to form H₂CO₃, which ionizes to hydrogen and bicarbonate. Hydrogen ions bind to histidine residues on deoxyHb while bicarbonate is actively pumped out of the cell. Chloride moves inwards to maintain electroneutrality (the chloride shift). Large increases in pCO₂ (respiratory acidosis) overwhelm this system, leading to a rapid, dramatic, drop in pH.

Chronic respiratory acidosis is associated with increase in total body CO₂ content, reflected principally by an increase in serum bicarbonate. Mathematically $\Delta\text{HCO}_3^- = 0.5$

$\Delta PaCO_2$. It is important that this not be confused with “metabolic compensation for hypercarbia” a slower process that reduces SID by increase urinary chloride excretion³.

What determines pH?

Using a physiochemical approach, it is possible to determine the effect of carbon dioxide, completely dissociated ions and partially dissociated ions on water dissociation, and hence hydrogen ion concentration. Six simultaneous equations can be constructed and solved for $[H^+]^{2,4}$:

(1) Water dissociation equilibrium: $[H^+] \times [OH^-] = K_w$

(2) Weak acid dissociation equilibrium: $[H^+] \times [A^-] = K_A \times [HA]$

(3) Conservation of mass for weak acids: $[HA] + [A^-] = [A_{TOT}]$

(4) Bicarbonate ion formation equilibrium: $[H^+] \times [HCO_3^-] = K_C \times PCO_2$

(5) Carbonate ion formation equilibrium: $[H^+] \times [CO_3^{2-}] = K_3 \times [HCO_3^-]$

(6) Electrical neutrality: $[SID] + [H^+] - [HCO_3^-] - [A^-] - [CO_3^{2-}] - [OH^-] = 0$

Interestingly, there are six independent simultaneous equations, and just six unknown, dependent variables determined by them: $[HA]$, $[A^-]$, $[HCO_3^-]$, $[CO_3^{2-}]$, $[OH^-]$ & $[H^+]$.

There are three known independent variables: $[SID]$, $[A_{TOT}]$ & PCO_2

Although the above equations look relatively simple, fourth order polynomials are required for resolution.

Solving the equations for $[H^+]$:

$$[SID] + [H^+] - K_C \times P_C / [H^+] - K_A \times [A_{TOT}] / (K_A + [H^+]) - K_3 \times K_C P_C / [H^+]^2 - K_w / [H^+] = 0$$

In other words, $[H^+]$ is a function of SID, A_{TOT} , PCO_2 and a number of constants. All other variables, most notably $[H^+]$, $[OH^-]$ and $[HCO_3^-]$ are dependent, and thus cannot

independently influence acid base balance. As a result, it is possible to reduce all acid base abnormalities into a problem related to one or more of these three variables.

Regulation of acid-base balance

Carbon dioxide tension is controlled principally by chemoreceptors in the medulla, carotid body and aortic arch. An increase in the PCO_2 or in the acidity of CSF stimulates central alveolar ventilation. When respiratory failure occurs, the principal CO_2 buffering system, Hb, becomes overwhelmed. This rapidly leads to acidosis. In response, the kidney excretes an increased chloride load, using NH_4^+ , a weak cation, for electrochemical balance³. Thus ECF osmolality is maintained. "Metabolic" acid is buffered principally by increased alveolar ventilation ("compensatory" respiratory alkalosis) and extracellular weak acids. These include plasma proteins, phosphate and bicarbonate. The bicarbonate buffering system (92% of plasma buffering, and 13% overall) probably is the most important extracellular buffer. The pKa of bicarbonate is relatively low (6.1) but the system derives its importance from the enormous quantity of carbon dioxide in the body. The coupling of bicarbonate and H_2O produces carbon dioxide to be excreted thru the lungs. This increases alveolar ventilation.

In metabolic acidosis, chloride is preferentially excreted by the kidney. Indeed this is the resting state of renal physiology, as sodium and chloride are absorbed in the diet in relatively equal quantities¹⁶. In metabolic alkalosis, chloride is retained, and sodium and potassium excreted.

Abnormalities in the renal handling of chloride may be responsible for several inherited acid base disturbances. In renal tubular acidosis, there is inability to excrete Cl^- in proportion to Na^+ ¹⁷. Similarly, pseudohypoaldosteronism appears to result from high

chloride reabsorption¹⁸. Bartter's syndrome is caused by a mutation in the gene encoding the chloride channel – CLCNKB - that regulates the Na-K-2Cl cotransporter (NKCC2)¹⁹. Clearly, the role of chloride in fluid volume, electrolyte and acid base regulation has been underestimated.

Analytic Tools Used In Acid-Base Chemistry

Acid-base balance abnormalities provide valuable information about changes in respiratory function, electrolyte chemistry and underlying diseases. Although blood gas analysis is widely used, it provides incomplete information about acid base chemistry. Abnormalities of pH, base-deficit-excess (BDE) or bicarbonate concentration are designed to reflect effect but not cause. Measurement of each of the strong and weak ions that influence water dissociation, while cumbersome, is essential.

