Diagnosing metabolic acidosis in the critically ill: bridging the anion gap, Stewart, and base excess methods

Le dépistage de l'acidose métabolique chez les patients gravement malades: un pont entre les méthodes du trou anionique, du modèle de Stewart et de l'excès de base

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Abstract

Purpose *Metabolic acid–base disorders are common in critically ill patients. Clinicians may have difficulty recognizing their presence when multiple metabolic acid–base derangements are present in a single patient. Clinicians should be able to identify the components of complex metabolic acid–base disorders since metabolic acidoses due to unmeasured anions are associated with increased mortality in critically ill patients. This review presents the derivation of three commonly used methods of acid–base analysis, which include the anion gap, Stewart physiochemical, and modified base excess. Clinical examples are also provided to demonstrate the subtleties of the different methods and to demonstrate their application to real patient data.*

Principal findings *A comparison of these methods shows that each one is equally adept at identifying a metabolic acidosis due to unmeasured anions; however, the Stewart physiochemical and the modified base excess methods better evaluate complex metabolic acid–base disorders.*

Conclusions *While all three methods correctly identify metabolic acidosis due to unmeasured anions, which is a predictor of mortality, it remains unclear if further delineation of complex metabolic acid–base disorders using the Stewart physiochemical or the modified base excess methods is clinically beneficial.*

Résumé

Objectif *Les troubles acidobasiques métaboliques sont répandus chez les patients gravement malades. Les cliniciens pourraient rencontrer des difficultés quant à la détection de leur présence lorsque de nombreux troubles acidobasiques métaboliques se manifestent chez un seul patient. Les cliniciens devraient être en mesure de déterminer les composantes des troubles acidobasiques métaboliques complexes, étant donné que les acidoses métaboliques causées par un niveau non mesuré d'anions sont associées à une mortalité accrue chez les patients gravement malades. Cette revue présente la dérivation de trois méthodes couramment utilisées pour réaliser une analyse acidobasique: le trou anionique, la méthode physiochimique de Stewart et l'excès de base modifié. Des exemples cliniques sont également fournis pour démontrer les subtilités des différentes méthodes ainsi que leur application à des données de patients réelles.*

Constatations principales *Une comparaison de ces méthodes montre qu'elles sont toutes efficaces pour dépister une acidose métabolique causée par des anions non mesurés ; toutefois, les méthodes physiochimique de Stewart et d'excès de base modifié permettent une meilleure évaluation des troubles acidobasiques métaboliques complexes.*

Conclusion *Bien que les trois méthodes détectent de façon adéquate l'acidose métabolique causée par des anions non mesurés, un prédicteur de mortalité, il reste à déterminer si une délinéation plus poussée des troubles acidobasiques métaboliques avec les méthodes physiochimique de Stewart et d'excès basique modifié présente des avantages cliniques.*

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Introduction

In the early 1900s, sufficient laboratory and observational evidence had been accumulated to define the influence of carbon dioxide on pH¹ and to suggest a role for serum bicarbonate in characterizing acid–base disorders.² Henderson recognized that carbon dioxide and bicarbonate were key elements of carbonate mass action, as shown by his famous equilibrium equation.³ Hasselbalch reformulated this equation by introducing the negative logarithmic pH notation and by applying Henry's Law to generate the pCO₂ term.⁴ It was quickly appreciated, however, that the Henderson–Hasselbalch equation failed to account for the influence of non-bicarbonate buffers and serum electrolytes on acid–base interpretation.⁵ Additionally, this equation lists pCO₂ and HCO₃[−] as independent predictors of pH when, in fact, these variables are interdependent. Consequently, this equation merely serves as a description of a patient's acid–base status but does not provide insight into the mechanism of the patient's acid–base disorder.

In the 1950s, Siggaard-Anderson sought to stay faithful to the bicarbonate approach to acid–base analysis while distinguishing the metabolic and the respiratory contributions.⁶ At a fixed temperature and partial pressure of carbon dioxide, these investigators measured the plasma bicarbonate concentration and compared the difference between this value and a reference. When corrected by a constant, this difference yields the base excess (BE). Clinically, this BE represents the amount of acid per unit volume that must be added to achieve a normal pH. Criticism of this method soon followed.^{7,8} For example, the laboratory BE value represents the net effect of all metabolic acid–base abnormalities. Therefore, the effect of co-existing metabolic acidoses and alkaloses may cancel to falsely suggest that no acid–base abnormality exists. In fact, two large series have observed a normal BE in one-sixth of critically ill patients with acid–base disorders.^{9,10} Furthermore, this BE does not suggest an etiology for the acid–base disorder once an abnormality is discovered.

