Review
Clinical review: The meaning of acid–base abnormalities in the intensive care unit – epidemiology
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Abstract

Acid–base abnormalities are common in critically ill patients. Our ability to describe acid–base disorders must be precise. Small differences in corrections for anion gap, different types of analytical processes, and the basic approach used to diagnose acid–base aberrations can lead to markedly different interpretations and treatment strategies for the same disorder. By applying a quantitive acid–base approach, clinicians are able to account for small changes in ion distribution that may have gone unrecognized with traditional techniques of acid–base analysis. Outcome prediction based on the quantitative approach remains controversial. This is in part due to use of various technologies to measure acid–base variables, administration of fluid or medication that can alter acid–base results, and lack of standardized nomenclature. Without controlling for these factors it is difficult to appreciate the full effect that acid–base disorders have on patient outcomes, ultimately making results of outcome studies hard to compare.

Introduction

Critically ill and injured patients commonly have disorders of acid–base equilibrium. Acidosis may occur as a result of increases in arterial partial carbon dioxide tension (P_{CO_2}; respiratory acidosis) or from a variety organic or inorganic, fixed acids (metabolic acidosis). There appears to be a difference in physiologic variables and outcomes between patients with respiratory acidosis and those with metabolic acidosis [1,2], leading some investigators to hypothesize that it is the cause of acidosis rather than the acidosis *per se* that drives the association with clinical outcomes. Even though metabolic acidosis is a common occurrence in the intensive care unit (ICU), the precise incidence and prevalence of metabolic acidosis has not been established for critically ill patients. Often these disorders are markers for underlying pathology. Although the true cause–effect relationship between acidosis and adverse clinical outcomes remains uncertain, metabolic acidosis remains a powerful marker of poor prognosis in critically ill patients [3-5].

Common etiologies of metabolic acidosis include lactic acidosis, hyperchloremic acidosis, renal failure, and ketones. All types of metabolic acidosis have a contributing anion responsible for the acidosis. Some causes may be obvious with a single contributing anion, such as a pure lactate acidosis, whereas other complex disorders may not have a single and identifiable, causative anion and only the strong ion gap (SIG) is elevated. There is recent evidence suggesting that outcomes may be associated with the predominant anion contributing to the metabolic acidosis.

In this review we use modern physical chemical analysis and interpretation to describe why these acid–base disorders occur, what is considered normal, and how variations in analytical technology affect results. We also attempt to describe the incidence between various etiologies of acid–base disorders in ICU patients and examine whether they might affect clinical outcomes. Finally, we discuss limitations of the current nomenclature system, or the lack thereof, with regard to acid–base definitions, and propose a standard approach to describing physical chemical influences on acid–base disorders.

The physical chemical approach

Critically ill patients commonly have acid–base disorders. When applying evolving technology in analytical techniques to measure acid–base variables, the quantitative acid–base (or physical chemical) approach is slowly emerging as a valuable tool in identifying the causative forces that drive acid–base disorders [6]. This review is built on the physical chemical approach (also referred to as the 'Stewart

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A_{TOT} = total amount of weak acids and proteins in plasma; ICU = intensive care unit; ISE = ion selective electrode; P_{CO_2} = partial carbon dioxide tension; SBE = standard base excess; SID = strong ion difference; SIDa = apparent strong ion difference; SIDe = effective strong ion difference; SIG = strong ion gap; Vd = volume of distribution.

approach' or the 'quantitative approach') to analyzing acid–base disorders, and there are many well written reviews that detail the intricacies of these approaches [7-10].

Traditional approaches to the analysis of acid–base disorders adapted from Henderson and Hasselbalch or those proposed by Siggaard-Andersen and colleagues are inadequate for appreciating causative mechanisms. These traditional approaches may identify the presence of a metabolic acidosis, but the categorization ends with a broad differential based on the presence or absence of an anion gap. Controversy has existed for many years over which approach to the analysis of acid–base balance is more accurate, but in general the results of these differing approaches are nearly identical [8,9,11].

