CHAPTER 66

Metabolic Acidosis

Fernando G. Zampieri

OBJECTIVES

This chapter will:

1. Provide a brief review of the quantitative (physiochemical) approach.
2. Describe the effects of acidosis in human physiology.
3. Describe the source of body acids during health and major critical care syndromes through the lens of the physiochemical approach.
4. Discuss the association between metabolic acid type and outcome in critically ill patients.
5. Provide therapeutic considerations.

BRIEF REVIEW OF THE QUANTITATIVE APPROACH

The traditional bicarbonate-based approach to acid-base equilibrium is not perfect and may not provide a sufficiently detailed analysis of acid-base balance. Constraints in the Henderson-Hasselbalch approach led to the development of the pivotal concept of base excess (BE) in the 1960s and, more recently, to the physiochemical approach described by Stewart. This latter approach is a hybrid conceptualization that relies on the electrical neutrality and conservation of mass principles to model the components of acid-base status in a single framework, as discussed in Chapter 64. The model is based on six thermodynamic equations (Table 66.1). Therefore the major difference in the physiochemical approach is its ability to account for changes in weak acids, especially albumin, which are frequent in critically ill patients. As Morgan stated, Stewart's approach is a reminder that the pH of a given solution is a "function of water dissociation modified by pCO_2, other weak acids and certain electrolytes."[1] That is to say that the major determinants of pH are as follows:

1. CO_2
2. The strong ion difference (SID), defined as the difference between the sum of strong cations and the sum of strong anions[2]:

$$SID = [Na^+] + [K^+] + [Mg^{2+}] + [Ca^{2+}] - [Cl^-] - [Lactate^-]$$

   This strong ion difference is usually referred to as "apparent" or "measured" SID (SID_a).
3. Weak acids (termed A_{tot}), which are partially dissolved in water and are mainly constituted of albumin and phosphate

SID can be estimated both through "apparent" SID or using values of CO_2 and A_{tot}. This latter measurement is termed "effective" SID as is calculated as:

$$SID_e = 2.46 \times 10^{-8} \times pCO2/(10^{-pH}) + Albumin \times (0.123 \times pH - 0.631) + Phosphate \times (0.309 \times pH - 0.469)$$

Because not all anions are accounted for in SID_e, there is a small difference ("gap") between measured and effective SID, which can be seen as an equivalent of all unmeasured anions present in plasma. This gap is termed the strong ion gap (SIG) and is usually present in plasma at low (<2 mEq/L) concentrations.[3] The SIG is therefore conceptually similar to the concept of anion gap (AG). In fact, when AG is corrected for albumin, phosphate, and lactate levels, its value shows good agreement with SIG.[4–6]

For the remainder of this chapter, we will refer to metabolic acidosis as the presence of a low SID (<32) with or without an increase in SIG. A list of causes of metabolic acidosis according to SIG values is shown in Table 66.2. For readers who are unfamiliar with the physiochemical approach, the corrected anion gap for albumin, lactate, and phosphate may be considered interchangeable for the sake of interpretation for the remainder of this chapter.[4,7]

TABLE 66.1

Thermodynamic Equations That Describe Human Plasma

THERMODYNAMIC PRINCIPLE	EQUATION	VARIABLES AND CONSTANT
Water dissociation equilibrium	$[H^+] \times [OH^-] = K'w$	K′w is the autoionization constant for water
Electrical neutrality equation	$[SID^+] + [H^+] = [HCO_3^-] + [A^-] + [CO_2] + [OH^-]$	SID = $Na^+ + K^+ - Cl^- -$ Lactate$^-$
Weak acid dissociation equilibrium	$[H^+] \times [A^-] = K_a \times [HA]$	K_a is the weak acid dissociation constant for HA
Conservation of mass for "A"	$[A_{tot}] = [HA] + [A^-]$	A_{tot} is the total concentration of weak acids
Bicarbonate ion formation equilibrium	$[H^+] \times [HCO_3^-] = K \times S \times pCO_2$	K is apparent equilibrium constant for the Henderson-Hasselbalch equation, and S is the solubility of CO_2 in plasma
Carbonate ion formation equilibrium	$[H^+] \times [CO_3^{2-}] = K3 \times [HCO_3^-]$	K3 is the apparent equilibrium dissociation constant for bicarbonate