Two alternative theoretical approaches, the anion gap (AG) method and the Stewart physiochemical method of acid–base analysis, were eventually introduced.^{11,12} Each of these methods provides the means to identify co-existing acid–base disorders. The modified base excess method was developed later as a simplified version of the Stewart physiochemical approach. Despite the perceived differences between these three methods, they all share a common theoretical foundation based on the principles of electroneutrality and the role of plasma weak acids.

This review presents the theory and the clinical application of each of these three methods of acid–base analysis: the AG, the Stewart physiochemical, and the modified base excess. This review further compares the ability of each

method to correctly diagnose metabolic acid–base disorders in critically ill patients. Current data are presented to determine if any one method is more advantageous in clinical practice. Clinical examples are given to highlight the ability of each approach to reliably recognize complex metabolic acid–base disorders in critically ill patients.

The anion gap method of acid–base analysis

The AG acts as a measure of accumulated acid by quantifying changes in the plasma ion composition.^{11,13,14} Plasma strong acids (XAH), which have a pK_a that is many orders of magnitude less than plasma pH, completely dissociate into the conjugate base (XA[−]) and a proton (H⁺). The proton subsequently joins with buffer to create a neutral species, and the conjugate base remains to signal the presence of the acid species. In other words, the conjugate base can be thought of as the footprint of the strong acid. The dissociation of strong acids changes the relative composition of plasma anionic species with a decrease in buffer and with an increase in conjugate base; however, electroneutrality still remains.¹⁵ This process is illustrated in Fig. 1. Increased amounts of conjugate base are reflected in an increased AG when the strong acid is organic.

The AG is defined as the difference between the unmeasured plasma anions and the unmeasured plasma cations. The derivation of the AG stems from the principle of electroneutrality, such that

$$\begin{aligned} &[\text{Na}^+] + [\text{K}^+] + [\text{Mg}^{2+}] + [\text{Ca}^{2+}] + [\text{H}^+] \\ &= [\text{Cl}^-] + [\text{HCO}_3^-] + [\text{protein}^-] + [\text{PO}_4^{2-}] + [\text{OH}^-] \\ &+ [\text{SO}_4^{2-}] + [\text{CO}_3^{2-}] + [\text{XA}^-]. \end{aligned} \quad (1)$$

Fig. 1 An organic acid (XAH) with a pK_a that is much less than pH dissociates immediately in the plasma. The proton is consumed by the buffer, while the conjugate base persists and signifies accumulated acid

The plasma concentrations of the ionic species OH^- , SO_4^{2-} , CO_3^{2-} , and H^+ are significantly small that their contributions to the electroneutrality equation can be ignored. The plasma concentrations of Na^+ , K^+ , Cl^- , and HCO_3^- are reported in a standard chemistry panel. The sum of the remaining anion species, protein^- , PO_4^{2-} , and XA^- , is defined as the unmeasured anions (UA), whereas the sum of the remaining cation species, Mg^{2+} and Ca^{2+} , is defined as the unmeasured cations (UC). Simple algebraic rearrangement of the electroneutrality equation yields the expression of the AG as

$$\text{AG} \equiv \text{UA} - \text{UC} = ([\text{Na}^+] + [\text{K}^+]) - ([\text{Cl}^-] + [\text{HCO}_3^-]). \quad (2)$$

A normal AG is 12 ± 4 mEq/L.¹³ The presence of organic acid (XAH), which dissociates to form the anionic species XA^- while consuming bicarbonate, results in increased UA and a subsequently increased AG. Therefore, an incremental increase in the calculated AG compared to the institutional reference suggests the presence of an organic metabolic acidosis.^{11,13,14}

While an elevated AG suggests an organic metabolic acidosis, it is important to realize that the calculated AG is affected by any change in the concentrations of either the unmeasured anions or the unmeasured cations. Typically, cation concentrations are tightly regulated while anion concentrations have a greater tendency to fluctuate. Therefore, alterations in anion concentrations contribute more significantly to the AG than alterations in cation concentrations. Regarding the unmeasured anions, plasma protein and phosphate levels can be significantly decreased in critically ill patients. Decreased protein and phosphate levels result in a decreased UA and a subsequently decreased AG. Therefore, an increase in AG from organic acids may be masked by the decrease in AG from low phosphate and protein levels, as shown in Fig. 2.