The physical chemical approach allows the clinician to quantify the causative ion. The basic principle of the physical chemical approach revolves around three independent variables: P_{CO_2}, strong ion difference (SID), and the total amount of weak acids (A_{TOT}). SID is the resulting net charge of all of the strong ions. This includes both the cations (Na^+, K^+, Ca^{2+}, and Mg^{2+}) and anions (Cl^- and lactate). This measurable difference is referred to as the 'apparent' SID (SIDa), with the understanding that not all ions may be accounted for. In healthy humans this number is close to +40 mEq/l [12]. The law of electroneutrality states that there must be an equal and opposing charge to balance the positive charge, and so the +40 mEq/l is balanced by an equal negative force comprised mostly of weak acids (A_{TOT}). These weak acids include plasma proteins (predominately albumin) and phosphates. The total charge of these must equal the SIDa. The product of all of the measurable anions contributing to the balancing negative charge is referred to as the effective SID (SIDe). Theoretically, the SIDa and SIDe should equal each other, but a small amount of unmeasurable anions may be present, even in good health, and so the resulting difference in healthy humans appears to be less than 2 mEq/l [12].

The role played by plasma proteins, specifically albumin, in acid–base balance is curiously neglected in the traditional approaches. This has led to numerous controversies regarding the usefulness of the anion gap [13] and the classification of metabolic acid–base disorders [14]. Several studies have supported the observation that a significant number of abnormal anion gaps go unrecognized without correction for the albumin level (which, in the critically ill, is usually low) [14-16]. The importance of correcting the anion gap for albumin is not limited to the adult population. Quite the contrary, there is a high incidence of hypoalbuminemia in pediatric patients who are critically ill, and the effect on anion gap measurements are similar to those in the adult population [17,18]. Hatherill and colleagues [18] demonstrated that, when the anion gap is not corrected in critically ill pediatric patients, approximately 10 mEq acid and up to 50% of abnormally elevated anion gaps are missed.

What is normal?
Strong ion gap metabolic acidosis
The SIG can simply be described as the sum of unmeasured ions. More specifically, it is the difference between the SIDa and the SIDe. The SIG and traditional anion gap differ in the sense that the traditional anion gap exists in a broad 'range' of normal values, whereas the SIG takes into account the effect of a wider range of ions, including weak acids, and thus should approach zero. Any residual charge represents unmeasured ions and has been termed 'SIG' [19]. Even though this theoretical value of zero should exist for patients who have no known acid–base abnormalities, a wide range (0–13 mEq/l) has been reported in the literature [14,19-22]. In the USA ranges for SIG in survivors tend to be low and are predictive of survival in critical illness [15,23]. However, in England and Australia – countries that routinely use gelatins for resuscitation – values of SIG have been reported as high as 11 mEq/l in ICU survivors [20] and do not appear to be predictive of outcome [20,24]. Gelatins are a class of colloid plasma expanders that are comprised of negatively charged polypeptides (mean molecular weight between 20 and 30 kDa) dissolved in a crystalloid solution commonly comprised of 154 mEq sodium and 120 mEq chloride. These negatively charged polypeptides have been shown to contribute to both an increased anion gap [25] and SIG [26], most likely due to their negative charge and relatively long circulating half-life. Moreover, these high levels of SIG may be seen in the absence of acid–base abnormalities using traditional acid–base measurements (e.g. P_{CO_2}, standard base excess [SBE], pH).

We recently compared quantitative acid–base variables between healthy volunteers (control) and 'stable' ICU patients. There were significant differences between these two groups. The control group had a SIDe (mean ± standard deviation) of 40 ± 3.8 mEq/l and SIG of 1.4 ± 1.8 mEq/l. The ICU patients had a SIDe of 33 ± 5.6 mEq/l and a SIG of 5.1 ± 2.9 mEq/l. The control group also had a higher albumin level (4.5 g/dl versus 2.6 g/dl in the ICU group). Interestingly, traditional acid–base variables (pH, P_{CO_2}, and SBE) were similar between the groups [12]. Controversy remains, but it appears that a normal range of SIG in healthy patients is 0–2 ± 2 mEq/l, and in stable ICU patients without renal failure SIG appears to be slightly higher, at 5 ± 3 mEq/l.

The SIG calculation is somewhat cumbersome to use at the bedside [19], and attempts have been made to simplify this technique based on normalizing the anion gap for the serum albumin, phosphate, and lactate concentrations [8,16,21,27]. By substituting the corrected anion gap in place of the SIG, we found a strong correlation between the two ($r^2 = 0.96$) [28]. The corrected anion gap was calculated as follows: ($[Na^+ + K^+] – [Cl^- + HCO_3^-]$) – 2.0(albumin [g/dl]) – 0.5(phosphate [mg/dl]) – lactate (mEq/l) [8]. An even simpler formula – ($Na^+ + K^+$) – ($Cl^- + HCO_3^-$) – 2.5(albumin [g/dl]) – lactate (mmol/l) – for the corrected anion gap without the use

of phosphate can be used and retain a strong correlation with SIG ($r^2 = 0.93$) [8,28]. For international units, the following conversion can be substituted for albumin and phosphate: 0.2(albumin [g/l]) − 1.5(phosphate [mmol/l]).

