

# [CHAPTER 19]

## Using the Stewart Model at the Bedside

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### 19.1 INTRODUCTION

Disorders of acid-base balance are among the most common abnormalities seen, especially in critically ill and injured patients. While many disorders are benign or self-limiting, severe disorders of acid-base balance are life threatening, especially when these derangements develop quickly. Although controversy exists as to the effect of mild to moderate acid-base disorders, severe abnormalities can be the direct cause of organ dysfunction [1]. For example, acidemia is associated with increased adrenergic tone [1] and, on this basis, can promote the development of cardiac dysrhythmias in critically ill patients or increase myocardial oxygen demand in patients with myocardial ischemia. Emerging evidence suggests that changes in acid-base variables influence immune effector cell function [2,3]. It is therefore important to understand both the causes of acid-base disorders and the limitations of various treatment strategies. It is the Stewart approach that may be most helpful in this respect. A list of terms and abbreviations are shown in Table 19.1.

### 19.2 AN ILLUSTRATIVE CASE

A 21-year-old female with a recent diagnosis of leukemia was admitted to the intensive care unit with acute onset of fever, progressive dyspnea and hypotension. Physical examination showed a severely ill patient with a temperature of 41 °C. Her heart rate was 135 beats per minute and her blood pressure was 80/40 mmHg. Her respiratory rate was 37 breaths per minute. Auscultation of the chest showed fine crackles over the left lower lobe. The rest of the physical examination was unremarkable. Arterial blood gas analysis with supplemental oxygen showed the following: pH 7.07,  $\text{PCO}_2$  6.6 kPa (50 mm Hg),  $\text{PO}_2$  9.0 kPa (68 mm Hg),  $[\text{HCO}_3^-]$  14 mmol/L, and BE -14 mEq/L. Other relevant laboratory data are shown in Table 19.2.

### 19.3 GENERAL INTERPRETATION

First, the patient has severe acidemia (pH 7.07). Acidemia can be brought about by

Term	Abbreviation	Definition/Equation
Anion Gap (corrected)	AG <sub>C</sub>	$AG_C = ([Na^+] + [K^+]) - ([Cl^-] + [HCO_3^-]) - 2 \times ([Albumin \text{ in g/dl}] + 0.5 \times ([Phosphate] \text{ in mg/dl}) - [Lactate^-])$
Strong ion difference	[SID]	The difference between all completely dissociated (or nearly completely dissociated) cations and anions. In practice [SID] is never actually known because not all strong ions can be measured.
Apparent strong ion difference	[SID <sub>A</sub> ]	SID calculated directly from the concentrations of measurable strong ions ( $[Na^+] + [K^+] + [Mg^{2+}] + Ca^{2+}$ ) - ( $[Cl^-] + [Lactate^-]$ ). Ionized concentrations of $[Mg^{2+}]$ and $[Ca^{2+}]$ are used.
Effective strong ion difference	[SID <sub>E</sub> ]	$(2.46 \times 10^{-8} \times PCO_2 / 10^{-pH}) + ([albumin \text{ in g/dL}] \times (0.123 \times pH - 0.631)) + ([PO_4 \text{ in mmol/L}] \times (pH - 0.469))$
Strong ion gap	[SIG]	$[SID_A] - [SID_E]$
Total weak acid concentration	[A <sub>TOT</sub> ]	Weak acids, as opposed to strong ions, can exist at physiologic pH as dissociated (A <sup>-</sup> ) or associated (AH) with a proton. $[A_{TOT}] = [A^-] + [AH]$ . Weak acids are often referred to as buffers. Note that in the absence of unmeasured ions, A <sup>-</sup> is equal to the anion gap.
Standard Base Excess	SBE	$0.9287 \times [HCO_3^- - 24.4 + 14.83 \times (pH - 7.4)]$
Standard Base Excess (corrected)	SBE <sub>C</sub>	$(HCO_3^- - 24.4) + [(8.3 \times Albumin \times 0.15) + (0.29 \times Phosphate \times 0.32)] \times (pH - 7.4)$

**Table 19.1.** Glossary of quantitative acid-base terms. Adapted from [64] with permission.

change in one or more of the three independent variables that control blood pH: PCO<sub>2</sub>, [SID] or [A<sub>TOT</sub>]. One source of acidemia in this case is clearly PCO<sub>2</sub>, but it is also apparent that a metabolic component is also present (either [SID] or [A<sub>TOT</sub>]). We can detect this second abnormality either by observing that the [HCO<sub>3</sub><sup>-</sup>] is decreased or because the standard base excess (SBE) is negative (also referred to as a base deficit).