Since alterations in protein and phosphate levels are common in critically ill patients, these changes must be taken into account when interpreting the AG.^{9,13,16–21} While numerical methods exist to estimate the charge contribution of phosphates and proteins,^{13,22,23} recent evidence suggests that only alterations in the albumin concentration affect the interpretation of the AG.^{24,25} Globulins, for example,

Fig. 2 Alterations in the anion gap, as demonstrated with Gamblegrams. The anion gap (AG) is visually shown to be the difference between the unmeasured anions (UA) and the unmeasured cations (UC).

a Normal serum ion concentrations and a normal anion gap without the presence of any metabolic acid–base disorder. **b** An increased anion gap, due to a metabolic acidosis from increased organic anions. **c** A normal anion gap in the setting of a metabolic acidosis from increased organic anions and a metabolic alkalosis from decreased protein and phosphate levels. In this situation, the increase in organic anions equals the decrease in phosphate and protein anions, so that the total unmeasured anions remain unchanged

constitute a major portion of plasma proteins but do not have a significant charge contribution compared to albumin since their pK_a is much greater than plasma pH. Furthermore, the charge contribution of albumin is significantly greater than that of phosphates. In fact, plasma pH is shown to be linearly related to plasma albumin concentration.²⁶ Based on these results, the AG can be corrected based on the albumin concentration. This corrected AG (AG_{Corr}), as determined empirically,^{11,13,16–18} is given by

$$AG_{Corr} = AG + 0.25 \times ([\text{albumin}]_{\text{Reference}} - [\text{albumin}]_{\text{measured}}), \quad (3)$$

where the albumin concentration is given in g/l. This AG_{Corr} can unmask an organic acidosis that was previously undetected in the setting of hypoalbuminemia.

While the AG is an important indicator of metabolic acidosis, not all metabolic acidoses result in an elevated AG. Consider an example in which acid in the form of HCl is added to the plasma. Upon dissociation, Cl^- remains as the conjugate base while the bicarbonate buffer is consumed by the proton. As a result, an increase in $[\text{Cl}^-]$ is balanced by a decrease in $[\text{HCO}_3^-]$.

Clinically, simple metabolic acid–base disorders are readily identified using the AG and can be separated into an easy differential based on the presence or absence of an elevated AG with the accompanying metabolic acidosis, as shown in Fig. 3. An AG metabolic acidosis results from an overabundance of strong organic acids due to an increased production of lactate or ketoacids, toxic ingestion, decreased renal excretion, or errors of metabolism.^{27,28}

Examples of non-AG hyperchloremic acidosis include increased chloride salts in the form of saline^{29,30} or hyperalimentation³¹ infusions and increased renal or gastrointestinal bicarbonate losses.²⁷ A metabolic alkalosis can result from either hypoalbuminemia or hypochloremia from chloride loss or bicarbonate gain.²⁷

Critically ill patients rarely have a single metabolic acid–base disorder. These patients typically manifest mixed acid–base physiology. The concept of the delta–delta can be used to elucidate mixed acid–base disorders.³² The delta–delta compares the delta corrected AG (ΔAG_{Corr}), which is defined as the difference between the calculated AG_{Corr} and the reference AG, to the delta $[\text{HCO}_3^-]$ (ΔHCO_3^-), which is defined as the difference between the reference $[\text{HCO}_3^-]$ and the measured $[\text{HCO}_3^-]$. As classically described, an incremental increase in AG_{Corr} should be mirrored by the same incremental decrease in $[\text{HCO}_3^-]$; such that ΔAG_{Corr} should equal ΔHCO_3^- if only an AG metabolic acidosis is present. However, this simplistic 1:1 ratio of ΔAG_{Corr} to ΔHCO_3^- fails to consider the role of non-bicarbonate buffers, assumes the same volume of distribution for both the conjugate base and the proton, and disregards the duration of acidosis.^{33,34} Taking these three conditions into account, the actual ratio of ΔAG_{Corr} to ΔHCO_3^- is quite variable depending on the acid species that is present.^{35,36} A review of the literature shows that this ratio ranges from 0.8:1 to 1.8:1 for lactate and from <0.8:1 to 1:1 for ketoacids and toluene.³⁷ For simplicity, the range of (1 to 1.6):1 can be used in the delta–delta calculations. To appreciate the clinical usefulness of the delta–delta, consider the case