TABLE 66.2

Causes of Metabolic Acidosis According to Strong Ion Gap

<5 mEq/L	>5 mEq/L
Lactic acidosis[a]	Ketoacidosis
Unbalanced crystalloids	Toxicity (alcohols, toluene, cyanide, isoniazid)
Renal tubular acidosis	Acute renal failure
Loss of high SID solutions (diarrhea)	Unmeasured anions acidosis
Chronic renal failure	
Total parenteral nutrition	

[a]If lactate is not accounted for in SID, it will be included in SIG; therefore Lactic acidosis can be considered an acidosis with high or low SIG depending on the availability to measure lactate.
SID, Strong ion difference; *SIG,* strong ion gap.

EFFECTS OF ACIDOSIS IN HUMAN PHYSIOLOGY

The presence and relevance of acidosis is not restricted to critically ill patients. In a large cohort of more than 4000 patients, more than one quarter had bicarbonate levels below 23 mEq/L.[8] Interestingly, lower bicarbonate levels were associated with inflammatory markers, such as higher leukocyte count and higher C-reactive protein levels, suggesting that there is an interplay between inflammation and acid-base status (which probably is, as one would expect, mediated by comorbidities).

This interplay between acidosis and inflammation is especially relevant during illness states, because several immune response mechanisms may be affected by changes in pH.[9,10] Acidosis, for example, may impair lymphocyte cytotoxicity and proliferation, while increasing complement activation and antibody binding to leukocytes.[11] In addition, acidosis may enhance the inflammatory effects of interleukin 1b in a *Pseudomonas aeruginosa* sepsis model.[12] Studies at the cell level suggest that the addition of chloridric acid produces inflammation mediated by nuclear-factor- κB, resulting in tissue necrosis factor (TNF) production.[9] Those studies also suggest that production in nitric oxide also may be increased by low pH levels.[13] The effect, of course, is dependent on the type and major determinant of the acidosis. It has been hypothesized that non-lactic acidosis would tend to induce a more proinflammatory pattern than lactic acidosis.[9] Parts of these findings have been supported recently in critically ill patients, where the type of acidosis was related to the inflammatory profile.[10] These findings highlight that acid-base always should be considered inside the context of host response to an aggressor force and not as an isolated figure.

Acidosis has a myriad of other effects in normal physiology. The most striking include its role in modulating hemoglobin oxygen affinity (Bohr effect), thereby allowing for greater tissue oxygen delivery when pH is low[14,15]; this apparently beneficial effect, however, may vanish shortly because of a reduction of 2,3-diphosphoglyceric acid in red blood cells.[16] In the lungs, acidosis will promote vasoconstriction and may enhance pulmonary hypoxic vasoconstriction.[17] Tidal volume increases with acidosis, while respiratory rate is less affected. Acidosis is associated with hyperkalemia (because of potassium shift) and hypercalcemia and also has been suggested to reduce glomerular filtration rate and effective plasma renal flow.[18] Hyperchloremia specifically has been associated with intrarenal vasoconstriction by a thromboxane-mediated mechanism.[19]

The central nervous system vasculature is exquisitely sensitive to changes in pH, but because of the presence of the blood-brain barrier, CO_2 (in the short term) is the most important determinant of central nervous system fluid pH. In the digestive and endocrine system, acidosis will reduce intestinal mobility[20] and increase cortisol and aldosterone production.[21] Acidosis also may impair coagulation by reducing clot strength and increasing clot formation time.[22]

There is a host of cardiovascular effects associated with acidosis and, again, the main acidosis determinant may play an important role. Acidosis may depress myocardial contractility[14] (partly because it may induce hyperkalemia[23]), but this effect is usually offset by the increase in catecholamine release induced by acidosis.[24] In the peripheral vascular system, acidosis will induce arteriolar vasodilation (again, partially compensated by increase in sympathetic tone) and venoconstriction. It has been suggested that lactic acidosis could produce deleterious effects in the cardiovascular system, including a reduction in calcium sensitivity to myofilaments, induction of myocardial apoptosis, membrane hyperpolarization, and inhibition of ATP production.[25] Nevertheless, other types of acidosis are not innocuous. Induction of hyperchloremia has been shown to decrease blood pressure in a rat model of acidosis, suggesting that hyperchloremia may not be innocuous for hemodynamics.[26] Hyperchloremia may decrease blood pressure as a result of an increase of the acetylcholine effect.[27] Another potential side effect of hyperchloremia is the reduction of glomerular filtration rate, an effect that has been suggested in animal models[19,28,29] and in human volunteers.[30]