Importantly, not only does the PCO<sub>2</sub> point to the type of disorder (respiratory vs. metabolic), it also corresponds to the magnitude of the disorder. This is not the case for bicarbonate and SBE is not completely successful either. In 1948, Singer and Hastings proposed the term “buffer base” (BB) to define the sum of [HCO<sub>3</sub><sup>-</sup>] plus the nonvolatile weak acid buffers ([A<sup>-</sup>]) [4]. A change in BB corresponds to a change in the metabolic component. The methods for calculating the change in BB were later refined to yield the base excess methodology [5-8]. Base excess (BE) is the quantity of metabolic acidosis or alkalosis defined as the amount of acid or base that must be added to a sample of whole blood in vitro in order to restore the pH of the sample to 7.40 while the PCO<sub>2</sub> is held at 40 mm Hg [6] (see chapter 14). Perhaps the most commonly used formula for calculating BE is the Van Slyke equation [9, 10]:

[Na <sup>+</sup> ]	135 mEq/L	[Albumin]	0.8 g/dl
[Cl <sup>-</sup> ]	113 mEq/L	[Phosphorus]	3.4 mg/dl
[K <sup>+</sup> ]	3.9 mEq/L	[Lactate]	3.3 mEq/L
[HCO <sub>3</sub> <sup>-</sup> ]	14 mEq/L		
pH	7.07	SID <sub>A</sub>	23.4 mEq/L
PCO <sub>2</sub>	50 mmHg	SIG	5.3 mEq/L
SBE	-14.1 mEq/L	AG	9 mEq/L
SBE <sub>C</sub>	-10.7 mEq/L	AG <sub>C</sub>	2.2 mEq/L

**Table 19.2.** Laboratory results for the illustrative case. See text for discussion.

$$BE = \{[HCO_3^-] - 24.4 + (2.3 \times [Hb] + 7.7) \times (pH - 7.4)\} \times (1 - 0.023 \times [Hb]) \quad (19.3.1)$$

Where [HCO<sub>3</sub><sup>-</sup>] and [Hb] are expressed in mmol/L. However there is great variability in the equations used for calculating BE. While BE is quite accurate in vitro, inaccuracy has always been a problem when applied in vivo in that BE changes slightly with changes in PCO<sub>2</sub> [11,12]. This effect is understood to be due to equilibration across the entire extracellular fluid space (whole blood plus interstitial fluid). Thus, the BE equation was modified to “standardize” the effect of hemoglobin on CO<sub>2</sub> titration in order to improve the accuracy of the BE in vivo. The term standard base excess (SBE) has been given to this variable which better quantifies the change in metabolic acid-base status in vivo. Again multiple equations exist but a common version is shown:

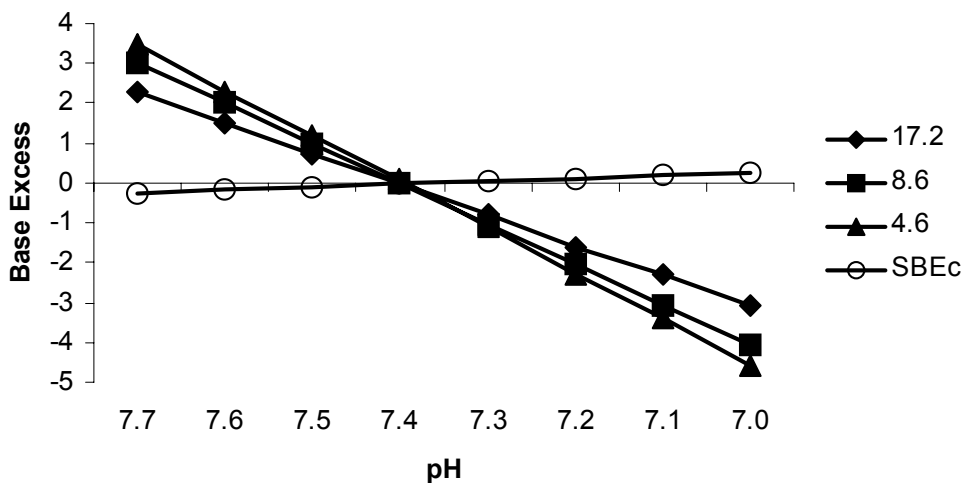
$$SBE = 0.9287 \times \{[HCO_3^-] - 24.4 + 14.83 \times (pH - 7.4)\} \quad (19.3.2)$$