Hyperchloremic metabolic acidosis

One of the obstacles in identifying the incidence of hyperchloremic metabolic acidosis is the actual definition itself. There are many references to hyperchloremic metabolic acidosis or 'dilutional' acidosis in the literature, and there are just as many definitions of hyperchloremic metabolic acidosis. In fact, classifying hyperchloremia as a 'metabolic acidosis' is misleading because chloride is not a byproduct of meta-bolism. This multitude of definitions is akin to the difficulty in defining acute renal failure, for which more than 30 different definitions have been reported in the literature [29]. It is more common to base the diagnosis of hyperchloremic metabolic acidosis on an absolute chloride value rather than to take into account the physicochemical principles of either the decreased ratio of sodium to chloride or the decreased difference between them. With regard to plasma, the addition of normal saline increases the value from baseline of chloride more so than does sodium. This difference in the ratio of sodium to chloride change is what is important. The increase in chloride relative to that of sodium reduces the SID, resulting in a reduction in the alkalinity of blood. The Na^+/Cl^- ratio has been proposed as a simple way to delineate the contribution of chloride to the degree metabolic acidosis [30]. In other words, 'euchloremia' or 'normal chloride' is completely dependent on the concentration of sodium. In this sense, chloride must always be interpreted with the sodium value because they both change with respect to the patient's volume status and the composition of intravenous fluids.

For example, a 70 kg person has 60% total body water and a serum Na^+ of 140 mEq/l and Cl^- of 100 mEq/l, resulting in a SIDa of approximately 40 mEq/l. This patient is now given 10 l saline (154 mEq of both Na^+ and Cl^-) over the course of his resuscitation. Accounting for his volume of distribution (Vd), the serum Na^+ would increase only to 143 mEq/l but the Cl^- would increase to 111 mEq/l. Although the true Vd of Cl^- is extracellular fluid, the movement of salt and water together creates an effective Vd equal to that of total body water [31]. The SBE would decrease at a similar rate but the Cl^- would be regarded as 'normal range' on most analyzers. In spite of the 'normal' absolute reading of Cl^-, the patient has had a reduction in SIDa from 40 mEq/l to 32 mEq/l. This patient now has a hyperchloremic metabolic acidosis with a 'normal' absolute value of chloride, and thus would likely be overlooked by applying traditional principles and nomenclature. Regardless of how it is diagnosed, hyperchloremic metabolic acidosis is common in critically ill patients, is most likely iatrogenic, and surprisingly remains controversial regarding the cause of the acidosis (strong ion addition [chloride] versus bicarbonate dilution) [32,33].

Lactic acidosis

Lactic acidosis is a concerning pathophysiologic state for critically ill patients, and there is a wealth of literature reporting on the significance of various etiologies of elevated lactate as it pertains to the critically ill patient [34-36]. During basal metabolic conditions, arterial lactate levels exist in a range between 0.5 and 1 mEq/l. Levels may be higher in hypoperfused or hypoxic states. However, critically ill patients may have conditions other than hypoperfusion that may lead to lactate elevations, such as increased catecholamine production in sepsis or trauma [37] or from production by lung in acute lung injury [38,39].

Even though elevated lactate levels can be a sign of underlying pathology, most patients in the ICU do not have elevated lactate levels. Five recent outcome trials comparing various approaches in diagnosing acid−base disorders had relatively low mean lactate levels: 2.7 mEq/l in survivors [40]; 1.88 mEq/l [24]; 1.0 mEq/l [30]; 2.3 mEq/l in survivors [20]; and 3.1 mEq/l [15]. In a cohort of 851 ICU patients with a suspected lactic acidosis, and using the highest lactate value if there were multiple values, the mean lactate level was still only 5.7 mEq/l [28]. Therefore, when an elevated lactate is present, it should not be dismissed without further investigation into the underlying etiology.

Outcome data: does the type of acidosis matter?

