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Research review

Metabolic acidosis and the role of unmeasured anions in critical illness and injury

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ABSTRACT

Acid–base disorders are frequently present in critically ill patients. Metabolic acidosis is associated with increased mortality, but it is unclear whether as a marker of the severity of the disease process or as a direct effector. The understanding of the metabolic component of acid–base derangements has evolved over time, and several theories and models for precise quantification and interpretation have been postulated during the last century. Unmeasured anions are the footprints of dissociated fixed acids and may be responsible for a significant component of metabolic acidosis. Their nature, origin, and prognostic value are incompletely understood. This review provides a historical overview of how the understanding of the metabolic component of acid–base disorders has evolved over time and describes the theoretical models and their corresponding tools applicable to clinical practice, with an emphasis on the role of unmeasured anions in general and several specific settings.

Introduction

The first clinical reports describing acid–base derangements stem from observations made during the cholera outbreaks in the nineteenth and early twentieth centuries.[1] Acid–base disorders are frequently identified in critically ill patients and may be associated with increased mortality.[2-4] Injury, acute or chronic disease, and therapeutic measures—such as fluid resuscitation or mechanical ventilation—can influence acid–base status. Timely recognition, quantification, and correct interpretation of acid–base disorders can aid in treatment of the underlying disease process and minimize iatrogenic morbidity.[5,6]

Maintenance of the pH within physiological limits is essential for normal protein structure and enzymatic function. Several regulatory mechanisms maintain the pH within the normal range.[7] The underlying mechanism causing the resultant disorder can be respiratory, metabolic, or a combination thereof. When the underlying disorder is respiratory, the resultant shift in pH is caused by a change in pCO_2. The metabolic influence on pH is more complex.[8] To better characterize nonrespiratory disorders, the traditional bicarbonate-based

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approach,[9] aided by the anion gap (AG) method,[10,11] as well as the more recent standard base excess (SBE)[12-14] and the modern physical–chemical strong ion-based models[15] have proposed surrogates for unmeasured nonvolatile acids or bases.

History

Svante August Arrhenius earned the Nobel Prize in Chemistry in 1903 for his work on dissociation and the theory of ionization. He postulated that acids are potential electrolytes, forming cations (H^+) and anions (A^-) when dissolved in water. Simply stated, acids are hydrogen salts.[16] Approximately 20 years later, Joannes Brønsted[17] and Thomas Lowry[18] independently defined an acid as a substance that could donate a proton and a base as a substance that could bind a proton. This extended the applicability of the definition of acids beyond water. Because body fluids are aqueous solutions, both the Arrhenius and the Brønsted–Lowry theories apply to human physiology.

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

HA is the acid dissociating into a hydrogen ion (H^+) and its conjugate base (A^-). The equilibrium constant (K) indicates the grade of dissociation or strength of an acid:

$$K = \frac{[H^+] \times [A^-]}{[HA]} \rightarrow [H^+] = \frac{K \times [HA]}{[A^-]}$$

A large K value indicates a strong acid, a small K value a weak acid. A strong acid fully dissociates, and a weak acid only partially.

Lawrence Henderson, a biochemist at Harvard, investigated the relationship between bicarbonate and carbon dioxide gas and its role as a buffer of fixed acids. In 1909, he rewrote the law of mass action for weak acids and their salts and applied it to the equilibrium reaction for carbonate species.[19]

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

Law of mass action for carbonic acid (H_2CO_3), which forms from carbon dioxide (CO_2) reacting with water (H_2O). HCO_3^- = bicarbonate.

$$K = \frac{[H^+] \times [HCO_3^-]}{[H_2CO_3]} \rightarrow [H^+] = \frac{K \times [CO_2]}{[HCO_3^-]}$$

The Henderson equation. The K value for this reaction is small, hence in water, H_2CO_3 only partially dissociates into H^+ and HCO_3^-.

The same year, Søren Sørensen introduced the pH as the dimensionless representation of a solution's H^+ concentration, defined as the negative decimal logarithm of the latter.[20] Karl Albert Hasselbalch performed the first blood pH measurement using a platinum electrode in 1912.[21] He later rearranged Henderson's equation into a logarithmic form and replaced the $[CO_2]$ with pCO_2 by applying Henry's law.[22]

$$pH = pK + \log\left(\frac{[HCO_3^-]}{S_{CO_2} \times pCO_2}\right)$$

The Henderson-Hasselbalch equation. S_{CO2} is the solubility coefficient for carbon dioxide (0.03) in blood, and pK is the acid dissociation constant.

In 1915, Hasselbalch and Svend Aage Gammeltoft demonstrated the influence of alveolar ventilation on pH and demonstrated that a decrease in bicarbonate was accompanied by an increased respiration and decreased CO_2 tension.[1]

Donald Dexter Van Slyke, at the Rockefeller University Hospital in New York, developed the Van Slyke apparatus, measuring the total carbon dioxide content in plasma, which is only slightly higher than bicarbonate.[23] It became the standard method for quantification of metabolic acid–base disorders for the next 40 years. Based on his clinical and experimental observations, Van Slyke developed the first diagram relating pH to bicarbonate.[24] Bicarbonate became the central element of acid–base interpretation and was not only viewed as an indicator but as a determinant of the pH. In 1948, Richard Singer and Albert Baird Hastings coined the term buffer base for the sum of all nonvolatile weak acids (mainly bicarbonate and proteins) in plasma.[25]