Fig. 3 The differential diagnosis for a metabolic acidosis can easily be delineated based on an analysis using the anion gap or the Stewart physiochemical methods. Using the anion gap method, the anion gap corrected for the altered albumin concentration (AG_{Corr}) and the chloride concentration ($[\text{Cl}^-]$) determine which of the three rightmost columns contains the differential diagnosis. A free water excess cannot be diagnosed using the anion gap method. Using the Stewart method, the strong ion gap (SIG), the corrected chloride concentration ($[\text{Cl}^-]_{Corr}$), the sodium concentration ($[\text{Na}^+]$), and the albumin concentration ($[\text{Alb}]$) determine the column that contains the differential diagnosis

in which the ΔAG_{Corr} is 10 mEq/l. Based on the (1 to 1.6:1) ratio of ΔAG_{Corr} to ΔHCO_3^- , the expected $[HCO_3^-]$ should be approximately 6–10 mEq/l less than the reference $[HCO_3^-]$. A measured $[HCO_3^-]$ that is above this range of expected values suggests a co-existing metabolic alkalosis, whereas a measured $[HCO_3^-]$ that is below this range of expected values suggests a co-existing non-AG metabolic acidosis.

The Stewart method of acid–base analysis

Peter Stewart developed a quantitative physiochemical model to explain acid–base physiology.^{5,12,38,39} This method is purely a mathematical analysis of a physiologic system, which lays the foundation for understanding acid–base disorders. He defined his system as follows: a solution that contains strong ions that are completely dissociated at physiologic pH, weak acids that are partially dissociated at physiologic pH, and carbon dioxide that is in equilibrium with an external partial pressure of carbon dioxide. He represented his model by a system of equations that satisfied the dissociation equilibrium of the partially dissociated species, conservation of mass, and electroneutrality. While a complete understanding of this model is not necessary for clinical acid–base analysis, it is important to understand a few basic principles that are derived from Stewart's analysis. First, Stewart identified only three independent variables, specifically, the strong ion difference (SID), the total concentration of weak acids (A_{TOT}), and the partial pressure of carbon dioxide (pCO_2). Second, only changes in these independent variables will result in changes in the dependent variables $[H^+]$ and $[HCO_3^-]$. Therefore, derangements in acid–base balance can only occur with changes in SID, A_{TOT} , and pCO_2 .

Since pCO_2 is regulated by respiration, changes in pCO_2 result in respiratory acid–base disorders. Metabolic acid–base disorders result from changes in either A_{TOT} or SID. The clinical meaning of the variables SID and A_{TOT} and the concept of how changes in these variables affect metabolic acid–base balance are reviewed here.

The SID is defined as the difference between the sum of the strong cations and the sum of the strong anions. Strong ions are those species that are fully dissociated at physiologic pH. The strong cations are Na^+ , K^+ , Ca^{2+} , and Mg^{2+} , and the strong anion is Cl^- . Therefore, the apparent SID is defined as

$$SID_{\text{App}} \equiv ([Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}]) - ([Cl^-]). \quad (4)$$

Under pathologic conditions, additional strong anions, which include lactate, formate, ketoacids, salicylate, and sulfate,

may be present. These unmeasured anions ($[XA^-]$) will change the SID such that the effective SID (SID_{Eff}) becomes

$$SID_{\text{Eff}} \equiv ([Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}]) - ([Cl^-] + [XA^-]). \quad (5)$$

The quantity $[XA^-]$ is of clinical significance, since it is indicative of an organic acidosis. These unmeasured anions can be quantified by the strong ion gap (SIG),^{5,40} which is defined as

$$SIG \equiv SID_{\text{App}} - SID_{\text{Eff}} = [XA^-]. \quad (6)$$

As stated above, SID_{App} is calculated by Eq. 4. An approximation for SID_{Eff} is calculated from the electroneutrality equation (Eq. 1) by rearranging the terms and ignoring the negligible terms ($[OH^-]$, $[SO_4^{2-}]$, $[CO_3^{2-}]$, and $[H^+]$), such that,

$$SID_{\text{Eff}} \equiv ([Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}]) - ([Cl^-] + [XA^-]) = [HCO_3^-] + [\text{protein}^-] + [PO_4^{2-}]. \quad (7)$$

The values for $[\text{protein}^-]$ and $[PO_4^{2-}]$ can be calculated based on the plasma concentrations for albumin and phosphate, as reported by the laboratory,⁹ such that

$$SID_{\text{Eff}} = [HCO_3^-] + 0.28 \times [\text{albumin (g/l)}] + 1.8 \times [\text{Phosphate (mmol/l)}].$$

Now, all of the components of SID_{App} and SID_{Eff} are determined with routine laboratory studies. As a result, $[XA^-]$ is easily approximated based on the SIG.