Metabolic acidosis may represent an overall poor prognosis, but does this relationship exist among the various types of metabolic acidosis? Lactic acidosis has garnered considerable attention in critically ill patients, but metabolic acidosis may result from a variety of conditions other than those that generate lactate [8]. The existing literature does not suggest a strong relationship between the type of acidosis and outcome. However, traditional methods of classifying and analyzing acid−base abnormalities have significant limitations, especially in critically ill patients [13]. Studies have usually failed to identify the effects that causative anions (lactate, chloride, and others) have on the resulting pH and SBE. Findings are typically reported as either 'nonlactate metabolic acidosis' or 'anion gap metabolic acidosis', without identifying a predominant source. These are major limitations of the traditional approach.

A large, retrospective analysis of critically ill patients in which clinicians suspected the presence of lactic acidosis [28] revealed that differing etiologies of metabolic acidosis were in fact associated with different mortality rates. It also appeared that a varying distribution of mortality, within these subgroups of metabolic acidoses existed between different ICU patient populations (Fig. 1). The study suggests that the effects of metabolic acidosis may vary depending on the causative ion.

Conflicting relationships have been reported between acid−base abnormalities, their treatment, and outcomes in

Figure 1
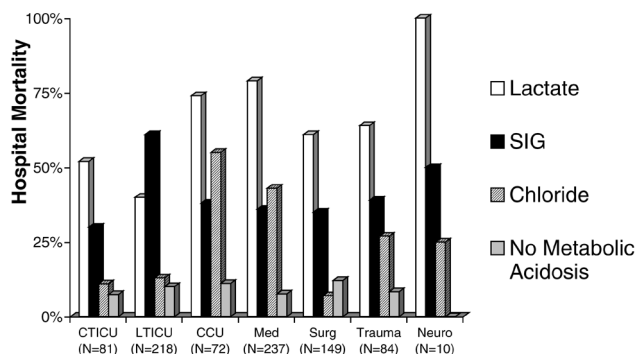
Distribution of patients and contributing ion responsible for majority of metabolic acidosis present. Shown is the distribution of patients within different types of intensive care unit (ICU) locations and their respective hospital mortality associated with the major ion contributing to the metabolic acidosis. These results were obtained from a large teaching institution comprised of two hospitals and seven ICUs over a 1 year period and included patients with a suspected lactic acidosis. No metabolic acidosis is defined as a standard base excess of −2 mEq/l or higher. CCU, cardiac (nonsurgical) ICU; CTICU, cardiothoracic ICU; LTICU, liver transplant ICU; Med, medical ICU; Neuro, neurosurgical and neurological ICU; Surg, general surgical ICU; Trauma, trauma ICU.

critically ill patients [15,20,23,24,40,41]. Some studies have suggested an independent association between low pH or SBE and mortality [42-44], whereas others have not [4,15]. We address further the impact that three major classifications of metabolic acidosis have on patient outcome.

Hyperchloremic metabolic acidosis

Even though many causes of metabolic acidosis may be unavoidable, often the source of metabolic acidosis is iatrogenic. In critically ill patients a common cause is related to the volume of saline infused during resuscitation from shock. Large volume saline infusion produces metabolic acidosis by increasing the plasma Cl^- concentration relative to the plasma Na^+ concentration [45-48]. This results in a decreased SID (the difference between positive and negative charged electrolytes), which in turn produces an increase in free H^+ ions in order to preserve electrical neutrality [8]. The clinical effects of these changes have been documented over the past several years.

The consequences of hyperchloremic metabolic acidosis are traditionally downplayed and accepted as a 'necessary evil' of saline resuscitation. However, recent studies may change this benign view of iatrogenic hyperchloremic metabolic acidosis, especially as it pertains to choice of fluid composition for resuscitation. Deusch and Kozek-Langenecker [49] recently demonstrated better platelet function *in vitro* when samples of whole blood were diluted with a hetastarch prepared in a balanced electrolyte solution instead of using saline as the

solvent. In the same study, similar results were observed when the starch molecule was removed and the samples were diluted with either a balanced electrolyte solution or 0.9% saline. This supports the hypothesis that the electrolyte composition of the solution may play a role in the coagulopathy associated with starch solutions greater than that of the starch molecule itself. Wilkes and colleagues [50] also demonstrated an increase in adverse events and worse acid–base balance when comparing similar hetastarch based solutions prepared in either a saline solution or balanced electrolyte solution. Gan and coworkers [51] reported similar findings in large volume resuscitation in major surgery comparing hetastarch prepared in a balanced electrolyte solution or in saline, and similar findings were reported by Williams and colleagues [52] when they compared lactated Ringers with 0.9% saline. In all of these studies, saline fared worse than did balanced electrolyte solutions.