Sources of Acids in Health and Disease

The living human body is an acid-production machine. More than 150 g of H^+ is produced daily in the form of fixed (i.e., nonvolatile) or volatile acids (mainly carbonic acid), which must be eliminated to keep hydrogen (H^+), and therefore pH, within a very narrow range.[31] This is an essential physiologic task that is performed by the lungs and liver. The name "metabolic acidosis" is used to describe the situation in which an abnormal increase in acid load occurs because of an accumulation of fixed (nonvolatile) acids for a given reason. As is the case with any demand and capacity problem, the accumulation of nonvolatile acids may be due to an excess of its production, a reduction of its clearance, or both. In addition, several types of acids may accumulate, producing acid-base pictures that may appear similar (when measured with traditional approaches, ignoring the role of A_{tot}), but could have profoundly different consequences to homeostasis and patient outcome. The intrinsic nature of metabolic acidosis is therefore neither good nor bad and may be either appropriate or harmful depending on the degree and context.

Acids usually are produced during the metabolism of proteins, carbohydrates, and fat; in a global sense, ATP hydrolysis implies production of H^+ (more than 90% of all H^+ produced comes from ATP hydrolysis[32]). Incomplete metabolism of carbohydrates, lipids, and proteins produces acids. Glycolysis converts glucose into pyruvate ($CH_3CO\text{-}COO^-$) and H^+, with two molecules of H^+ produced for each glucose molecule consumed. In the absence of oxygen (or when pyruvate is unable to enter and be metabolized by the mitochondria), pyruvate is reduced to lactate (see later in this chapter). Daily lactate turnover is close to 1500 mEq, with the liver and the kidney accounting for most of its

clearance.[32] Triacylglycerol degradation produces acid during their conversion to free fatty acids and through metabolism to ketone bodies (acetoacetate, acetone, β-hydroxybutyrate, which are the hallmark of diabetic ketosis). Finally, amino acid metabolism accounts for most of the daily production of fixed acids (mostly sulphate and phosphate). The conversion of ammonia to urea in the liver also increases H^+, because it consumes ATP.

For a simple approach at the critical care bedside, the physician has three major possibilities when faced with metabolic acidosis: lactic acidosis (a special case of low SID acidosis), SIG acidosis (unmeasured anions acidosis), and hyperchloremia (i.e., low SID, low lactate, low SIG). The presence of high SIG acidosis should prompt the evaluation of toxins and/or poisons in appropriate clinical contexts (as discussed in Chapter 71).

Lactate metabolism, and its role in health and disease, deserves special attention. Please refer to Chapter 67 in this book for more information. More than 1500 mEq of lactate are produced each day in the human body. Traditionally, hyperlactemia has been classified as type A (when there is tissue hypoxia) and type B (not associated with tissue hypoxia and anaerobic metabolism). This classification is mostly theoretical and frequently both mechanisms also may exist. Lactate levels may increase because of poor shuttling (in patients with kidney or liver injury), accelerated glycolysis, cytopathic hypoxia, and dysoxia.[33–35] More than one mechanism may occur in the same clinical picture.[36] Elevated lactate levels are common in critically ill patients, with more than 40% of all admitted patients presenting at least one episode of increased lactate levels during their stay in the intensive care unit (ICU).[37]