Based on the previous discussion, the strong anions are conjugate bases, which are the footprint acids. Similarly, the strong cations are the conjugate acids, which are the footprints of bases. Therefore, an increase in SID, which indicates a net increase in cations, results in a metabolic alkalosis. A decrease in SID, which indicates a net increase in anions, results in a metabolic acidosis. At physiologic pH, which is slightly alkaline at about 7.44, the SID is positive.

From the above discussion, it becomes apparent that changes in the independent variable SID will result in alterations in acid–base balance. By understanding how SID can change, one can better appreciate the cause of a given acid–base disorder. Changes in SID result from either a relative or an absolute change in strong ion concentrations.

An alteration in the relative concentration of the strong ions, and a subsequent change in SID, occurs with a change in free water content. For example, if enough free water is added to dilute the strong ion concentrations in half, the SID will also decrease by half. To better understand this concept, consider a patient with Na^+ , K^+ , Ca^{2+} , Mg^{2+} , and Cl^- concentrations (mEq/l) of 140, 4, 6, 2, and 102,

respectively. The SID for this patient is 50 mEq/l ($140 + 4 + 6 + 2 - 102$). By adding enough free water to decrease these concentrations by half, the SID becomes 25 mEq/l ($70 + 2 + 3 + 1 - 51$). Thus, excess free water lowers SID and results in a metabolic acidosis. By a similar analysis, a free water deficit causes a metabolic alkalosis by increasing the SID through a relative increase in concentration of all strong ions.

Absolute changes in strong ions will also alter SID. Changes in sodium concentration primarily result from osmoregulation and are only reflective of changes in free water, as mentioned above. The remaining strong cations, which are magnesium, potassium, and calcium, do not vary significantly to cause alterations in acid–base status. Changes in strong anion concentrations, however, are significant to acid–base balance. A decrease in the strong anion, chloride, results in a metabolic alkalosis. This hypochloremia occurs with gastrointestinal (vomiting) or renal losses. An increase in the strong anion, chloride, results in a metabolic acidosis. This hyperchloremia results from saline or hyperalimentation infusions. When analyzing chloride concentration, it is important to account for alterations in free water content that may be present. As mentioned above, a change in free water content will result in a relative change in chloride concentration. Therefore, the chloride concentration should be corrected based on the sodium concentration, such that

$$[\text{Cl}^-]_{\text{Corr}} = ([140/[\text{Na}^+]] \times [\text{Cl}^-]). \quad (8)$$

The presence of other strong anions, which include lactate, formate, ketoacids, salicylate, and sulfate, also cause an absolute decrease in SID with a resultant metabolic acidosis.

According to Stewart, A_{TOT} is the second independent variable that affects metabolic acid–base balance. A_{TOT} is defined as the total amount of weak acid species in both the dissociated and the non-dissociated form. In physiologic systems, the major weak acids are albumin and phosphate. An increase in the weak acid concentration results in a metabolic acidosis. The primary examples are hyperphosphatemia in renal failure and hyperalbuminemia of hemoconcentration. A decrease in weak acid concentration results in a metabolic alkalosis. The primary example is hypoalbuminemia due to malnutrition, liver cirrhosis, or nephrotic syndrome. Since normal serum phosphate concentration is relatively small, hypophosphatemia alone will not result in a significant metabolic alkalosis.

Based on the Stewart method, metabolic acid–base disorders can be elucidated by analyzing changes in SID and A_{TOT} . The differential diagnosis for metabolic acid–base disturbances can be determined based on changes in SID and A_{TOT} , as shown in Fig. 3.

The base excess method of acid–base analysis

The classical base excess theory is limited by its inability to differentiate co-existing metabolic acid–base disorders. Gilfix et al. describe a base-excess method, which is based on the fundamental principles of Stewart's physiochemical model, to quantify the metabolic component of acid–base disorders.⁴¹ Based on an analysis of Stewart's model, Gilfix proposed that only four conditions create non-respiratory acid–base disturbances. These conditions are: (1) a free water deficit or excess, as determined by changes in sodium concentration; (2) changes in chloride concentration; (3) changes in protein charges, mainly albumin; and (4) the presence of organic unmeasured anions.