Saline induced acidosis has a side effect profile similar to that of ammonium chloride. This includes abdominal pain, nausea, vomiting, headache, thirst, hyperventilation, and delayed urination [53,54]. This striking similarity may be related to the chloride concentration. Aside from avoiding these adverse reactions, the treatment of metabolic acidosis *per se* has not yet been shown to improve clinical outcome [41] and, based on a large retrospective database [28], mortality does not appear to be significantly increased. However, there is mounting evidence that iatrogenic metabolic acidosis may be harmful and should be avoided when possible.

Lactic acidosis

Much interest has been directed at lactate metabolism and its role in metabolic acidosis in critically ill patients since the first description of lactate associated with circulatory shock [55]. It has also been the focus of several recent reviews [34,35,56,57]. An early approach to the broad classification of elevated lactate levels based on the presence (type A) or absence (type B) of hypoperfusion was described by Cohen and Woods [58] in their classic monogram. Contemporary understanding of the complexity of lactate production and metabolism in critical illness has practically relegated this classification system to that of a historical one [56].

Our improved understanding of the complexities of lactate metabolism has fueled the controversy regarding lactate's role in the care of critically ill patients. Aside from hypoperfusion leading to cellular dysoxia, elevated lactate has been associated with a number of common cellular processes that are present in critical illness. These include increased activity of Na^+/K^+-ATPase in normoxia [59], increased pyruvate and lactate due to increased aerobic glycolysis [60], and decreased lactate clearance [61], to name but a few.

Regardless of the etiology, lactic acidosis has been associated with worse outcomes in critically ill patients. Elevated lactate has been associated with oxygen debt since

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the 1930s [62] and has been associated with poor outcome since the 1960s [3,63-65]. Elevated lactate on presentation [65] and serial measurements [36,66] are both associated with worse outcome. More importantly, the ability to clear lactate rapidly has been associated with improved mortality [67-69]. Although our understanding of the metabolism of lactate has greatly improved since these early studies [56], critically ill patients with elevated lactate levels continue to have worse outcomes than those who do not [35,36,69]. Recent goal-directed strategies incorporating lactate either as an acute marker for acuity [70] or as an end-point of resuscitation [71] have been shown to improve mortality.

Strong ion gap metabolic acidosis

Lactate serves not only as a marker for severity or an end-point of resuscitation but also as an important variable in the quantification and determination of the primary etiology of a metabolic acidosis. In the presence of a metabolic acidosis and a normal lactate and SIDa, the resulting charge balance must be composed of unmeasured anions (SIG). There is still much debate as to how well SIG acidosis predicts mortality [15,20,23,24]. The ability of SIG to predict mortality in the critically ill is not as clear as that of lactate. There have been varying findings regarding absolute values and the significance of all quantitative acid–base variables, especially SIG. It appears that a pattern is emerging in which studies conducted in different countries have shown different baseline levels of SIG and have noted differences in their clinical significance [15,20,23,24,40]. This may be related to the technology used to measure acid–base variables [72-74] or administration of medications or fluid (e.g. gelatins) [25,26] that alter the SIG.

Two recent prospective studies [23,40] controlled for the limitations noted above when evaluating the ability of the SIG to predict mortality. The findings of these two studies are unique in the sense that they are the first reports of SIG predicting mortality in patients with trauma [23] and severe malaria [40]. Acid–base variables were measured, in both studies, before any significant amount of volume resuscitation.

Kaplan and Kellum [23] evaluated the relationship between SIG, before significant fluid resuscitation, and mortality. In patients with major vascular injury requiring surgery, a SIG in excess of 5 mEq/l was predictive of mortality. Interestingly, SIG outperformed lactate as a predictor of mortality based on receiver operator curve characteristics. SIG was also a stronger predictor of mortality than was the Injury Severity Score, based on multivariate logistic regression analysis. Nonsurvivors had a mean SIG above 10 mEq/l. These levels of unmeasured anions were generated in the absence of resuscitative fluids known to contribute to unmeasured anions such as gelatin based solutions, which are not used for resuscitation in the USA. This important study supports the hypothesis that SIG may be a rapidly accumulating biomarker that reflects severity of injury or illness, similar to other acute phase proteins.