In this section we will consider some of the tools that have been used to assist interpretation of acid-base conundrums. None are entirely accurate, and each has a dedicated group of followers²⁰. Clinicians often confuse mechanisms of interpretation with the underlying causes of acid base abnormalities. For example, decreased $[\text{HCO}_3^-]$ during metabolic acidosis reflects hyperventilation and the activity of the carbonate system as an extracellular buffer. The acidosis is not caused by depletion or dilution of bicarbonate but rather by decreased SID (usually by unmeasured anions (UMA)) or increased A_{TOT} . We will examine each and discuss individual merits and demerits.

The CO₂-Bicarbonate (Boston) approach

Schwartz, Brackett and colleagues at Tufts University in Boston developed an approach to acid-base chemistry using acid base maps and the mathematical relationship between carbon dioxide tension and serum bicarbonate (or total CO₂), derived from the

Henderson-Hasselbalch equation to predict the nature of acid-base disturbances ²¹. A number of patients with known but compensated acid-base disturbances were evaluated. The degree of compensation from “normal” was measured for each disease state. The investigators used linear equations or maps to describe six primary states of acid-base imbalance. These related hydrogen ion concentration to PCO_2 for respiratory disturbances and PCO_2 to HCO_3^- concentration for metabolic disturbances. For any given acid-base disturbance, an expected HCO_3^- concentration was determined. The major drawback of this approach is that it treats HCO_3^- and CO_2 as independent rather than interdependent variables

The most valuable application of this approach is in the use of total CO_2 on serum chemistry to determine resting PaCO_2 in patients with chronic respiratory failure. In simple acid-base disturbances, where the magnitude of increased unmeasured anions parallels the drop in bicarbonate, this approach is effective. However, it should be used with caution in critically ill patients, who may be subject to multiple simultaneous acidifying and alkalinizing processes.

The Base Deficit/Excess (Copenhagen) approach

In 1948, Singer and Hastings pioneered an alternative approach to acid base chemistry by moving away from Henderson-Hasselbalch and quantifying the metabolic component ¹². They proposed that the whole blood buffer base (BB) could be used for this purpose. The BB is the sum of $[\text{HCO}_3^-]$ and of [non volatile buffer ions] (essentially serum albumin, phosphate and hemoglobin). Applying the law of electrical neutrality, the buffer base was forced to equal the electrical charge difference between strong (fully dissociated) ions. Thus, normally $\text{BB} = [\text{Na}^+] + [\text{K}^+] - [\text{Cl}^-]$. Alterations in BB essentially represented

changes in strong ion concentrations (that could not be measured easily in 1948). BB increases in metabolic alkalosis and decreases in metabolic acidosis. The major drawback of the use of BB measurements is the potential for changes in buffering capacity associated with alterations in hemoglobin concentration.

Siggard-Anderson and colleagues, in 1958, developed a simpler measure of metabolic acid base activity, the Base-deficit-excess (BDE). They defined base excess as the amount of strong acid or base required to return the pH of 1 liter of whole blood to 7.4, assuming a PCO₂ of 40mmHg, and temperature of 38°C. The initial use of whole blood BE was criticized because it ignored effects imposed by changes in [Hb]. To correct this, the approach was modified in the 1960s to use only serum, and the calculation became the *standardized* base excess (SBE). Current algorithms for computing the SBE are derived from the Van Slyke equation (1977)²². The BDE approach has been validated by Schlitig²³ and Morgan²⁴.

Simple mathematical rules can be applied using the BDE in common acid-base disturbances. For example, in acute respiratory acidosis or alkalosis, BDE does not change. Conversely, in acute metabolic acidosis, the magnitude of change of the PCO₂ (in mmHG) is the same as that of the BDE (in mEq/L) (table 1). The change in BDE represents the overall sum total of all acidifying and alkalinizing effects. This makes interpretation of acid base abnormalities simple but the conclusions may be misleading.

The major limitations of the base deficit approach are 1) there is no way to separate a hyperchloremic metabolic acidosis from that associated with unmeasured anions and 2) the Van Slyke equation assumes normal serum proteins, which is rare in critical illness.

Table 1

Changes in standardized base deficit or excess (BDE) in response to acute and chronic acid base disturbances

Disturbance	BDE vs PaCO₂
AcuteRespiratory Acidosis	$\Delta\text{BDE} = 0$
AcuteRespiratory Alkalosis	$\Delta\text{BDE} = 0$
Chronic Respiratory Acidosis	$\Delta\text{BDE} = 0.4 \Delta\text{PaCO}_2$
Metabolic acidosis	$\Delta\text{PaCO}_2 = \Delta\text{BDE}$
Metabolic alkalosis	$\Delta\text{PaCO}_2 = 0.6 \Delta\text{BDE}$

Modified from Narins RB, Emmett M: Simple and mixed acid-base disorders: A practical approach.