The BE is the amount of titratable acid per unit volume that needs to be added to a sample at a $p\text{CO}_2$ of 40 mmHg and a temperature of 37°C to achieve a neutral pH. A positive BE indicates an alkalosis, whereas a negative BE indicates an acidosis. The BE is readily reported by a clinical laboratory. Gilfix et al. show that the BE reported by the laboratory should equal the sum of the BE for each of the four conditions listed above, such that,

$$\text{BE}_{\text{lab}} = \text{BE}_{\text{fw}} + \text{BE}_{\text{Cl}} + \text{BE}_{\text{alb}} + \text{BE}_{\text{XA}}, \quad (9)$$

where each of the determinants of BE_{lab} are calculated as follows:^{41,42}

$$\text{BE}_{\text{fw}} (\text{mEq/l}) = 0.3([\text{Na}^+] - 140) \quad (10)$$

$$\text{BE}_{\text{Cl}} (\text{mEq/l}) = 102 - [\text{Cl}^-]_{\text{Corr}} \quad (11)$$

$$\text{BE}_{\text{alb}} (\text{mEq/l}) = 0.34([\text{Albumin} (\text{g/l})]_{\text{Reference}} - [\text{Albumin} (\text{g/l})]_{\text{Measured}}). \quad (12)$$

Since $[\text{XA}^-]$ represents the unmeasured anions, BE_{XA} is calculated from Eq. 9 once the other four quantities are known.

This base excess method of acid–base analysis provides a simple method that can be readily used at the bedside to determine the non-respiratory disturbances in a patient's acid–base status.

Comparison of the three methods of acid–base analysis

Critically ill patients manifest complex acid–base disorders. While the respiratory component is readily diagnosed by analyzing $p\text{CO}_2$, the metabolic component requires a more complex analysis. The three methods that are described above are used clinically to diagnose and understand a patient's acid–base status. The question arises as to which method is the most useful in the clinical setting. In order to understand the answer to this question, one must look at predictors of mortality in critically ill patients and consider which method of acid–base analysis correlates well with mortality in these patients.

In a retrospective review of 851 critically ill patients with a documented metabolic acidosis, Gunnerson et al. show that mortality associated with lactic acidosis (56%) and non-lactate strong anion acidosis (39%) is significantly higher than that associated with hyperchloremic acidosis (29%) and controls (25%).⁴³ Therefore, the identification of unmeasured anions is crucial in any acid–base analysis in critically ill patients. Using the three methods described above, the unmeasured anions ($[XA^-]$) are identified by the AG_{Corr} , SIG, and BE_{XA} , respectively. Several studies have looked at the correlation of these different measures of $[XA^-]$ with mortality. Balasubramanyan et al. show that BE_{XA} correlates with mortality in pediatric ICU patients,⁴² whereas Cusack et al. do not find that correlation in adult ICU patients.⁴⁴ Since the results of these two studies are limited by a small sample size, Rocktaeschel et al. retrospectively reviewed 300 adult ICU patients.⁴⁵ This study shows that the unmeasured anions were the only acid–base variables that had limited prediction of mortality in critically ill patients. They further show a strong correlation between all methods of calculating the unmeasured anions (AG, AG_{Corr} , SIG, and BE_{XA}).

This correlation between indicators of unmeasured anions is confirmed by several clinical studies. Kellum et al. demonstrate a tight correlation between SIG and AG_{Corr} , but not AG, in 75 ICU patients with sepsis ($r = 0.93$) and those with severe liver disease ($r = 0.91$).⁴⁶ Moviat et al. also show a strong correlation between SIG and AG_{Corr} ($R^2 = 0.93$) in 50 consecutive ICU patients with a documented metabolic acidosis.⁴⁷ More recently, Dubin et al. confirm the strong correlation between SIG and AG_{Corr} ($R^2 = 0.97$) in a prospective study of 935 patients admitted to a mixed medical–surgical ICU.¹⁰ Based on these data, all three methods of acid–base analysis are equally adept at identifying an acidosis due to unmeasured anions, provided that the AG is corrected for hypoalbuminemia.