Hyperchloremia is by far the most common cause of low SID, low SIG, non-lactic acidosis. Four main mechanisms can account for hyperchloremia in critical illness (Box 66.1). Hyperchloremia may be iatrogenic, related to copious use of large volumes of solutions with low SID, whose prototype is NaCl 0.9%. In fact, the SID of the infused solution is linearly associated with change in plasma SID[38]; any infused solution with an SID lower than 24.5 mEq/L is theoretically capable of inducing metabolic acidosis.[39] Hyperchloremia is a frequent cause of metabolic acidosis once the initial resuscitation (or salvage) phase of intensive care has passed.[40] Interestingly, the picture of a late phase acid-base profile in the ICU frequently involves some degree of hyperchloremic acidosis that is partially offset by low albumin levels.[40] Another potential source of hyperchloremia in critically ill is an increase in urinary SID resulting from acute kidney injury, resulting in a reduction of a net excretion of chloride and therefore in a decrease of serum SID[41,42]; in fact, the association of low urinary chloride and acute kidney injury has been long known.[43] It has been suggested that low urinary chloride could be a major determinant of chloride serum levels shortly after ICU admission.[42] Hyperchloremia may be due to chloride shift to intravascular spaces. In an endotoxemia model, Kellum has shown that more than 52% of all acid load could not be explained by lactate, CO_2, or exogenous chloride load, therefore suggesting a potential role for compartment shift.[44] A reduction in serum negative charges resulting from reduced serum albumin could play a role in chloride shift. Finally, hyperchloremia may arise after loss of high SID fluids (such as pancreatic fistula). Regardless of its origin, hyperchloremia appears to be related to outcome in septic patients, although putative mechanisms are not particularly clear.[45]

In many critical situations (e.g., shock states, increases in catecholamine levels, systemic inflammatory response, intestinal disorders, infection), other anions are produced leading to an increase in unmeasured anions and therefore an increase in SIG.[46] Despite best efforts to identify and measure the nature of unmeasured anions, only 7.9% of all SIG anions can be measured when advanced techniques are applied (mostly amino acids, uric acid, and organic acids).[47] Data from veterinary literature suggest that D-lactate, acetoacetate, and 3-hydroxybutyrate are the most relevant compounds of SIG.[48] These anions may be more frequently produced by the liver.[49] Pyroglutamic acid has been reported as a potential source of SIG in critically ill patients, but this has not been confirmed.[50]

Because several processes coexist, multiple profiles of metabolic acidosis arise in different clinical scenarios. The profiles change not only according to the main underlying condition but also with time.[40] Unmeasured anions may be so prevalent that they could be responsible for most of the metabolic acidosis in patients with diagnosed "lactic" acidosis.[51] We will briefly review the sources of metabolic acidosis in some major clinical syndromes in the ICU.

BOX 66.1

Causes of Hyperchloremia in Critically Ill

Exogenous administration of low SID solution (i.e., NaCl 0.9%)
Reduction of urinary chloride excretion (increase in urinary SID)
Chloride shift to the intravascular space
Loss of high SID body fluid

SID, Strong ion difference.

Sepsis

Metabolic acidosis is common in patients with sepsis and septic shock; nevertheless, the exact incidence of metabolic acidosis in sepsis is largely unknown,[52] with several small studies reporting temporal trends in specific populations.[40,52] Lactic acidosis has been considered the hallmark of acid-base change in sepsis, but this is not the case. It has been more than 15 years since the strict association between anaerobiosis, hyperlactatemia, and sepsis was first questioned,[34] and recent evidence points toward an acid-base profile in infection that is more complex than mere elevation in lactate levels. This does not mean that lactate is not important; in fact, lactate is related intrinsically to outcome in critically ill patients[53] and has been incorporated into the new definitions of septic shock.[54]

In a prospective study of 60 patients with severe sepsis or septic shock admitted to a single tertiary ICU, Noritomi et al.[40] highlighted the complexity and time trends of acid-base variables in sepsis. In brief, most of the acidosis was caused by hyperchloremia (and not because of high lactate levels, as may be presumed). Interestingly, survivors corrected their metabolic acidosis during their ICU stay through reduction of lactate levels and by reduction in SIG. Hypoalbuminemia had an important alkalizing effect in survivors and nonsurvivors.[40]

Malaria is an infectious disease in which acidosis and its components have been studied in greater detail. In this population, despite a high prevalence of hyperlactatemia,[55] SIG was a more important determinant of mortality than lactate.[56] An increase in SIG was associated with illness severity and encephalopathy, with many anions contributing to SIG (mostly hydroxyphenyllactic acid, α-hydroxybutyric

acid, and β-hydroxybutyric acid).[57] In children with meningococcemia, hyperchloremia accounts for the majority of metabolic acidosis occurring after the first 12 hours.[58]