Medicine 1980; 59:161-187 ¹

Anion Gap Approach

To address the primary limitations of the Boston and Copenhagen approaches, Emmitt and Narins used the law of electrical neutrality to develop the anion gap (AG) ²⁵. The sum of the difference in charge of the common extracellular ions, reveals an unaccounted for “gap” of -12 to -16mEq/L (anion gap = $(\text{Na}^+) - (\text{Cl}^- + \text{HCO}_3^-)$) (figure 1). If the patient develops a metabolic acidosis, and the gap “widens” to, for example -20mEq/L, then the acidosis is caused by unmeasured anions – lactate or ketones. If the gap does not widen, then the anions *are* being measured and the acidosis has been caused by hyperchloremia (since bicarbonate cannot fluctuate independently). This useful tool is weakened by the assumption of what constitutes a normal gap ²⁶. The majority of critically ill patients are hypoalbuminemic and many are also hypophosphatemic ²⁷.

Consequently, the gap may be normal in the presence of unmeasured anions. Fencl and Figge have provided us with a variant known as the “corrected anion gap”²⁸:

$$\text{Anion gap corrected (for albumin)} = \text{calculated anion gap} + 2.5(\text{normal albumin g/dl} - \text{observed albumin g/dl}).$$

The second weakness with this approach is the use of bicarbonate in the equation. An alteration in $[\text{HCO}_3^-]$ can occur for reasons independent of metabolic disturbance – hyperventilation for example. The base deficit (BD) and anion gap (AG) frequently underestimate the extent of this sort of metabolic disturbance²⁹.

Stewart-Fencl Approach

A more accurate reflection of true acid base status can be derived using the Stewart-Fencl approach^{4,7}. This, like the anion gap, is based on the concept of electrical neutrality. In plasma there is a strong ion difference (SID) $[(\text{Na}^+ + \text{Mg}^{2+} + \text{Ca}^{2+} + \text{K}^+) - (\text{Cl}^- + \text{A}^-)]$ of 40-44mEq/L. It is balanced by the negative charge on bicarbonate and A_{TOT} (the buffer base). There is a small difference between the apparent SID (SIDa) and BB or effective SID (SIDE). This represents a strong ion gap (SIG), which quantifies the amount of unmeasured anion present (figure 2).

$$\text{SIDa} = ([\text{Na}^+] + [\text{K}^+] + [\text{Mg}^{2+}] + [\text{Ca}^{2+}]) - [\text{Cl}^-].$$

The SIDE is $[\text{HCO}_3^-] + [\text{charge on albumin}] + [\text{charge on Phosphate}]$ (in mmol/L)

Weak acids' degree of ionization is pH dependent, so one must calculate for this:

$$[\text{alb}^-] = [\text{alb g/l}] \times (0.123 \times \text{pH} - 0.631)$$

$$[\text{Phosphate}^-] \text{ (in mg/dl)} = [\text{Phosphate}]/10 \times \text{pH} - 0.47.$$

$$\text{Strong Ion Gap (SIG)} = \text{SIDa} - \text{SIDE}$$

It is important to observe that, although the SIDe appears identical to the Buffer Base ¹², ³⁰ it is not. The BDE and SIG approaches are consistent with one another and can be derived from a master equation ³¹. The Stewart approach ⁷, refined by Figge ^{5,32}, FencI ^{4;29} and others, more accurately measures the contribution of charge from weak acids, which changes with temperature and pH.

The weakness of this system is that the SIG does not necessarily represent unmeasured strong anions but rather all unmeasured anions. Further, SID changes quantitatively in absolute and relative terms when there are changes in plasma water concentration. FencI²⁹ has addressed this by correcting [CL-] for free water ([Cl⁻]_{corr}) using the following equation:

$$[Cl^-]_{corr} = [Cl^-]_{observed} \times ([Na^+]_{normal} / [Na^+]_{observed}).$$

This corrected Chloride concentration may be inserted into the SIDa equation above. Likewise, the derived value for unmeasured anions (UMA), should also be corrected for free water using UMA instead of Cl⁻ in the above equation ²⁹. In a series of 9 normal subjects, FencI estimated the “normal” SIG as 8 +/- 2 mEq/l ²⁹.

Although accurate, the SIG is cumbersome and expensive, requiring measurement of multiple ions and albumin.

An alternative approach, used by Gilfix et al ³³ and others ^{34 35} is to calculate the base deficit-excess gap (BEG). This allows recalculation of BDE using strong ions, free water and albumin. The resulting BEG should mirror the SIG, and, indeed, AG.

We find the simplified calculation of Story to be most useful ³⁵. They use two equations to calculate base deficit excess for sodium/chloride/free water (BDE_{NaCl}) and for albumin.

$$BDE_{NaCl} = ([Na^+] - [Cl^-]) - 38$$

$$BDE_{\text{Alb}} = 0.25 (42 - \text{albumin g/L})$$

$$BDE_{\text{NaCl}} - BDE_{\text{Alb}} = BDE_{\text{calc}}$$

$BDE - BDE_{\text{calc}} = BDE \text{ gap} = \text{the effect of unmeasured anions or cations.}$

These calculations simplify the framework for “eyeballing” a chemistry series:

Normal Na = 140:

- For every 1mEq/L increase in Na from 140, base excess increases by +1
(Na 150 = BDE +10 = contraction alkalosis)
- For every 1mEq/l decrease in Na from 140, base deficit increases by -1
(Na 130 = BDE - 10 = dilutional acidosis)

Normal Cl = 102

- For every 1mEq/L increase in Cl from 102, base deficit increases by +1
(Cl 110 = BDE -8 = hyperchloremic acidosis)
- For every 1mEq/L decrease in Cl from 102, base excess increases by +1
(Cl 90= BDE +12 = hypochloremic, chloride sensitive, alkalosis)

Normal albumin = 42 g/L or 4.2 g/dl

- For every 0.4g/dl decrement in albumin from 4.0, there is a 1.0mEq/L increase in the base excess (table 2 below).