During the poliomyelitis epidemic in Denmark from 1952 to 1953, Poul Astrup and Ole Siggaard-Andersen refined the buffer base method.[26,27] Measurements of blood pH by glass electrodes and total carbon dioxide content with the Van Slyke method were performed on a large scale. It was recognized that total CO_2 alone was a poor indicator of the metabolic component of the acid–base status. The high total of CO_2 content measured in patients with poliomyelitis was erroneously interpreted as metabolic alkalosis instead of respiratory acidosis with a concomitant increase in bicarbonate.[28] Inspired by the clinical importance of the correct identification of acid–base disorders, Astrup, Siggaard-Andersen, and Knud Engel, who embraced the "modern" Brønsted–Lowry definition of acids, developed the base excess (BE) method,[27] the first technique to quantify the CO_2-invariant metabolic component of an acid–base disorder and was based on the pH, pCO_2 and the hemoglobin (Hb) concentration. Electrodes capable of directly measuring pCO_2 had become available in 1957.[29] Base excess was defined as the quantity of base or acid added to blood (at 37° and pCO_2 adjusted to 40 mmHg, to eliminate the respiratory component of the change in pH) *in vitro* to bring its pH to 7.40. First with a nomogram,[30,31] then with a mathematical formula, the Van Slyke equation,[32] allowed blood gas machines to calculate the BE from whole blood by measuring pH, pCO_2 and Hb.

$$BE = HCO_3^- - 24.4 + (2.3 \times Hb + 7.7) \times (pH - 7.4) \times (1 - (0.023 \times Hb))$$

The Van Slyke equation. BE is expressed in mEq/L, HCO_3^- and Hb concentrations in mmol/L.

The opinions regarding the new tool BE differed between the schools of Copenhagen and Boston. The so-called great transatlantic debate began.[33] The main critique from Boston was that the BE was an *in vitro* method that could not reproduce the *in vivo* carbon dioxide titration curve[34] because only the intravascular compartment is assessed, excluding the interstitial space, which has a much weaker buffering capacity than blood due to the absence of erythrocytes and a lower concentration of albumin.[35,36] Instead of the BE, the American

contingent proposed the "six Bostonian rules of thumb"[9] to recognize the CO_2-invariant changes in bicarbonate. Many clinicians thus continued to focus on the Henderson–Hasselbalch (HH) equation, with the concept that not only pCO_2 but also HCO_3^- influenced the pH. In 1977, the AG was proposed to characterize the metabolic component and distinguish acidosis due to accumulation of organic acids from the loss of alkali.[37] James Figge later demonstrated that the AG is imprecise if albumin is not considered.[11,38,39]

In 1978, Peter Arthur Stewart, a Canadian physiologist who was at that time professor at Brown University, published a physical–chemical approach to quantify the metabolic components of the acid–base status of plasma focusing on the dissociation equilibrium of water. The difference between the charges of strong cations and strong anions, the strong ion difference (SID), is the major force driving the dissociation of water and thus the H^+ concentration.[15,40] Stewart embraced the Arrhenius definition of acid. By integrating six formulas and applying the principles of electroneutrality, conservation of mass, and dissociation of electrolytes, he found three independent effectors on the plasma pH. These are the SID, the sum of weak acids (A_{TOT}), and the pCO_2. According to Stewart, the bicarbonate and BE methods are useful for determining the extent of a disorder rather than its mechanism. Norman Jones and John Kellum coined the term strong ion gap (SIG), which by the Stewart method represents unmeasured ions (UIs) (alkali or fixed acids other than lactate, which is routinely measured).[41,42] The original Stewart approach was later refined,[38,39,43-46] with the most recent version integrating all relevant body fluid compartments.[47,48]

Principal methods of acid–base interpretation

There are four major descriptors of metabolic acid–base derangements. They are based on plasma HCO_3^-, whole blood SBE, plasma AG, the plasma SID, and the plasma A_{TOT}.

The HH method

Merely serving as a description of the acid–base status, this traditional approach allows for the classification of an acid–base disorder as primarily respiratory or metabolic. The only values that are measured with this method are the pCO_2, and the pH, HCO_3^- being calculated from the first two using the HH formula:

$$HCO_3^-(\text{mmol/L}) = 2.46 \times 10^{-8} \times pCO_2(\text{mmHg}) / 10^{-pH}$$

Based on experimental and clinical measurements of pH, pCO_2, and HCO_3^- *in vivo*, empirical rules (Table 1) were derived.[9] Analyzing the patterns of pH, pCO_2, and HCO_3^- with these rules can determine the true metabolic (CO_2-invariant) component of HCO_3, the magnitude of any mixed disorders, and differentiate acute from chronic respiratory changes.[9,49]

The SBE method

The original BE method was developed in an attempt to isolate and objectively quantify the metabolic component of acid–base disorders.[26] To account for the weaker buffering capacity of the interstitial space due to the lack of hemoglobin compared to whole blood, and thus more accurately reproduce *in vivo* conditions, Siggaard-Andersen modified the original Van Slyke equation[32] by using a lower than normal blood hemoglobin concentration of 50 g/L.[50] SBE is a three compartment (interstitium, plasma, and erythrocytes) model and is thus also called extracellular BE.

$$SBE = 0.9287 \times \left(\left[HCO_3^- - 24.4 \right] + 14.83 \times \left[pH - 7.4 \right] \right)$$

SBE: The Van Slyke equation standardized for a blood Hb concentration of 50 g/L. The SBE reproduces the *in vivo* CO_2 titration curve better than the original BE,[47,51] but still not perfectly. As for the HH approach, rules of thumb (Table 2) have been derived to calculate the expected BE or pCO_2 for a given measured pCO_2 or BE.[13] Any superimposed respiratory disorder or an expected BE for a chronic respiratory disorder can be identified. Edward Wooten recently refined the SBE by integrating the plasma weak acids in a formula that more closely reproduces the data obtained experimentally.[43,52] In clinical practice, SBE correlates significantly with the sequential organ failure assessment score,[53] and thus clinical outcome.[54]

The AG method

The AG is defined as the difference between unmeasured anions (UAs) and unmeasured cations.[10,37] Given the law of electroneutrality, it must be identical to the difference between the measured cations [primarily sodium (Na^+) and

Table 1 – The six Bostonian Rules to identify pCO_2-invariant changes in $HCO3^-$ and mixed disorders.