The AG method is traditionally used and understood by most clinicians. This method, however, requires an empirically derived correction factor to account for the effects of alterations in albumin concentration. Additionally, the simplifying assumptions in the delta–delta calculations of the AG method may hide subtle abnormalities. For

example, the AG method does not identify acid–base abnormalities that are due to alterations in plasma free water. Additionally, the AG method does not account for the correction of chloride concentration in the setting of altered plasma free water. As a result, a hyperchloremic acidosis in the setting of a dilutional alkalosis would not be identified with an analysis using the AG method. In contrast, both the Stewart physiochemical method and the modified base excess method are better able to delineate co-existing acid–base disorders. The Stewart physiochemical method, however, is mathematically rigorous and may be difficult to routinely use at the bedside. The modified base excess method is based on the principles of the Stewart physiochemical method but is mathematically simple and can be readily applied at the bedside. It remains unclear, however, if the identification of subtle acid–base abnormalities, by either the Stewart physiochemical or the modified base excess method, is of clinical significance.

Since all three methods identify a metabolic acidosis that is associated with unmeasured anions and since it remains uncertain whether any one method is more advantageous than the others, clinicians can decide which method is more suitable for clinically diagnosing metabolic acid–base disorders in their critically ill patients. A summary of the qualitative changes in physiologic variables, as determined by the AG, Stewart physiochemical, and base excess methods, is shown in Table 1. The key equations for each method are summarized in Table 2.

Clinical examples

Fencel et al. provide clinical data on the ability of the AG and the physiochemical methods to detect acid–base abnormalities in 152 critically ill patients.⁹ The laboratory data and the associated calculated values for two representative patients and nine controls are shown in Table 3. The following discussion demonstrates the application of the AG, Stewart, and modified base excess methods to the analysis of the acid–base disturbances in these two sample patients.

Table 1 Qualitative changes in physiologic variables with a metabolic acidosis, as determined by the anion gap, Stewart physiochemical, and modified base excess methods of acid–base analysis

	Anion gap	Physiochemical	Base excess
Free water excess	—	↓ SID, ↓ $[Na^+]$	− BE_{fw}
Hyperchloremia	↔ AG, ↑ $[Cl^-]$	↓ SID, ↑ $[Cl^-]_{\text{Corr}}$	− BE_{Cl}
Presence of unidentified anions	↑ AG_{Corr}	↓ SID, ↑ SIG	− BE_{XA}
Hyperalbuminemia	↓ AG_{Corr}	↑ [Albumin]	− BE_{alb}

Definition of abbreviations: AG anion gap; AG_{Corr} anion gap corrected for altered albumin concentration; $[Cl^-]_{\text{Corr}}$ corrected chloride concentration for alterations in sodium concentration; SID strong ion difference; SIG strong ion gap; BE_{fw} , BE_{Cl} , BE_{XA} , BE_{alb} base excess of free water, chloride, unmeasured anions, and albumin, respectively

Table 2 Key equations for diagnosing metabolic acid–base disorders using the anion gap, Stewart physiochemical, and modified base excess methods of acid–base analysis

Anion gap	$AG \equiv UA - UC = ([Na^+] + [K^+]) - ([Cl^-] + [HCO_3^-])$
Stewart physiochemical	$SID_{Eff} \equiv ([Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}]) - ([Cl^-] + [XA^-]) = [HCO_3^-] + [protein^-] + [PO_4^{2-}]$
Modified base excess	$BE_{lab} = BE_{fw} + BE_{Cl} + BE_{alb} + BE_{XA}$

Definitions of abbreviations: AG anion gap; UA unmeasured anions; UC unmeasured cations; SID_{Eff} the effective strong ion difference that accounts for unmeasured anions ($[XA^-]$); BE_{lab} base excess as measured in the plasma and reported by the clinical laboratory; BE_{fw} , BE_{Cl} , BE_{XA} , BE_{alb} base excess of free water, chloride, unmeasured anions, and albumin, respectively

Table 3 Measured and calculated values for two representative patients with acid–base disorders and for nine controls

	Patient 88	Patient 59	Controls ($n = 9$)
<i>Measured values</i>			
pH	7.40	7.33	7.42
p_aCO_2 (mm Hg)	39	30	38
$[Na^+]$ (mEq/l)	137	117	142
$[K^+]$ (mEq/l)	4.9	3.9	4.1
$[Cl^-]$ (mEq/l)	102	92	106
$[Mg^{2+}]$ (mEq/l)	1.6	1.4	0.8
$[Ca^{2+}]$ (mEq/l)	3.2	3.0	2.3
Albumin (g/l)	6	6	44
P_i (mmol/l)	0.3	0.6	1.0
<i>Calculated values</i>			
$[HCO_3^-]$ (mEq/l)	24	15	24.5
$[Cl^-]_{corr}$ (mEq/l)	106	112	106
ΔAG_{corr} (mEq/l)	13	11	3
SIG (mEq/l)	19	18	8
BE_{lab} (mEq/l)	0	−10	0.3