Trauma and Hemorrhagic Shock

In animal models of hemorrhagic shock—the prototype of acidosis induced by reduction in tissue oxygen supply—lactate levels do not account for the entirety of the acid load that is produced, with significant levels of acetate and citrate being involved as well (almost 2.2 mEq/L of each being present in the blood of dogs after major bleeding).[59] In addition, smaller levels of other compounds such as α-ketoglutarate, fumarate, sulfate, and urate also were increased. The same holds true in humans. In a meta-analysis of more than 2000 blood gas analyses from 427 trauma patients, abnormal SIG values were present in 92% of all cases, whereas hyperlactatemia and hyperchloremia occurred in only 18% and 21%, respectively.[60] In patients with trauma and vascular injury, the role of unmeasured anions was confirmed.[61] Additional analyses by the same group confirmed that only SIG (but not lactate, pH, and HCO_3^-) was a good mortality predictor after major injury, with only one survivor having an SIG higher than 5 mEq/L.[62]

Excessive Low SID Solution and Albumin Infusion

Infusion of low SID solutions ("unbalanced") is one important cause of metabolic acidosis. In saline 0.9%, each liter contains 154 mEq of Na+ and Cl^- and therefore has an SID of zero. The addition of NaCl 0.9% to human plasma (which has lower chloride concentrations) tends to disproportionately increase chloride levels, thereby reducing SID and causing acidosis. The speed of infusion is also an important factor, because rapid infusions will result in chloride levels being diluted in plasma water (and thereby cause larger shifts in SID), whereas slower infusions will result in chloride being diluted over the total body water (with smoother, less pronounced, changes in SID).[63] In a recent review, Reddy reported that most (if not all) studies that compared balanced versus unbalanced solutions reported lower pH values and low bicarbonate and/or BE for patients receiving saline.[64]

As was mentioned earlier, multiple mechanisms account for hyperchloremia in critically ill patients (see Box 66.1). In a subanalysis of 4457 patients in the MIMIC II database that received at least some volume of balanced solution,[65,66] there was a weak correlation between the change in serum sodium-chloride difference (day 3 minus day 1 values), and the volume-indexed difference between sodium and chloride load (a proxy of SID load) in the first 2 days after admission, as shown in Fig. 66.1. R^2 for this model was low (7%), suggesting that in clinical practice the difference between sodium and chloride load may not be a major determinant of changes in acid-base. Of course, the impact of normal saline on acid-base may be more pronounced in the short term and under more controlled conditions, such as elective surgery.[63] Nevertheless, the association does exist and hyperchloremia is not a benign bystander in critical illness, as will be discussed. Because fluid type is ubiquitous in the ICU, and moving from unbalanced to balanced solutions is not a cumbersome change in practice, this may represent an important opportunity to improve outcomes.[65]

Albumin frequently is used in critically ill patients for a wide range of reasons. The effects of albumin solution on acid-base are not strictly related to an increase in A_{tot}, but also may cause an increase in SID.[67] In patients submitted to normovolemic hemodilution, the use of 5% albumin solutions is associated with metabolic acidosis.[68]

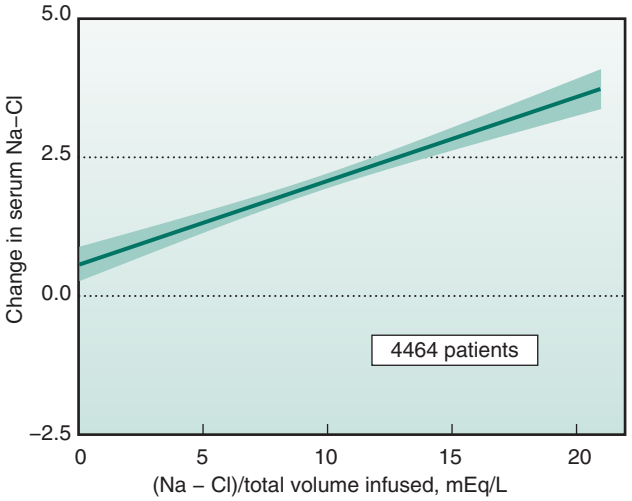

FIGURE 66.1 Association between the volume-indexed difference between sodium and chloride load (a proxy of SID load) for the first 2 days after admission with change in serum sodium-chloride difference in the same time frame. Despite significant ($p < .001$), only a small part of the change in serum sodium-chloride difference could be explained by this proxy of SID load. (Data from Zampieri, et al. from MIMIC-II database, not previously published.)