Dondorp and colleagues [40] evaluated the relationship between SIG and mortality in critically ill patients diagnosed with severe malaria. Severe falciparum malaria is frequently associated with metabolic acidosis and hyperlactatemia. The etiology of both of these conditions has been thought to be based on both hepatic dysfunction and hypoperfusion. The authors found that even in fatal cases of this disease state, the predominant form of metabolic acidosis was not lactate but rather unaccounted anion, or SIG, acidosis. Mean lactate levels were surprisingly low in both survivors (2.7 mEq/l) and nonsurvivors (4.0 mEq/l), whereas SIG levels were elevated in both (9.7 mEq/l and 15.9 mEq/l, respectively). SIG was also a strong predictor of mortality in this study.

The overall value of SIG as a predictor of mortality is yet to be determined. Future studies that control for technology and the composition of resuscitative fluids are required. Regardless of the etiology of these anions, our understanding of the importance of SIG is rapidly evolving.

Technology limitations

Technologic advances in the measurement of electrolytes have an influence on how quantitive acid–base parameters are calculated. Currently, there are three techniques commonly used to measure quantitive acid–base variables: flame photometry and potentiometry using direct ion selective electrodes (ISEs) or indirect ISEs. Flame photometry is used infrequently in developed countries. It is the measurement of the wavelength of light rays emitted by excited metallic electrons exposed to the heat energy of a flame. The intensity of the emitted light is proportional to the concentration of atoms in the fluid, such that a quantitative analysis can be made on this basis. Examples are the measurements of sodium, potassium, and calcium. The sample is dispersed into a flame from which the metal ions draw sufficient energy to become excited. On returning to the ground state, energy is emitted as electromagnetic radiation in the visible part of the spectrum, usually as a very narrow wavelength band (e.g. sodium emits orange light, potassium purple, and calcium red). The radiation is filtered to remove unwanted wavelengths and the resultant intensity measured. Thus, the total concentration of the ion is measured.

Flame photometry has several limitations, one of the more common being the influence of blood solids (lipids). These lipids have been shown to interfere with the optical sensing (due to increased turbidity) and by causing short sampling errors (underestimating true sample volume) [75]. Flame photometry also measures the concentration of ions, both bound and unbound, whereas newer techniques (ISEs) measure the disassociated form (or 'active' form) of the ion.

An ISE measures the potential of a specific ion in solution, even in the presence of other ions. This potential is measured against a stable reference electrode of constant potential. By measuring the electric potential generated across a

Table 1

Summary of quantitative acid–base studies in critically ill patients and the distribution of type of metabolic acidosis

Ref.	Patient population	Sample size	Metabolic acidosis	Unmeasured acids	Lactate	Chloride	Mixed
[30]	Pediatric ICU patients	540 samples (282 patients)	230 (45.5%) [a]44 – base deficit	120 (52%) – M	22 (9.6%) – M	88 (38.2%) – M	57 (25%) – M
[80]	Pediatric ICU post-cardiac surgery	150 samples (44 patients)	[a]24 – anion gap [a]57 – anion gap corrected	44	6	19	10
[15]	Pediatric ICU, patients only with acid–base measurements	255 patients	69 (27%)	55 (79.7%) – M	N/A	N/A	N/A
[79]	Pediatric ICU in shock	46 patients	42 (91%)	33 (72%) – M	39 (85%) – M	29 (63%) – M	N/A
[21]	Adult ICU with met acidosis	50 patients	50 (100%)	49 (98%) – M,T	31 (62%) – M,T	40 (80%)– M,T	N/A
[28]	Adult ICU with suspicion of lactic acidosis (highest lactate used)	851 patients	548 (64%) – T	204 (37%) – M	239 (44%) – M	105 (19%) – M	N/A

[a]Authors defined metabolic acidosis using three different techniques; measurement of other variables by quantitive approach. M, the percentage of the samples with a metabolic acidosis; T, the percentage of the 'total' number (n) of patients.

membrane by 'selected' ions and comparing it with a reference electrode, a net charge is determined. The strength of this charge is directly proportional to the concentration of the selected ion. The major advantage that ISEs have over flame photometry is that ISEs do not measure the concentration of an ion; rather, they measure its activity. Ionic activity has a specific thermodynamic definition, but for most purposes it can be regarded as the concentration of free ion in solution.