Table 2: Base deficit excess adjustment for serum albumin

Albg/dl	Base deficit-excess component
1.0	+8
1.4	+7
1.8	+6

2.2	+5
2.6	+4
3.0	+3
3.4	+2
3.8	+1
4.2	0
4.6	-1
5.0	-2

The following is an example of the utility of this approach:

A 75 year old female is admitted to the ICU with necrotizing fasciitis. Seven days following admission, after several debridements and while on mechanical ventilation, the following labs are obtained.

Na⁺ 146 mEq/L, Cl⁻ 113 mEq/L, K⁺ 4.6 mEq/L, TCO₂ 25 mEq/L, Urea 19 mEq/L,

Creat 1.1 Albumin 6g/L (0.6 mg/dl)

pH 7.45, PO₂ 121mmHg, PCO₂ 39 mmHg, HCO₃⁻ 27 BDE + 3.3

Eyeballing this series one would be unimpressed – perhaps noting a mild metabolic alkalosis. Using the Stewart-FencI-Story approach the picture is different:

$$\text{BDE}_{\text{NaCl}} = (146-113) - 38 = -5$$

$$\text{BDE}_{\text{Alb}} = 0.25(42-6) = +9$$

$$\text{CBDE} - \text{BD} = +4 - 3.3 = 0.7$$

In this case, the patient has a significant hypoalbuminemic alkalosis, contraction alkalosis and hyperchloremic acidosis, all clinically significant, despite what appeared to be a normal blood gas.

Two days later, following correction of electrolytes with hypotonic saline, the patient becomes confused and hypotensive. Another series of labs are drawn.

Na^+ 140mEq/L, Cl^- 103 mEq/L, K^+ 4.6 mEq/L, TCO_2 24 mEq/L, Urea 19 mEq/L,

Creat 2.1 Albumin 6g/L

pH 7.38, PO_2 121mmHg, PCO_2 38 mmHg, HCO_3^- 23 BDE - 0.3

$$\text{BDE}_{\text{NaCl}} = (140-103) - 38 = -1$$

$$\text{BDE}_{\text{Alb}} = 0.25(42-6) = +9$$

$$\text{CBDE} - \text{BD} = +9 - 1 = -8$$

$$\text{CBDE} - \text{BD} = -8 - 0.3 = -7.7$$

The patient's base-deficit gap of -7.7 represented unmeasured anions. Serum lactate was measured as 4.5mEq/L. The remaining 2.2mEq/L of unmeasured anion was presumed to be due to fixed renal acids. Hence the patient had emerging lactic and renal acidosis despite an apparently normal blood gas. Importantly, the anion gap corrected for albumin was 22, revealing the extent of the acidosis.

An algorithmic approach to simple acid base disturbances is provided (figure 3)..

Acid Base Disturbances

Acid base disturbances are an important part of laboratory investigation in critically ill patients.

There are six primary acid base abnormalities:

1. Acidosis due to increased PaCO_2 .
2. Acidosis due to decreased SID.
 - Increased chloride (hyperchloremic), increased sodium (dilutional) / increased free water
3. Acidosis due to increased A_{TOT} .
 - Hyperphosphatemia, hyperproteinemia
4. Alkalosis due to decreased PaCO_2 .
5. Alkalosis due to increased SID.
 - Decreased Chloride (hypochloremic), increased Sodium (contractional)/decreased free water
6. Alkalosis due to decreased A_{TOT}
 - Hypophosphatemia, hypoalbuminemia

It is important to realize that the body use specific compensatory mechanisms to aggressively restore pH to its resting position. This is accomplished via different buffers, altered ventilation and changes in renal handling of a number of charged species. Hence pH may be “within normal limits” despite significant acid base abnormalities. The exception to this is acute respiratory acidosis.

Acute respiratory acidosis results from hypoventilation. This may result from loss of respiratory drive, neuromuscular or chest wall disorders or rapid-shallow breathing, which increases the dead space ventilation. Acute respiratory alkalosis is caused by hyperventilation. The causes of this disorder are anxiety, central respiratory stimulation (as occurs early in salicylate poisoning) or excessive artificial ventilation. Acute respiratory alkalosis most often accompanies acute metabolic acidosis. In these cases, the reduction in PCO_2 from baseline (usually 40mmHg) is equal to the magnitude of the base deficit. For example, in a patient with acute lactic acidosis with a lactate of 10mEq/L

will have a the base deficit of -10, and a PCO_2 of 30mmHg. A PCO_2 that is higher than expected indicates a problem with the respiratory apparatus. Such a situation may arise, for example, in a trauma patient with lactic acidosis secondary to massive blood loss, and a flail chest, causing respiratory acidosis.