Primary disorder	Expected $HCO_3^- = 24 + \ldots$	Expected $pCO_2 = \ldots$
Acute respiratory acidosis	$([pCO_2]-40)/10$	
Chronic respiratory acidosis	$([pCO_2]-40)/3$	
Acute respiratory alkalosis	$(40-[pCO_2])/5$	
Chronic respiratory alkalosis	$(40-[pCO_2])/2$	
Metabolic acidosis		$1.5 \times [HCO_3] + 8$
Metabolic alkalosis		$0.7 \times [HCO_3] + 21$

pCO_2 = partial carbon dioxide pressure (mmHg).

Table 2 – Compensation rules for BE in relation to pCO_2.

Primary disorder	Expected ΔBE	Expected ΔpCO_2
Acute respiratory	0	
Chronic respiratory	$0.4 \times \Delta pCO_2$	
Metabolic acidosis		ΔBE
Metabolic alkalosis		$0.6 \times \Delta BE$

pCO_2 = partial carbon dioxide pressure (mmHg).

potassium (K^+)] and anions [primarily chloride (Cl^-) and HCO_3^-]. If an organic acid accumulates, it will dissociate into a conjugate base (A^-) and a hydrogen ion (H^+). The latter is then neutralized by a buffer (primarily HCO_3^-). An increase in anions in the form of conjugate bases (footprints of organic acids) therefore increases the AG. When using Na^+, K^+, Cl^- and HCO_3^-, the normal AG is 12 ± 4 mmol/L.[55]

$$AG = (Na^+ + K^+) - (HCO_3^- + Cl^-) = 12 \pm 4 \text{ mEq/L}$$

or, if K^+ is not accounted for:

$$AG = (Na^+) - (HCO_3^- + Cl^-) = 8 \pm 4 \text{ mEq/L}$$

Proteins and phosphate are weak acids. Their levels can be significantly altered in critical illness and not taking them into account leads to misinterpretation of the AG.[56] Hypoalbuminemia in critically ill patients is very common.[57-59] Figge demonstrated that the plasma protein effect on the acid–base status was accurately represented by albumin alone and developed formulas to calculate the AG corrected for albumin (AG_c),[11,38,39] the simplest of which is:

$$AG_c = AG + \frac{\left(\text{Albumin(g/L)}_{\text{Reference}} - \text{Albumin(g/L)}_{\text{Measured}}\right)}{4}$$

or, as lactate is a routinely measured anion:

$$AG_c = AG + \frac{\left(\text{Albumin(g/L)}_{\text{Reference}} - \text{Albumin(g/L)}_{\text{Measured}}\right)}{4} - \text{Lactate(mmol/L)}$$

The AG_c has been demonstrated to have a strong correlation with the mathematically more complicated SIG as a surrogate for UA.[3,54] Still, it does not consider the phosphate (Phos) level and assumes a fixed negative charge for albumin (Alb), which depends on the pH. Figge's more complex formula considers both of these factors[39]:

$$AG_c = (Na^+ + K^+) - (HCO_3^- + Cl^-) - ([\text{Alb}] \times ((0.123 \times \text{pH}) - 0.631) + [\text{Phos}] \times ((0.309 \times \text{pH}) - 0.469))$$

Stewart's physical–chemical approach

For Stewart, the water dissociation equilibrium plays the central role in his model, in which the physical–chemical properties of a solution act as the forces dictating the dissociation of water and thus H^+ concentration. Cations are conjugate acids and anions are conjugate bases. Strong ions are fully dissociated at physiological pH and thus do not participate in proton-transfer reactions.[43] This applies to anions with pK values of 4 or less (e.g., sulfate, lactate, β-hydroxybutyrate). Applying the principles of electroneutrality, conservation of mass, and mass action (electrolyte dissociation), and combining six equations, the following formula is obtained.[60]

$$\text{pH} = \text{pK}_1' + \log \frac{[\text{SID}^+] - K_a[A_{TOT}]/K_a + 10^{-\text{pH}}}{S \times P_{CO_2}}$$

The three variables independently influencing the pH are the SID, A_{TOT} and the pCO_2. If A_{TOT} (albumin and inorganic phosphate) is set to zero, the formula is identical to the HH equation. This demonstrates that considering the weak acids albumin and phosphate is the major difference between the traditional and physical–chemical theories. Since pCO_2 is regulated by alveolar ventilation, the metabolic component of the acid–base status only depends on two variables, the SID and A_{TOT}. Because of the law of electrical neutrality, the electrical sum of strong ions, the apparent SID (SID_a), must mirror the electrical sum of weak ions, the effective SID (SID_e), which includes the negative charges of HCO_3^- and A_{TOT}.