However, SBE still yields results that are slightly unstable as PCO<sub>2</sub> changes (Figure 19.1). Furthermore, the equation assumes normal [A<sub>TOT</sub>]. When albumin and/or phosphate are decreased, a common scenario in the critically ill, SBE will result in even more instability (Figure 19.1). Wooten developed a multi-compartment model using quantitative techniques and has suggested a correction for SBE that results in a formula for SBE that agrees much more closely with experimental data in humans [13,14].

$$SBE_C = [HCO_3^-] - 24.4 + \{8.3 \times [Alb] \times 0.15 + 0.29 \times [Phos] \times 0.32\} \times (pH - 7.4) \quad (19.3.2)$$

Where [Alb] = [Albumin], expressed in g/dl and [Phos] = [Phosphate] in mg/dl. In this way, SBE<sub>C</sub> can be seen as the quantity of strong acid or base required to restore the pH to 7.40 with PCO<sub>2</sub> = 40 mmHg.

Importantly the change in SBE<sub>C</sub> is equal to the change in strong ion difference ([SID]) [15-



**Figure 19.1.** Shown are the results of a computer simulation of in vivo  $\text{CO}_2$  titration curves for human plasma using the traditional Van Slyke equation. In these simulations,  $\text{CO}_2$  is altered and the resulting pH and SBE are plotted. The various curves are produced using different concentrations of total weak acids ( $[\text{A}_{\text{TOT}}]$ ) from normal (17.2) to 25% of normal. Also shown is the titration curve using the  $[\text{A}_{\text{TOT}}]$ -corrected standard base excess ( $\text{SBE}_c$ ). From [17], used with permission).

[17] when  $[\text{A}_{\text{TOT}}]$  is held constant. If  $[\text{A}_{\text{TOT}}]$  changes then  $\text{SBE}_c$  still quantifies the amount of strong acid or base required to change the  $[\text{SID}]$  to a new equilibrium point where  $\text{pH} = 7.40$  and  $\text{PCO}_2 = 40$  mmHg. This relationship between  $\text{SBE}_c$  and  $[\text{SID}]$  is not surprising. The term  $[\text{SID}]$  refers to the absolute difference between completely (or near completely) dissociated cations and anions. According to the principle of electrical neutrality, this difference is balanced by the weak acids and  $\text{CO}_2$  such that  $[\text{SID}]$  can be defined either in terms of strong ions or in terms of the weak acids and  $\text{CO}_2$  offsetting it. Of note, the  $[\text{SID}]$  defined in terms of weak acids and  $\text{CO}_2$ , which has been subsequently termed the effective  $[\text{SID}]$  ( $[\text{SID}_e]$ ) [18] is identical to the Buffer Base term coined by Singer and Hastings over half a century ago (4). Thus changes in SBE also represent changes in  $[\text{SID}]$  [15-17].

## 19.4 METABOLIC ACIDOSIS

Clearly this patient has a severe metabolic acidosis in addition to mild respiratory acidosis. Thus, the next appropriate step is to determine the etiology. If we simply examine the AG (9 mEq/L) we might falsely conclude that it is normal. If we instead examine the corrected anion gap ( $\text{AG}_c$ ) or better yet, the strong ion gap (SIG) we will see a different picture. Why does this occur? Because the “normal range” for the AG only applies when the conditions are normal. Critically ill patients hardly ever have a normal AG.

The AG is calculated, or rather estimated, from the differences between the routinely mea-

sured concentrations of serum cations ( $\text{Na}^+$  and  $\text{K}^+$ ) and anions ( $\text{Cl}^-$  and  $\text{HCO}_3^-$ ) [19]. Normally, this difference or “gap” is made up by two components. The major component is the ionic portion of the weak acids ( $\text{A}^-$ ) - essentially the charge contributed by albumin, and to a lesser extent, by phosphate. The minor component is made up by strong ions such as sulfate and lactate, whose net contributions are normally less than 2 mEq/L. However, there are also unmeasured (by the AG) cations such as  $\text{Ca}^{2+}$ , and  $\text{Mg}^{2+}$  and these tend to offset the effects of sulfate and lactate except when either is abnormally increased. Plasma proteins other than albumin can be either positively or negatively charged but in the aggregate tend to be neutral [18] except in rare cases of abnormal paraproteins such as in multiple myeloma. In practice the AG is calculated as follows:  $\text{AG} = ([\text{Na}^+] + [\text{K}^+]) - ([\text{Cl}^-] + [\text{HCO}_3^-])$ .