Acute metabolic acidosis results from an alteration in SID or A_{TOT} . SID is altered when the relative quantity of strong anions to strong cations changes. This can be caused by anion gain, as occurs with lactic-, renal-, keto- and hyperchloremic acidosis, or cation loss, as occurs with severe diarrhea or renal tubular acidosis. Acidosis also results from increased free water relative to strong ions – dilutional acidosis, which occurs with excessive hypotonic fluid intake, certain poisonings – methanol, ethylene glycol or isopropyl alcohol or hyperglycemia. Hyperphosphatemia, which increases A_{TOT} , is most commonly associated with the acidosis of renal failure. Hyperalbuminemia is very unusual; nonetheless, in cholera, when associated with hemoconcentration, it is associated with acidosis³⁶.

In acute metabolic acidosis, three diagnoses should be immediately investigated – lactic acidosis (send a serum lactate – it should mirror the magnitude of base deficit), ketoacidosis due to diabetes (the patient should be hyperglycemic and have positive urinary ketones) and acute renal failure, demonstrated by high serum urea and creatinine and low total CO_2 . The latter is a diagnosis of exclusion. The presence of a low serum sodium (<135mEq/L) should alert the clinician to the possibility of a dilutional acidosis caused by alcohol poisoning. Alcohols such as ethanol, methanol, isopropyl alcohol and ethylene glycol are osmotically active molecules that expand extracellular water. Glucose and mannitol have the same effect but also promote diuresis, as the molecules are small

enough to be filtered by the kidney. Alcohol poisoning should be suspected by the presence of an osmolar gap. This is defined as a difference between the measured and calculated serum osmolality of greater than 12mOsm, indicating the presence of unmeasured osmoles.

Renal acidosis is caused by accumulation of strong ion products of metabolism excreted exclusively by the kidney. These include sulphate and formate. In addition, there is accumulation of a weak acid, phosphate.

The administration of intravenous fluids to patients has significant impact on acid base balance (table 3). There are changes in free water volume, SID and A_{TOT} (principally albumin). “Dilutional acidosis” results from administration of pure water to extracellular fluid (which is alkaline). This can occur with large volume administration of any fluid whose SID is 0: 5% dextrose, 0.9% Saline (contains 154mEq of both Na^+ and Cl^+), or other hypotonic saline infusions. Dilutional acidosis thus results from a reduction in serum sodium or an increase in chloride relative to sodium. This “hyperchloremic acidosis” is frequently seen in the operating suite following large volume administration of 0.9% saline solution, 5% albumin solution or 6% hetastarch (both formulated in normal saline)^{37 38}. Kellum³⁹ has shown that septic dogs treated with lactated ringers solution and 5% hydroxyethyl starch diluted in lactated ringers (Hextend®) (both with a SID of 20) have less acidosis and longer survival than those treated with normal saline.

What is the relevance of hyperchloremic acidosis? Brill and colleagues found that acidosis due to hyperchloremia was associated with better outcomes than those caused by lactic or ketoacidosis⁴⁰. This supports the contention that the underlying problem increases patient risk. Nonetheless, metabolic acidosis, regardless of origin, can depress

myocardial contractility, reduce cardiac output and tissue limit perfusion. Acidosis inactivates membrane calcium channels and inhibits the release of norepinephrine from sympathetic nerve fibers. This results in vasodilatation and maldistribution of blood flow. Additionally, metabolic acidosis is associated with an increased incidence of postoperative nausea and emesis ⁴¹. Plasma chloride levels affect afferent arteriolar tone through calcium activated chloride channels and modulate the release of renin ⁴². Hyperchloremia can reduce renal blood flow and glomerular filtration rate ⁴³. Hyperchloremia reduces splanchnic blood flow ⁴⁴. In a study of healthy volunteers, normal saline was associated with reduced urinary output compared with lactated ringers ⁴⁵. Finally, in a study of fluid prehydration to prevent contrast nephropathy, the use of sodium bicarbonate was associated with a 11.9% absolute reduction in the risk of renal injury (defined as a 25% increase in creatinine) ⁴⁶.

Perioperative metabolic alkalosis is usually of iatrogenic origin. Hyperventilation of patients with chronic respiratory failure results in acute metabolic alkalosis due to chronic compensatory alkalosis associated with chloride loss in urine ³. More frequently, metabolic alkalosis is associated with increased SID due to sodium gain. This results from administration of fluids in which sodium is “buffered” by weak ions, citrate (in blood products), acetate (in parenteral nutrition) and, of course, bicarbonate.

The most important single disturbance in acid-base chemistry in critically ill patients is hypoalbuminemia ⁴⁷. This is ubiquitous and causes an unpredictable metabolic alkalosis. This may mask significant alterations in SID, such as lactic acidemia.