$$SID_a = (Na^+ + K^+ + Mg^{2+} + Ca^{2+}) - (Cl^- + \text{Lactate}^-) = 42$$

$$SID_e = HCO_3^- + A_{TOT} = -42$$

$$A_{TOT} = 2.7 \times [\text{Alb(g/dL)}] + 0.6 \times [\text{Phos(mg/dL)}]$$

The two independent non-respiratory determinants of pH (SID and A_{TOT}), allow for classification of metabolic acid–base disorders into four categories: high SID alkalosis from hypochloremia[61] or hypernatremia (free water deficiency),[62] low SID acidosis from hyperchloremia[63] or hyponatremia (free water excess),[64] high A_{TOT} acidosis from hyperphosphatemia[65] or hyperalbuminemia[66] and low A_{TOT} alkalosis from hypoalbuminemia.[59]

The influence of chloride on the SID explains its role in compensatory mechanisms for acid–base disorders. For example, in accumulation of fixed acids, renal chloride excretion counteracts the acidosis by increasing the SID. In one study, 23% of patients with a metabolic acidosis due to accumulated fixed acids had a normal SBE, the reason being the presence of a concomitant hypochloremia.[61] Another frequent situation encountered in the critically ill patient is hypoalbuminemic alkalosis[59] being neutralized by a low SID "acidosis", thus normalizing the net SBE. Wilkes *et al.*[67] have demonstrated that the renal compensatory mechanism for the loss of negative charges (as in hypoalbuminemia) is increased chloride reabsorption. In an in-vivo study of pigs, Langer *et al.*[68] have demonstrated that the kidney responds to changes in plasma SID with opposite changes in the urinary SID. A clinical study in critically ill patients with impaired renal function has demonstrated that the blood pH was inversely related to the urinary SID, illustrating the importance of renal chloride handling.[69] Exploiting this regulatory mechanism, the plasma chloride-to-sodium ratio has been proposed as a simple method to detect UAs.[70,71] Given its important role in metabolic compensatory mechanisms for acid–base disturbances,[67] it is questionable whether hyper- or hypochloremia should be considered as causing acidosis or alkalosis or simply as normal compensation for the underlying primary disorder.[50]

Any difference between the SID_a and SID_e indicates the presence of UIs (Fig. 1) and was termed SIG,[41,42] which is somewhat a misnomer, because any UI, strong or weak, can influence its value. In a healthy person, the SIG should equal zero.[72]

$$SIG = SID_a - SID_e = 0 - 2 \text{ mEq/L}$$

A positive SIG indicates the presence of UAs, a negative SIG the presence of unmeasured cations. As lactate is a routinely measured strong anion, it is usually included in the SID.

In analogy to the AG_c, the original Stewart formula has been revised, and the method for evaluation of A_{TOT} has been further refined.[38,39,44,45] Wooten recently developed a multicompartment model that in addition corrects for hemoglobin and thus brings it to the same quantitative level as the SBE method.[43]

An approach that combines Stewart's with Siggaard-Andersen's BE method has been described by Vladimir Fencl[14] and Brian Gilfix.[73] The contribution of the SID (which can be further separated into free water and chloride disorders) and A_{TOT} to the net BE allows for determination of the amount of BE that is caused by UAs (BE_{UA}). David Story proposed a simplification of the method by partitioning the BE into three parts: the BE_{SID}, BE_{Alb}, and BE_{UA}.[74] The BE_{SID} is calculated using only the two dominant ions sodium and chloride.

$$BE_{SID}(mEq/L) = Na^{+} - Cl^{-} - 38$$

$$BE_{Alb}(mEq/L) = 0.25 \times (42 - [Alb](g/L))$$

$$BE_{UA} = BE_{measured} - BE_{SID} - BE_{Alb}$$

Strengths and weaknesses of the methods

Recent studies have demonstrated a good correlation of HCO_3^-, SBE, and SID in diagnosing metabolic acidosis in critically ill and healthy patients.[57,75] Controversy exists regarding which method is best used for further characterizing acid–base disorders, and no single model has proven to be superior to another.[33,50,76] Combining the traditional bicarbonate-based and modern electrolyte-based approaches could allow for optimal understanding of acid–base disorders and their relationship to electrolyte homeostasis.[77]

The HH method

Used in isolation, this method fails to identify and quantify the underlying contributors of the metabolic component of the acid–base disorder. The bicarbonate level varies with the pCO_2, mediated by chemical equilibrium, not compensatory adaptation.[72] Chloride, not bicarbonate, may play the central compensatory role in regulating the metabolic contribution to the pH.[67,78] Even when applying the Bostonian rules of thumb,[9] the observed discrepancies in bicarbonate do not truly reflect the quantity of accumulated acid or alkali because nonbicarbonate buffers, such as albumin and hemoglobin, as well as electrolytes are not considered.[14] Both electrolyte and albumin abnormalities are very common in critically ill patients.[79] In addition, the rules for calculation of the expected bicarbonate level have their limitations and become unreliable for pCO_2 values above 80-100 mm Hg.[80] The HH calculations have the advantage of being easily performed at the bedside. Combining this method with the AG_c method may allow for a more accurate characterization of the acid–base disorder.