Modified from Fencl et al.⁹

Definition of abbreviations: P_i inorganic phosphate; $[Cl^-]_{corr}$ corrected chloride concentration for alterations in sodium concentration; ΔAG_{corr} the difference between the calculated corrected anion gap for altered albumin concentration and the reference anion gap; SIG strong ion gap; BE_{lab} base excess as measured in the plasma and reported by the clinical laboratory

A cursory analysis of the data for patient 88, who has post-operative multiple organ failure, shows a normal pH, pCO_2 , and BE, which suggest that no acid–base abnormalities exist. Using the AG method, an acidosis due to unmeasured anions is identified by an elevated AG_{Corr} ($\Delta AG_{Corr} = 13$ mEq/l). Based on the delta–delta calculation, the expected decrement of $[HCO_3^-]$ would be 8–13 mEq/l, which corresponds to a $[HCO_3^-]$ value of 11–16 mEq/l. However, the actual $[HCO_3^-]$ is 24 mEq/l, which suggests a co-existing metabolic alkalosis. An analysis using the Stewart method reveals an elevated SIG, a normal $[Na^+]$, a normal $[Cl^-]_{Corr}$, and decreased albumin and phosphate levels. These changes indicate an acidosis due to unmeasured anions with a concomitant hypoalbuminemic and hypophosphatemic alkalosis. The modified base excess approach yields a BE_{lab} , BE_{fw} , and BE_{Cl} that

all equal 0 mEq/l. The BE_{alb} is calculated to be 13 mEq/l. Subsequently, the BE_{XA} must equal −13 mEq/l. These results indicate an acidosis due to unmeasured anions and a hypoalbuminemic alkalosis. For this sample patient, each of the three methods correctly identifies each of the metabolic acid–base derangements.

Patient 59 also has post-operative multiple organ failure; however, this patient has a more complex acid–base physiology. The pH of 7.33, pCO_2 of 30, and negative BE suggest an acidemia, a metabolic acidosis, and a respiratory alkalosis; however, there is no indication as to the etiology of the metabolic acidosis. Using the AG method, an elevated AG_{Corr} ($\Delta AG_{Corr} = 11$ mEq/l) indicates a metabolic acidosis due to unmeasured anions. With the delta–delta calculation, the expected decrement of $[HCO_3^-]$ would be 7–11 mEq/l, which corresponds to a $[HCO_3^-]$ value of 13–17 mEq/l. The actual $[HCO_3^-]$ is 15 mEq/l, which is consistent with the expected value. Therefore, no further metabolic acid–base disorders are appreciated, although, intuitively, a hypoalbuminemic alkalosis is present. The Stewart approach demonstrates an increased SIG, a decreased $[Na^+]$, an increased $[Cl^-]_{Corr}$, and decreased albumin and phosphate levels. These results indicate a triple acidosis, which is due to unmeasured anions, free water excess, hyperchloremia, and a concomitant hypoalbuminemic and hypophosphatemic alkalosis. Similarly, the modified base excess method yields a positive BE_{alb} (13 mEq/l), a negative BE_{Cl} (−8 mEq/l), a negative BE_{fw} (−7 mEq/l), and a negative BE_{XA} (−8 mEq/l), which indicate co-existing hypoalbuminemic alkalosis, hyperchloremic acidosis, dilutional acidosis, and unmeasured anion acidosis. For this sample patient, only the Stewart method and the modified base excess method correctly identify all of the metabolic acid–base disorders, whereas the AG method fails to fully identify the hypoalbuminemic alkalosis, the hyperchloremic acidosis, and the dilutional acidosis. The clinical implication of this oversight, however, remains unknown.

Conclusions

The traditional BE and bicarbonate approaches to acid–base physiology can fail to detect complex metabolic disorders in critically ill patients. While their derivations

differ, the AG, Stewart, and modified base excess methods share similar starting assumptions and are equally adept at identifying a metabolic acidosis due to unmeasured anions, which is a predictor of mortality. As demonstrated by the second sample patient, if multiple complex acid–base disorders are present, the Stewart method or the modified base excess method may more effectively delineate the different disorders. It remains unclear if the identification of these additional acid–base disorders justifies the additional effort required for the routine use of the Stewart method. The modified base excess approach may best combine the ease of use with clinical effectiveness while staying true to the principles of acid–base physiology.

Conflicts of interest None declared.

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