Because potentiometry measures the activity of the ion at the electrode surface, the measurement is independent of the volume of the sample, unlike flame photometry. In indirect potentiometry, the concentration of ion is diluted to an activity near unity. Because the concentration will take into account the original volume and dilution factor, any excluded volume (lipids, proteins) introduces an error (usually insignificant). When a specimen contains very large amounts of lipid or protein, the dilutional error in indirect potentiometric methods can become significant. A classic example of this is seen with hyperlipidemia and hyperproteinemia resulting in a pseudo-hyponatremia by indirect potentiometry. However, direct potentiometry will reveal the true sodium concentration (activity). This technology (direct potentiometry) is commonly used in blood gas analyzers and point-of-care electrolyte analyzers. Indirect ISE is commonly used in the large, so-called chemistry analyzers located in the central laboratory. However, there are some centralized analyzers utilizing direct ISE. The methodologies can produce significantly different results [72-74,76].

Recent evidence reinforces how technology used to measure acid–base variables affects results and may affect inter-pretation of clinical studies. Morimatsu and colleagues [77] have demonstrated a significant difference between a point-of-care analysis and the central laboratory in detecting sodium and chloride values. These differences ultimately affect the quantitative acid–base measurements. The study emphasizes that differences in results may be based on technology rather than pathophysiology. One reason may be related to the improving technology of chloride and sodium specific probes. On a similar note, it also appears that there is variation in the way in which the blood gas analyzers calculate base excess [78].

Unfortunately, many studies evaluating acid–base balance have failed to report details of the technology used to measure these variables. This limitation was discussed by Rocktaeschel and colleagues [24] in 2003. Since then, detailed methods sections that include specific electrode technology have become more common when acid–base disorders are evaluated [23,40,79,80].

## Incidence of metabolic acidosis in the intensive care unit

The incidence of metabolic acidosis in the ICU is difficult to extrapolate from the current literature. It is even harder to find solid epidemiology data on the various types of metabolic acidosis. A major hurdle is the various definitions used to describe the types of acid–base disorder. The development and implementation of the physical chemical approach has made identifying the etiology of acid–base abnormalities possible. Even though we can quantify these abnormalities, a classification system has yet to be developed. The literature is full of pre-Stewart acid–base descriptions, but the major

taxonomy of metabolic acidoses was limited either to the presence or to the absence of an anion gap, which also has major limitations. Even when reviewing the quantitative acid−base literature specifically, there is no agreement on how to classify patients with metabolic acidosis.

In a retrospective review of 851 ICU patients, we classified patients into categories representing the predominant causative anion associated with the metabolic acidosis [28]. However, others simply reported absolute values of SID, SIG, chloride, anion gap, and SBE in association with mortality prediction rather than attempting to classify various subtypes of metabolic acidosis [15,20,24]. Still others used a combination of quantitative acid−base variables and the sodium/chloride ratio [30] or absolute chloride levels [21,80] to further classify disorders. Table 1 summarizes several recent studies using the same physical chemical approach to address acid−base disorders. Even though the authors all applied the same methodology to identify acid−base disorders, each one used different classification schemes to describe the acid−base state. The absence of a uniform classification system and different study designs limit our ability to appreciate fully the incidence of the various acid−base categories. For example, the incidence of unmeasured anions contributing to metabolic acidosis ranged from 37% to 98%. Lactate as the major contributing ion had an even wider distribution, from almost 10% to 85%. Until the nomenclature can become standardized, the true incidence of acid−base disorders may never be fully appreciated.

We recommend the use of a classification system that is based on physicochemical principles and the predominant anion responsible for the acidosis (Fig. 2). In this system, metabolic acidosis is defined as a SBE below 2 mEq/l; lactic acidosis is an acidosis in which lactate accounts for more than 50% of the SBE; in SIG acidosis the SIG (unmeasured ions) accounts for more than 50% of SBE (in the absence of lactic acidosis); and hyperchloremic acidosis is defined a SBE below −2 mEq/l that is not accounted for by lactate or SIG. As one can see, an absolute level of chloride was not used for the definition of hyperchloremic acidosis because it is the relative relationship between the sodium and chloride concentrations that contribute to the SIDa, which is one of the independent variables that comprise acid−base equilibria. Therefore, if a metabolic acidosis is present and the SIG or lactate does not make up the majority of the acid load, then the only strong ion left is chloride. For example, let us consider a scenario in which the SBE is −8 mEq/l, lactate is 2 mEq/l, and SIG is 2 mEq/l. In this scenario, lactate and SIG together account for only 50% of all of the (−) charges, as represented by the SBE of −8 mEq/l. There remain 4 mEq/l of unaccounted anions that would be explained by a proportional excess of Cl^- in relation to Na^+. Thus, the final classification would be hyperchloremic metabolic acidosis, regardless of the absolute Cl^- level.