The SBE method

SBE levels have been demonstrated to predict intensive care unit (ICU) mortality at admission.[3,54,81-83] The SBE method and its refinements[43] provide accurate quantitative information regarding the metabolic acidosis but are not helpful to determine the mechanism of the derangement.[57] As described by

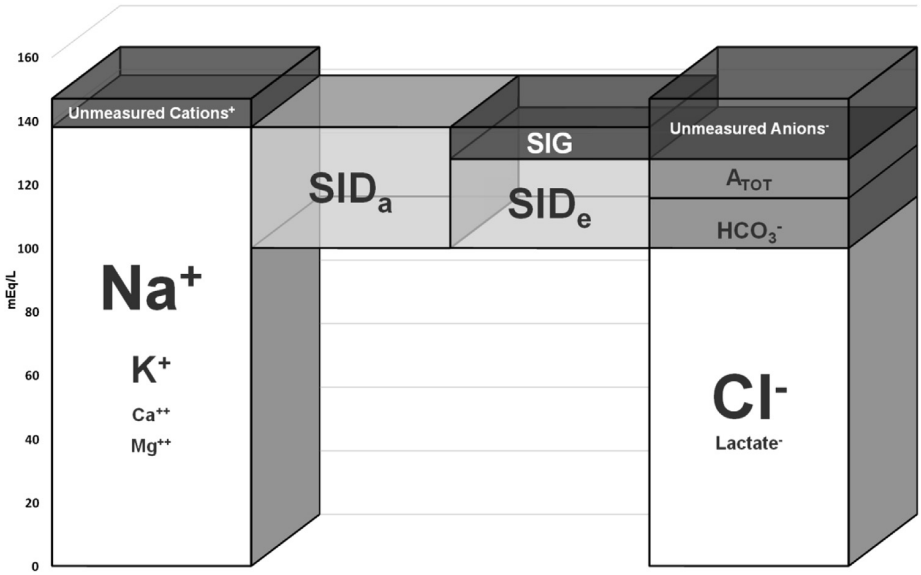

Fig. 1 – Graphical representation of the Stewart model. A_{TOT} = sum of weak acids (albumin$^-$ + inorganic phosphate$^-$). SID_a (apparent strong ion difference) = electrical net sum of strong ions ($Na^+ + K^+ + Mg^{++} + Ca^{++} + Cl^- +$ lactate$^-$), normal = 40-42 mEq/L. SID_e (effective strong ion difference) = electrical net sum of weak ions ($A_{TOT} + HCO_3^-$), normal = negative 40-42 mEq/L. SIG (strong ion gap) = SID_a-SID_e, normal = 0-2 mEq/L.

Kaplan *et al.*,[5] this may have important clinical implications. A decreased SBE in the setting of hyperchloremia, a frequent occurrence,[84] may be misinterpreted as acidosis from inadequate tissue perfusion and, therefore, lead to inappropriate volume loading, potentially worsening the acidosis, especially if chloride-rich fluids are used.[85] Experimental and clinical data suggest potential harm from hyperchloremic acidosis.[84,86-88]

As described earlier, the SBE is an *in vitro* measure and represents the net sum of all metabolic acid–base disorders present. Thus, the SBE can be normal in the presence of complex metabolic acid–base disorders, as observed in several clinical studies.[5,57,61,79,89-92] Partitioning the SBE into its three physical–chemical contributors with the Fencl-Stewart approach allows for a better qualitative description of metabolic acid–base disorders.[73] Conditions like hypochloremia in the setting of a SIG acidosis or hyperchloremia in the context of hypoalbuminemia might actually not represent complex metabolic acid–base disorders per se, but just physiological compensatory mechanisms.[72] A normal SBE in this situation may thus mask something irrelevant, and this raises the question about the clinical significance of complex acid–base disorders in the setting of a normal SBE. Part of SBE can be physiological compensation for a chronic respiratory disorder and thus, in order not to overlook mixed acid–base disturbances, rules of thumb, based on clinical and experimental observations, have also been developed for SBE.[13]

The AG method

The uncorrected AG potentially misses the presence of significant acid–base disorders.[56] The corrected AG (AG_c) can unmask the presence of an organic acidosis previously masked by hypoalbuminemia.[57] The AG_c has been demonstrated to be an adequate tool to quantify UAs[54,57,63] and is mathematically simpler to calculate than the SIG. The AG_c does not account for the measured cations magnesium (Mg^{++}) and calcium (Ca^{++}), but these are tightly regulated and fluctuate less than phosphate and albumin levels.

Stewart's physical–chemical approach

The claimed advantage of this approach resides in its capacity to detect complex metabolic acid–base disorders. In up to 64% of critically ill patients with a normal SBE, simultaneous mixed metabolic acid–base disorders can be diagnosed using the physical–chemical approach.[91,93] Kaplan *et al.* demonstrated that trauma patients in whom the etiologies of metabolic acidosis were identified with the strong ion method normalized their acid–base status more rapidly and spent less days on mechanical ventilation, possibly from avoiding inappropriate fluid resuscitation. The same study also demonstrated that the method identified acid–base disorders not identified by the traditional methods.[5] The choice of resuscitation fluid, by virtue of its physical–chemical properties, can influence the acid–base balance in hemorrhagic shock.[94] The SID of the resuscitation fluid has been demonstrated to influence the SBE[95] and the plasma pH.[68,96] Some investigators and clinicians consider the SIG to be the gold standard for quantification of UIs.[97,98] Studies on surrogates for UA among kidney transplant patients[74] and 365 patients in an emergency department[99] demonstrated better sensitivity of the SIG compared to the AG_c for detecting UA.