Critically ill patients are vulnerable to significant changes in SID and free water. Nasogastric suctioning causes chloride loss while diarrhea leads to sodium and potassium

loss. Surgical drains may remove fluids with varying electrolyte concentrations (the pancreatic bed, for example, secretes fluid rich in sodium). Fever, sweating, oozing tissues and inadequately humidified ventilator circuits all lead to large volume insensible loss and contraction alkalosis. Loop diuretics and polyuric renal failure may be associated with significant contraction alkalosis due to loss of chloride and free water.

Infusions administered to patients may be responsible for unrecognized alterations in serum chemistry. Many antibiotics, such as piperacillin-azobactam, are diluted in sodium rich solutions. Others, such as vancomycin, are administered in large volumes of free water (5% dextrose). Lorazepam is diluted in propylene glycol, large volumes of which will cause metabolic acidosis similar to that seen with ethylene glycol ⁴⁸.

Continuous renal replacement therapy (CRRT) is used in critical illness to hemofiltrate and hemodialyze patients who are hemodynamically unstable. Rocktaschel ⁴⁹ and colleagues have demonstrated that CRRT resolves the acidosis of acute renal failure by removing strong ions and phosphate. However, metabolic alkalosis ensued due to the unmasking of metabolic alkalosis due to hypoalbuminemia.

Treating Acid Base Disturbances

Some aspects of treatment of acid base disturbances are self-evident. Lactic acidosis is treated volume resuscitation and source control. Diabetic ketoacidosis is treated with volume resuscitation and insulin. Renal acidosis is treated with dialysis. The use of sodium bicarbonate, once a mainstay of acid-base management, is no longer emphasized. There is no evidence that sodium bicarbonate administration improves outcomes in circulatory shock ⁵⁰. Infusing sodium bicarbonate has three effects: 1. volume expansion,

as the 7.5% solution is hypertonic (hence the often remarked improvement in cardiovascular performance). 2. Increased SID, due to the administration of sodium without an accompanying strong anion (table 3)⁵¹. 3. Increased CO₂ generation. Only the first is likely to be useful in the setting of the volume depletion that accompanies many forms of acidosis. While much discussion has focused on bicarbonate inducing intracellular acidosis⁵², this is probably clinically insignificant^{50;53}.

Hyperchloremic or dilutional acidosis (caused by inappropriate infusion of intravenous fluids – table 3), is treated by increasing the SID of infused fluids, for example by infusing sodium without chloride. Although no such fluid is available commercially, one can be easily made by diluting 3 ampules of 7.5% sodium bicarbonate into 1 liter of 5% dextrose or pure water. An alternative is the use of sodium acetate. This is run as maintenance fluid (the SID is 144) until the base deficit returns to zero.

Sodium gain is “chloride sensitive” alkalosis, treated by administration of net loads of chloride – 0.9% NaCl, potassium chloride, calcium chloride and, occasionally, hydrogen chloride. It is important to correct chloride sensitive alkalosis, as the normal compensatory measure is hypoventilation, increasing PaCO₂, which may lead to CO₂ narcosis, or failure to liberate from mechanical ventilation.

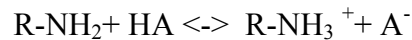
There is no specific treatment for hypoalbuminemic alkalosis

Contraction alkalosis is treated by correcting the free water deficit using the formula:

$$\text{Free water deficit} = 0.6 \times \text{patient's weight in kg} \times ((\text{patient's sodium}/140) - 1)$$

Renal acidosis is treated with dialysis to remove fixed acids. However, altering the SID with sodium bicarbonate or sodium acetate can be used as a bridge.

There has been significant interest in hypercapnic acidosis over the past decade. This stems from the use of “permissive hypercapnia” to prevent ventilator associated lung injury in ARDS⁵⁴. There is accumulating evidence that hypercapnia has a lung protective effect and that reversing the acidosis may have adverse effects⁵⁵. Nevertheless, in patients with hypercapnic acidosis and associated cardiovascular instability, we recommend the use of THAM⁵⁶ (*Tris-Hydroxymethyl-Amino-Methane*). This compound titrates hydrogen ions (e.g. lactic acid or CO₂) according to the following reaction:



THAM is a proton acceptor that generates NH₃⁺/HCO₃⁻ without generating CO₂. The protonated R-NH₃⁺, along with chloride, is eliminated by the kidneys,. THAM has the significant advantage of buffering acidosis without increasing serum sodium or generating more carbon dioxide.

Table 3. Changes in acid-base balance related to fluid administration, assuming a 70kg male with 17 liter extracellular fluid volume and no fluid loss.