Figure 2
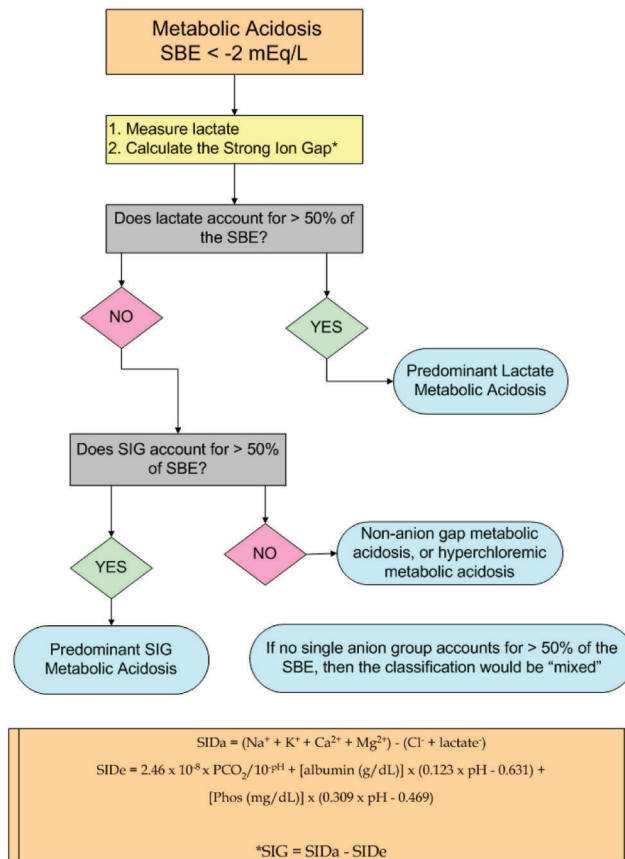
Proposed metabolic acidosis classification flow diagram based on the contributing anion group. This flow diagram is one proposed way to classify metabolic acidosis based on the major contributing anion group. The definition of metabolic acidosis component is a standard base excess (SBE) below −2 mEq/l. It is not based on pH because of the possibility of respiratory compensation. SIDa, apparent strong ion difference; SIDe, effective strong ion difference; SIG, strong ion gap.

This classification system will serve two major purposes. First, we will have a way to describe consistently the predominant anion that drives the acid−base status. This may potentially contribute to a clearer understanding of the underlying pathology. Second, by using the quantitative approach, the clinician can still recognize a sizeable contribution of other anions, regardless of the predominate anion. An example would be that of a patient with a predominant hyperchloremic metabolic acidosis but with a substantial amount of unaccounted anions (SIG), even though SIG may not account for more than 50% of the SBE. In this case, the clinician may consider whether to pursue a possible diagnosis of concomitant ethylene glycol toxicity (or other unmeasured anions) along with the hyperchloremia.

Our classification scheme leaves open the possibility that a combined lactic and SIG acidosis could be misclassified as

hyperchloremic. Conversely, some cases of hyperchloremic acidosis could also be misclassified as either SIG or lactic acidosis if pre-existing or concomitant metabolic alkalosis was also present, reducing the apparent impact of chloride. However, these limitations exist with any acid–base classification scheme, and given that hyperchloremic acidosis is defined on the basis of 'acidosis without an anion gap', rather than on the basis of chloride levels, some imprecision is always going to be present.

Conclusion

Acid–base disorders in critically ill patients are common. Traditional approaches used to measure acid–base disorders may actually underestimate their presence. Currently, the relationship between metabolic acidosis and clinical outcome remains uncertain, but it appears that a difference in mortality may depend on the varying contribution of causative anions. Major limitations in the interpretation of current literature evaluating outcomes can be condensed into three areas: varying results based on technologic differences between flame photometry, indirect ISEs, and direct ISEs; lack of consistent nomenclature classifying subgroups of metabolic acidosis; and confounding of results by administration of medications or fluids used for resuscitation that will exogenously elevate the SIG (e.g. gelatins). These limitations can and should be addressed in future study designs. Without consistency in reporting acid–base methodology, conflicting reports will continue.

Competing interests

The author(s) declare that they have no competing interests.

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