In vivo physiology includes four compartments: plasma, erythrocytes, interstitium, and intracellular space. Stewart's original model is based on a single compartment (plasma). Erythrocytes, containing the potent buffer hemoglobin, were not included. One can argue that the electrolyte distribution is even in the extracellular space, but this does not hold true for albumin. It has, therefore, been questioned whether the SID, pCO_2, and A_{TOT} can be considered as independent from each other.[100] Wooten refined the original Stewart equations to account for plasma, the interstitial space, and erythrocytes (Fig. 2).[43,47]

Clinical relevance of metabolic acidosis

Both metabolic alkalosis and acidosis, of which the latter is present in the majority of critically ill patients,[3] are associated with increased morbidity and mortality,[4,58,81,101] with acid–base changes being more profound in nonsurvivors.[58,101] Whether the acid–base derangement is simply a marker of the severity of disease or directly contributes to mortality is controversial.[102] Acidosis has many adverse effects on the respiratory, hemodynamic, cerebral, and immunological systems.[103] Conversely, it has been observed in animal models that acidosis can protect myocardium and liver tissue during ischemia.[104,105] Respiratory acidosis, as in the setting of permissive hypercapnia for acute respiratory distress syndrome management,[106] is usually well tolerated over longer periods of time. At similar pH, different etiologies of acidosis have been demonstrated to have different effects on the myocardium of rabbits.[107] The question arises whether it is the H^+ concentration or the type of accumulated anion that is

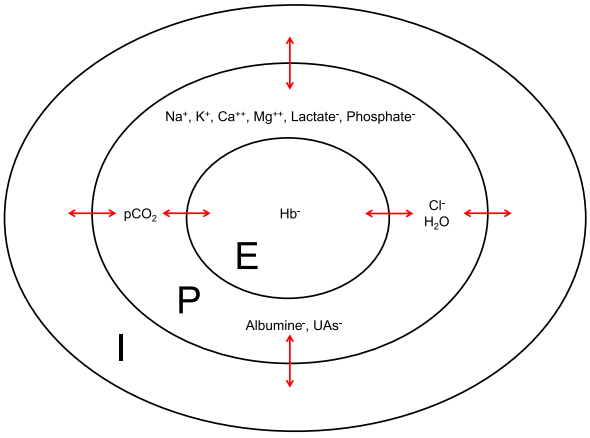

Fig. 2 – IPE model for body compartments relevant for acid–base metabolism. Arrows indicate the movements and distribution of each determinant of acid–base status (Na^+, K^+, Mg^{++}, Ca^{++}, Cl^-, lactate$^-$, phosphate$^-$, albumin$^-$, CO_2, UAs^- and Hb^-) across the compartments. I = interstitial space; P = plasma; E = erythrocytes. (Color version of figure is available online.)

deleterious. The importance of lactate and lactate clearance as markers for shock and prognosis in critically ill patients is well established.[3,84,101,108] Lactate levels correlate with mortality in shock,[109] sepsis,[110] and trauma.[111] Gunnerson *et al.*[3] found a significant association between metabolic acidosis and mortality for lactate and UA, but not for hyperchloremia. For hyperchloremia, although a common cause of metabolic acidosis,[58,61,63,84] most studies have not demonstrated any association with mortality.[3,58,85,101,112,113] However, in severe sepsis and septic shock, acidosis of hyperchloremic origin may be associated with unfavorable outcomes. Noritomi *et al.*[84] found the SID, primarily attributed to hyperchloremia, to not only contribute significantly more to the negative BE in nonsurvivors than in survivors (8.94 ± 7.06 *versus* 5.64 ± 4.96 mEq/L, $P = 0.039$), but after multivariate analysis also to be independently associated with mortality ($P = 0.004$), along with the creatinine level ($P = 0.020$) and the APACHE II score ($P = 0.042$). Similarly, in a study of 22,851 patients undergoing noncardiac surgery, postoperative hyperchloremia was an independent predictor of mortality ($P < 0.01$).[114]

Contribution of unmeasured anions to metabolic acidosis

The only ion routinely measured as a surrogate for a dissociated acid is lactate, of which the plasma levels correlate with mortality in several clinical scenarios.[109-111] However, it has been demonstrated in animal experiments that during metabolic acidosis in sepsis, lactate comprises less than 50% of fixed acids.[115] This is in agreement with a clinical study among patients with severe sepsis, where lactate comprised only 50% of the AG_c.[116] Several of the clinical studies that quantified the acidosis by cause reported nonlactate UAs[91,117] and hyperchloremia[61,63,84,118] as the predominant causes of metabolic acidosis. One study of patients after out-of-hospital cardiac arrest demonstrated that UAs and hyperphosphatemia combined made up for 46% of the (predominantly lactic) metabolic acidosis.[119]

Unmeasured anions: surrogates and reference values

UIs are defined as the net sum of electrical charges originating from cations and anions that are not routinely measured. Given the law of electrical neutrality, it must be equal to the negative net sum of measurable ions.[15,40] Because metabolic acidosis is predominant in critically ill patients, this sum is most often negative, caused by the presence of UAs. Depending on the method used for analysis, the surrogates allowing for quantification of UIs are the SIG,[41] AG_c,[39] and BE_{UA}.[14,73] All three surrogates perform well and have a strong correlation.[3,57,61,63,120,121]

Healthy subjects and laboratory animals have few, if any, circulating UIs. Exercising healthy humans exhibited UI levels of 0.3 ± 0.6 mEq/L in one study.[41] A recent study has demonstrated a mean SIG of 1.4 ± 1.8 mEq/L in healthy volunteers compared to a significantly higher value of 5.1 ± 2.1 mEq/L in stable ICU patients with a normal SBE (defined as 0 ± 2 mEq/L). Two-thirds of the latter had occult acid–base disorders revealed by the Stewart approach.[89] Normal values for the SIG or BE_{UA} indicated in the literature range from 0 to 13 mEq/L.[41,63,79,82,83,89,90,112] Most clinical studies defined a cut-off level of 5 mEq/L, if the SIG was used as the surrogate for UA, with values ranging from 3-8.9 mEq/L.[82,122,123] In more recent studies, defining reference SIG values in blood drawn from healthy volunteers, cut-off values varied between 6 and 8.9 mEq/L.[54,57,61,84,120] Using a Monte Carlo methodology, Anstey derived a reference range with a 95% confidence interval of 3.9 ± 6.4 mEq/L.[124] Laboratories should establish a local reference range for the SIG, considering population and measurement variability.[125] The risk of errors from accumulating imprecision from each of the variables required for the physical–chemical approach is a factor limiting the definition of a reference range.[126]