Volume and Type of Fluid Administered	BDE_{NaC}	BDE_{Abl}	CBDE
3 L NaCl 0.9%	-5.6	+1.6	-4.0
5 L NaCl 0.9%	-8.6	+2.4	-6.2
3 L LR	-2.6	+1.6	-1.0
5 L LR	-4.0	+2.5	-1.5
3 L Normosol	0.6	+1.6	+2.0

5 L Normosol	+1.0	+2.4	+3.4
3L Normosol + 25g Alb	+2.3	+2.0	+4.3
2L NS + 3L Normosol	-3.0	+2.5	-0.5
3 amps NaHCO ₃	+7.4	+0.1	+7.5

Conclusions

Much of the confusion regarding acid-base chemistry relates the attempt to apply observational approaches, such as that of Henderson-Hasselbalch, and Schwartz and Brackett, to the entire spectrum of pathophysiologic processes. The use of physical chemistry principles has improved our ability to teach, understand and diagnose acid base abnormalities. All acid base disorders can be explained in terms of SID, A_{TOT} and PCO_2 . This is important to intensivists, who are routinely faced with complex acid base abnormalities in practice.

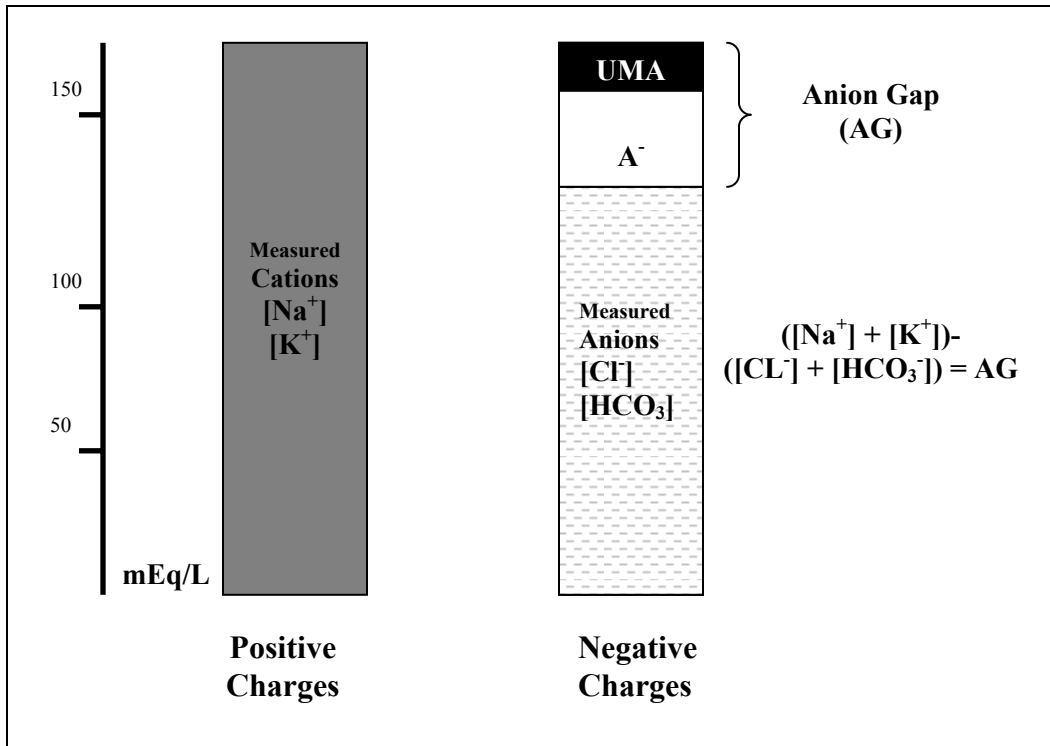


Figure 1: The Anion Gap. This represents the difference in charge between measured cations and measured anions. The missing negative charge is made up of weak acids (A⁻), albumin and phosphate, and strong anions (UMA), such as lactate