Because of its low and narrow extracellular concentration,  $[\text{K}^+]$  is often omitted from the calculation. However, this too is insufficient for the critically ill. Patients in the ICU may have serum  $[\text{K}^+]$  concentrations ranging from 2 to 6 mEq/L, sometimes even higher. To assume that a 4 mEq/L range can be ignored is the same as assuming that a 4 mEq/L concentration of unmeasured anion can be ignored. As we will illustrate, such an assumption is hazardous. Respective “normal” values for the AG, with relatively wide ranges reported by most laboratories are  $12 \pm 4$  (if  $[\text{K}^+]$  is considered) and  $8 \pm 6$  mEq/L (if  $[\text{K}^+]$  is not considered). The “normal AG” has decreased in recent years following the introduction of more accurate methods for measuring  $[\text{Cl}^-]$  concentration [20, 21].

Many authors have raised doubts about the diagnostic value of the AG in certain situations [22, 23]. The primary problem with the AG is its reliance on the use of a “normal” range produced by albumin and to a lesser extent phosphate as discussed above. These constituents may be grossly abnormal in patients with critical illness leading to a change in the “normal” range for these patients. Moreover, because these anions are not strong anions their charge will be altered by changes in pH. This has prompted some authors to adjust the “normal range” for the AG by the patient’s albumin and phosphate concentration. Each g/dl of albumin has a charge of 2.8 mEq/L at pH 7.4 (2.3 mEq/L at 7.0 and 3.0 mEq/L at 7.6) and each mg/dl of phosphate has a charge of 0.59 mEq/L at pH 7.4 (0.55 mEq/L at 7.0 and 0.61 mEq/L at 7.6). Thus, the anion gap (AG) must be corrected (or “zeroed”) to yield a corrected AG ( $\text{AG}_c$ ) [24].

$$\text{AG}_c = ([\text{Na}^+] + [\text{K}^+]) - ([\text{Cl}^-] + [\text{HCO}_3^-]) - (2 \times [\text{Alb}]) + (0.5 \times [\text{Phos}]) - [\text{Lactate}] \quad (19.4.1)$$

or

$$\text{AG}_c = ([\text{Na}^+] + [\text{K}^+]) - ([\text{Cl}^-] + [\text{HCO}_3^-]) - (0.2 \times [\text{Alb}]) + (1.5 \times [\text{Phos}]) - [\text{Lactate}] \quad (19.4.2)$$

The choice of formula is determined by which units are desired, the upper using g/dl for  $[\text{Alb}]$  and  $[\text{Phos}]$ , the lower mmol/L. Here the  $\text{AG}_c$  should approximate zero. This is because the terms for albumin and phosphate approximate  $[\text{A}^-]$ . Note that coefficients for Albumin and Phosphate are slightly lower than expected given their charges at normal pH. Although the

reader is cautioned that the formula is theoretically less accurate as pH increases, empirical data in humans suggest no degradation in accuracy over the physiological range of pH [25]. Some authors have chosen to “correct” the AG using the same (or slightly simplified) equations [26] by adding to the calculated value rather than lowering the expected range. Either approach would be acceptable but if the point is to quantify unmeasured anions the former then requires the additional step of subtracting a normal value, and therefore seems unnecessary cumbersome.

A further limitation to the  $AG_c$  is that it does not consider all the available information. For example cations such as  $Mg^{2+}$  or  $Ca^{2+}$  may still affect the  $AG_c$  and the corrections for Albumin and Phosphate are merely approximations. To be more exact, one can calculate the strong ion gap ([SIG]) [27, 28].

$$\begin{aligned} SIG = & ([Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}]) - ([Cl^-] + [Lactate^-]) \\ & - 2.46 \times 10^{-8} \times \frac{PCO_2}{10^{-pH}} \\ & + [Alb] \times 0.123 \times (pH - 0.631) \\ & + [PO_4^-] \times (pH - 0.469) \end{aligned} \quad (19.4.3)$$

with [Alb] in g/dl,  $[PO_4^-]$  in mmol/L and all the strong ions are expressed in mEq/L and only the ionized portions of  $Mg^{2+}$  and  $Ca^{2+}$  are considered (to convert total to ionized  $Mg^{2+}$  multiply by 0.7). Note also, that lactate is not considered “unmeasured”. Because the concentration of unmeasured anions is expected to be quite low (<2 mEq/L) the SIG is expected to be quite low. However, some investigators have found elevations in SIG, particularly in critically ill patients even when no acid-base disorder is apparent [29-33]. By contrast, results from studies in normal animals [28, 34] and from values derived from published data in exercising humans [27], put the “normal” SIG near zero. Most studies [29, 30, 33, 35, 36] found that the SIG is about 5 mEq/L for critically ill subjects while a few studies [31, 32] report values > 8 mEq/L. The difference may lie with the use of gelatins used for volume resuscitation in these centers [37, 38].