Sources of unmeasured anions

The nature and origin of the largest part of UAs is unknown.[61,127] Based on observations from clinical and experimental studies, several hypotheses pertaining to the nature of UAs have been proposed. In general, UAs result from protein dissociation and from intermediate products of energy metabolism, accumulated because of a disequilibrium between UA production and clearance in the setting of critical illness or trauma.

Elevated levels of UA are observed during global hypoxemic states.[82,91,117,119-121,128] Besides lactate, intermediate metabolites of the Krebs Cycle, particularly acetate and citrate,[121] have been observed with UA metabolic acidosis, suggesting mitochondrial dysfunction[129] as an etiology. Diverse metabolites such as urate, amino acids (aspartate, isoleucine, and ornithine), and organic acids (acetate, citrate, succinate, pyroglutamate, and p-hydroxyphenyl-lactate) accounted for only 7.9% of all UAs. Urate had the largest contribution to the UA, with 2.2%.[127] Another potential source of UA during hypoperfusion states is shedding of the endothelial glycocalyx[130] rich in negatively charged heparan sulfate.[128] Increased levels of UAs have also been observed in renal[63,65,69,131] and hepatic[41,132,133] dysfunction. A correlation between both bilirubin and creatinine values with the SIG as demonstrated in patients with severe malaria also suggests hepatic and renal contributions to the generation or nonclearance of UAs.[117] Anions accumulating during chronic renal failure include primarily sulfate[134] and phosphate,[69] but also urate, hydroxypropionate, hippurate, oxalate, glutamate, aspartate, and furanpropionate.[135] Bellomo *et al.*[136] demonstrated that high-intensity continuous venovenous hemodiafiltration significantly reduced the SIG, increased the mean arterial pressure, and decreased the vasopressor requirement compared to baseline in patients with metabolic acidosis and acute kidney injury. As 25%-30% of lactate is metabolized by the kidneys, it can also accumulate during renal failure.[137] The acute phase proteins C-reactive protein and fibrinogen do not contribute significantly to UAs.[138] A more recent study by Zampieri *et al.*[139] demonstrated an association between an increased SIG and the presence of inflammatory cytokines in critically ill patients.

Exogenous sources such as intravenous fluids like polygelines or tromethamine,[140-142] toxins (ethanol, methanol, ethylene glycol, propylene glycol, formaldehyde, and formate), and various drugs, such as lithium (strong cation), salicylates, antibiotics (polymyxin B, disodium carbenicillin), infusions of nimodipine (dissolved in 20% ethanol), lorazepam and etomidate (in propylene glycol solvent), as well as paraldehyde and methylene blue administration can contribute to the UI load.[102,143] Pyroglutamate (5-oxoproline) is observed with the administration of acetaminophen, flucloxacillin, and vigabatrin and is generated when hepatic glutathione synthase is reduced.[144,145]

Prognostic value of unmeasured anions

Elevated levels of UAs were associated with increased mortality or unfavorable outcome in diverse settings,[3,57,79,82,83,91,112,117,120,122,123,146-149] whereas some studies did not demonstrate any association of UAs with outcome.[58,63,79,84,101,118,147,150] The interpretation of the currently available data on the prognostic value of UA is rendered difficult by the fact that therapeutic agents, such as certain antibiotics or resuscitation fluids can by themselves contribute UAs.[79,121,140-143,151]

Critically ill children (general pediatric & pediatric cardiac surgery ICU)

Balasubramanyan *et al.*[83] observed a stronger correlation of mortality with UA (BE_{UA}) levels >5 mEq/L than for any other acid–base variable, including SBE, AG, and lactate (>5 mmol/L), in critically ill pediatric patients. Mann *et al.* compared the ability of the SIG, SBE, and lactate to predict unfavorable neurological outcomes of neonates with hypoxic-ischemic encephalopathy and found better outcomes associated with lower UA levels with an overall similar prognostic value as lactate. Both performed significantly better than SBE.[148] On the other hand, Hatherill *et al.*,[150] in a prospective observational study among patients in a general pediatric intensive care unit, demonstrated a significant association between lactate levels (>2 mmol/L), but not UAs (SIG) > 3 mEq/L, and unfavorable outcomes.

Durward *et al.* demonstrated superiority of the SIG (>3 mEq/L) to predict mortality after cardiopulmonary bypass (CPB) in children, measured on admission to the pediatric intensive care unit and 24 hours later, when compared to lactate (>2 mmol/L) levels. The fluids used for priming the CPB circuit in this study were packed red blood cells, hydroxyethyl starch, Ringer's lactate solution, and sodium bicarbonate. Levels of UAs and lactate correlated with the complexity of the surgery but not with the duration of CPB.[112] Murray *et al.*[122] demonstrated that postcardiac surgery admission UA levels (>3 mEq/L), but not lactate levels (>2 mmol/L), were predictive of major adverse events. As in the study by Durward *et al.*,[112] there was no relation between CPB duration and UA level. The typical priming solution used in this study was composed of packed red blood cells, PlasmaLyte (balanced crystalloid solution), 20% albumin solution, and sodium bicarbonate.[122] The results of these two studies are in contrast to a study by Park *et al.*,[152] who compared intraoperative (after weaning from CPB and again after chest closure) levels of UAs (SIG) and lactate and observed a significant association between major adverse event and lactate levels, but not UAs. No information on the nature of the CPB priming solution was provided in this study. This could play a role in the study results because there are data to demonstrate that certain fluids used for priming of the CPB circuit, such as polygelines, contain a significant UA load.[140,141,153] Thus, in such a setting, elevated levels of UAs may not necessarily be associated with unfavorable outcomes.