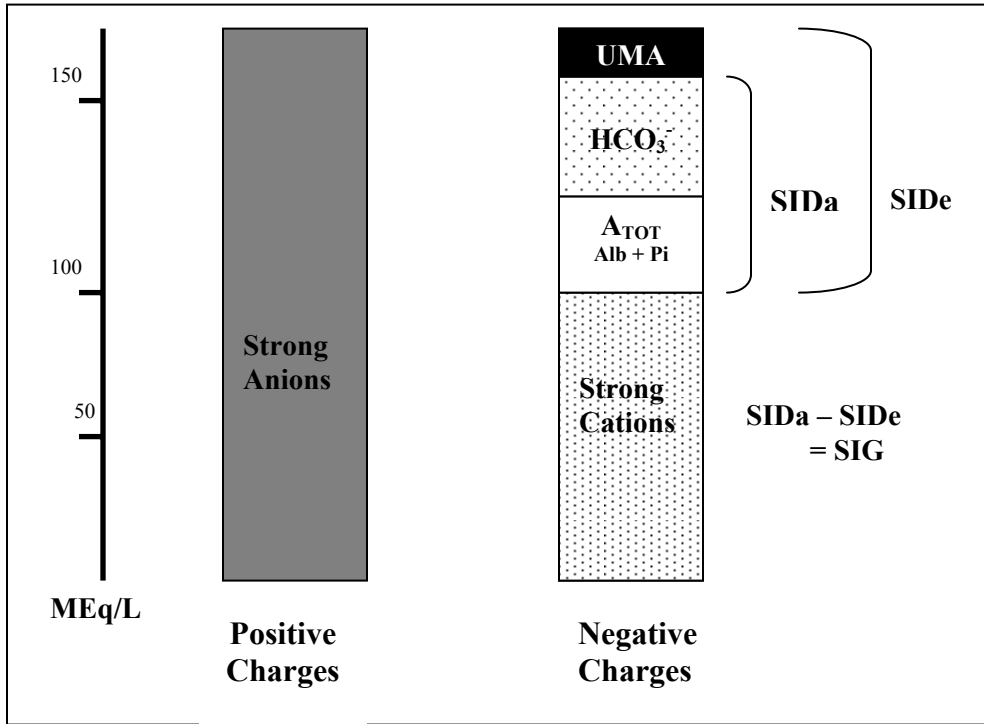


Figure 2. The Strong Ion Gap: SID_{apparent} is the sum of ATOT plus [HCO₃⁻]. SID_{effective} is the real SID. The difference between the two is made up of unmeasured anions (UMA)

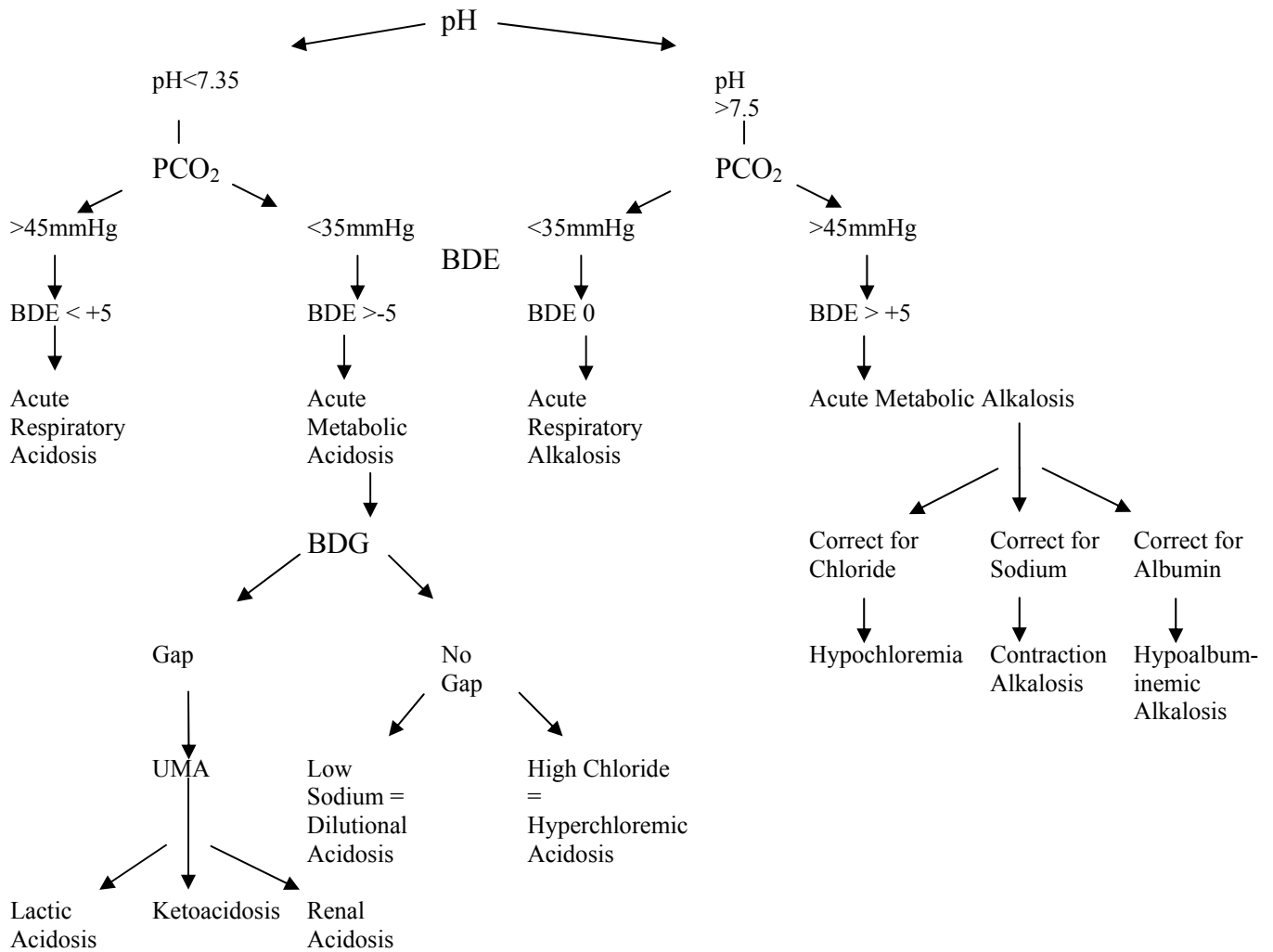


Figure 3: Algorithm for working acid base problems

BDE = Base deficit (-) or base excess (+), BDG = Base deficit gap (corrected base deficit – calculated base deficit)

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