Finally, it is important to calculate the [SIG] or  $AG_c$  when analyzing acid-base balance, even in the absence of acidemia, because an increase may be the only clue to detect a complex acid-base disorder. Alkalemia itself will increase the  $AG_c$  (but not the [SIG]) slightly owing to titration of weak acid, mainly albumin, but large increases (>5 mEq/L) can only mean that unexplained anions are present.

Returning to our case and Table 19.2, we observe that one source of the metabolic acidosis is lactate. It is important to realize that lactate is the source of acidosis because in biologic terms it is a strong acid (pK 3.9). Some investigators have suggested that ATP hydrolysis is the source of acidosis in lactic acidosis because  $H^+$  ions are generated. However, as pointed out by Bellomo [39] this argument is flawed in several ways. Most importantly, very little ATP is completely hydrolyzed and even if it is so, phosphate is a weak acid and therefore very large

Disorder	[HCO <sub>3</sub> <sup>-</sup> ] (mEq/L)	PCO <sub>2</sub> (mm Hg)	SBE (mEq/L)
Metabolic acidosis	< 22	= (1.5 × [HCO <sub>3</sub> <sup>-</sup> ] + 8 = 40 + SBE	< -5
Metabolic alkalosis	> 26	= (0.7 × [HCO <sub>3</sub> <sup>-</sup> ] + 21 = 40 + (0.6 × SBE)	> +5
Acute respiratory acidosis	= [(PCO <sub>2</sub> - 40) / 10] + 24	> 45	= 0
Chronic respiratory acidosis	= [(PCO <sub>2</sub> - 40) / 3] + 24	> 45	= 0.4 × (PCO <sub>2</sub> - 40)
Acute respiratory alkalosis	= 24 - [(40 - PCO <sub>2</sub> ) / 5]	< 35	= 0
Chronic respiratory alkalosis	= 24 - [(40 - PCO <sub>2</sub> ) / 2]	< 35	= 0.4 × (PCO <sub>2</sub> - 40)

**Table 19.3.** Acid-base patterns observed in humans. From [24] with permission.

increases would be required to produce acidosis—which are not routinely seen.

However, lactate is not the only source of acidosis. Assuming that under baseline conditions, this patient’s arterial lactate concentration was approximately 1 mEq/L, the increase in lactate to 3.3 mEq/L explains far less than half of the SBE<sub>C</sub>. The source of the remaining 8.4 mEq/L (10.7– 2.3 from the change in lactate) must be sought. The [SIG] is 5.3 mEq/L demonstrating that a large part of the remaining acid comes from unmeasured anions. Note, if one were to only examine the AG, it would be impossible to detect these unmeasured anions. Furthermore, while the AG<sub>C</sub> is a reasonable approximation of the [SIG] in most cases, in this particular patient AG<sub>C</sub> is only 2.2 mEq and thus “misses” 3 mEq of unexplained anions. As discussed in chapter 18, these unexplained anions can be very important.

## 19.5 UNMEASURED ANIONS

For many years, clinicians have understood that certain poisons (e.g. methanol, ethylene glycol) and salicylate are important causes of metabolic acidosis with increased AG (see also Chapter 29). In table 19.2, 5.3 mEq/L of unmeasured anion is unaccounted for. For methanol and ethylene glycol, a useful screening tool is the osmolar gap (40).

$$\text{Osmolar gap} = \text{Measured osmolality} - [(1.86 \times [\text{Na}^+]) + \text{glucose}/18 + \text{BUN}/2.8 + \text{ethanol}/4.6]$$

Glucose, BUN and ethanol are given in mg/dl. An osmolar gap greater than 10 mOsm/L is abnormal. In our example case, the osmolar gap was 5 mOsm/L, and thus normal. A salicylate level was also obtained and was negative.

As discussed in Chapter 18, numerous unmeasured anions (and cations) have been identified in the blood of critically ill patients [41, 42]. Forni et al. have identified multiple unmea-