Critically ill adults (general medical or mixed medical-surgical ICU)

Three studies found an elevated UA level (either expressed as SIG or AG_c) to be an independent predictor of mortality, with lactate performing equally well.[3,91,146] Rocktaeschel *et al.*[147] found that UAs could predict mortality similarly to lactate, but all acid–base variables performed worse than the APACHE II score. Similarly, in a prospective observational study by Dubin *et al.*,[57] although all associated with mortality, UAs (SIG and AG_c), lactate, SBE, and bicarbonate levels performed worse than the sequential organ failure assessment score. In a study by Cusack *et al.*,[79] only one of the surrogates for UA (AG_C) was predictive of 28-day mortality, whereas the SIG was not. In this study, the APACHE II score performed best, followed by the pH and SBE. Two other studies from the same group demonstrated no correlation between UAs and survival in this patient population.[58,118] In their first study, Maciel *et al.*[118] found significant prognostic value for APACHE II, pH, bicarbonate, SBE, and lactate, but not for UAs. In their second study, survivors and nonsurvivors didn't differ in type, but in severity (expressed as SBE) of metabolic acidosis. They found increased levels of UAs in nonsurvivors, both on their day of admission and on day of death, without reaching statistical significance.[58] UAs have also predicted mortality in adult burn patients,[154] general emergency department patients,[155] patients with renal failure,[131] acute pancreatitis,[156] and hypoxic hepatitis.[133]

Adult ICU patients with sepsis

In a study by Noritomi *et al.*, adult ICU patients with severe sepsis or septic shock had variables measured at predetermined time points during the first five days after admission. Utilizing the quantitative physicochemical methodology, they extrapolated that although patients requiring ICU admission had severe metabolic derangements, these derangements were attributable to elevated lactate and chloride levels, and a decrease of these strong ions over time was associated with increased survival. They found that for prognosis, SBE, mostly because of a hyperchloremic decrease of the SID, was the only acid–base variable associated with mortality at ICU admission, in addition to the APACHE II score and serum creatinine level. Admission UAs and lactate levels were similar in survivors and nonsurvivors. Interestingly, clearance of UAs and lactate was associated with survival, whereas clearance of hyperchloremia was not.[84] Part of the large contribution of hyperchloremia to acidosis could be

explained by fluid resuscitation with normal saline, although chloride shifts during endotoxemia have been described in an animal model.[157] Experimental data demonstrate decreased renal blood flow[158] and a proinflammatory effect of hyperchloremic acidosis in sepsis.[159]

Adult ICU patients after cardiac arrest

Cardiac arrest leads to severe systemic metabolic acidosis and death if not reversed rapidly. Funk *et al.* examined the contribution of UAs on the acid–base derangement in patients after cardiac arrest with return of spontaneous circulation after more than 20 minutes and whether acidosis had an impact on patient survival. Patients were placed into hypothermic conditions with standard resuscitative efforts being continued. Multivariate analysis demonstrated that UAs (SIG >8.9 mEq/L), measured 12 hours after return of spontaneous circulation, were correlated with an unfavorable neurological outcome and an increased mortality rate over the 6 months immediately following cardiac arrest ($P = 0.0021$), whereas lactate levels were not ($P = 0.8035$).[120]

Adult trauma patients

Multiple analyses have been performed on trauma patients with severe injuries requiring ICU admission. Kaplan *et al.*[82,123] demonstrated that when comparing survivors to nonsurvivors, UAs (SIG >5 mEq/L) had the strongest correlation with mortality among all acid–base parameters. Martin *et al.*[149] found UAs (BE_{UA}) to have the strongest overall correlation with mortality among acid–base parameters in a trauma ICU, particularly in patients with normal lactate levels.

Adult ICU patients with severe malaria

Falciparum malaria is commonly accompanied by a high AG metabolic acidosis from anaerobic glycolysis in the setting of tissue hypoxia. Severe anemia and hemodynamic shock are the usual contributors to tissue hypoxia. The metabolic acidosis associated with severe malaria can only be partially explained by lactate, phosphate, or acute renal failure. Acids associated with currently unidentified anions are quantitatively the most important contributors to acidosis in this disease. The presence of high concentrations of UAs, measured as the SIG, had major prognostic significance in patients with severe malaria, independent of lactate levels.[117]

Conclusions

There is no consensus regarding preferred methodology for the evaluation of acid–base derangements in critically ill patients. The physical–chemical approach by Stewart does not have a clear advantage over the traditional bicarbonate-based method. Both should be regarded as complementary for optimal understanding of acid–base disorders.

UAs pose an as yet undetermined effect on mortality in patients who have significant physiological derangements and who are unable to regain appropriate homeostasis by eliminating excess anions. Based on observations from clinical and experimental studies, it seems that at similar pH values, the type of accumulated anions exerts a greater effect on outcome than the H^+ concentration itself. Further studies and clinical investigations are required to better delineate the role and origin of UAs in severely ill patients, for better prognostication and to identify potential targets for therapy.

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