Gastrointestinal Losses

The metabolic acidosis arising from gastrointestinal losses depends on the type of fluid that is mislaid, a concept that has been known for almost a century.[69,70] As a consequence, acid-base profile can be remarkably different in patients with gastric acid loss, pancreatic fistula, and secretory diarrhea, such as cholera.[69] As a general approach, SID of the drained solution is inversely related to serum SID changes (i.e., loss of pancreatic secretions, which have a low [Cl^-], cause a decrease in serum SID). This relationship is not usually as straightforward as it seems, because other factors (such as acute kidney injury) may superimpose. Cholera is characterized by profuse diarrhea with a loss of approximately 50 mEq of HCO_3^- per liter of stool. That is equivalent to saying that, if the effect of A_{tot} in feces is ignored, feces SID is approximately 50 mEq/L. Nevertheless, despite the major loss of a high SID solution, unmeasured anions appear to be the most predominant cause of metabolic acidosis, with several reports suggesting that sodium and chloride levels may be only slightly altered in cholera patients.[71] Interestingly, an increase in protein levels and in phosphate also may explain a significant part of the acidosis in cholera.[71]

Poisoning

The presence of high SIG with an appropriate clinical background (see Chapter 71) should prompt the clinician to calculate the osmolar gap, as follows:

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

The normal value range for the osmolar gap is lower than 10 mOsm/L; higher values should prompt the investigation of alcohol poisoning and other sources of unmeasured anions. It should be highlighted that poisoning also can affect other components of acid-base values (as discussed in Chapter 71). One such example is the long-known association between methanol poisoning and increase in lactate levels.[72]

Association Between Type of Acidosis and Outcome in Critically Ill Patients

Metabolic acidosis is a risk factor for mortality. Prognosis is usually dismal for patients presenting with extreme acidosis (pH < 7.0), with the exception of ketoacidosis and metformin-induced lactic acidosis.[73,74] In a series of 851 critically ill patients, 548 patients had metabolic acidosis at ICU admission, with higher mortality found predominantly in cases of lactic metabolic acidosis; however, considerable increases in mortality also were found in instances of SIG and hyperchloremic acidosis (56%, 39%, and 29%, respectively).[36] The association between lactic acidosis and mortality also has been demonstrated in several reports[75–77]; nevertheless, the association between unmeasured anions (SIG) and hyperchloremic acidosis and outcome is still less frequently reported and more debatable. Most reports lack sequential evaluation of dynamic aspects of acid-base status and rely on a single measurement to predict outcome. As reiterated in this chapter, acid-base is dynamic, and predicting outcome based on a single measurement is likely to be highly inaccurate.[78]

There is no consensus whether unmeasured anions can predict mortality in critically ill patients.[4,79,80] There are reports of positive association between unmeasured anions in adult[81] and pediatric burn patients,[82] malaria,[56] and in specific subgroups of patients with acute kidney injury.[83] There is a dearth of large studies assessing the significance of unmeasured anions in unselected critically ill patients. A recent meta-analysis assessed whether anion gap or unmeasured anions were associated with worse outcome in critically ill patients. After pooling 12,497 patients from 19 published studies, the observed heterogeneity was high, thus making any effect size estimative unreliable. Nevertheless, AG had good discriminative ability (AUC 0.72; 95 % CI 0.59–0.86). No clear-cut point for worse outcome could be estimated.[84]

Hyperchloremic acidosis recently has gained more attention together with the active discussion regarding balanced versus unbalanced solutions.[85] One of the putative benefits of balanced solutions is reducing hyperchloremic acidosis, which could improve prognosis. Nevertheless, this link is not completely understood at the moment. In addition, not all hyperchloremic patients will develop metabolic acidosis (because hypoalbuminemia, for example, may coexist[40,86]). In a series of septic patients, Neyra et al. have demonstrated that hyperchloremia (serum $[Cl^-] \geq$ 110 mEq/L) is independently associated with worse prognosis. This was particularly true for patients who developed hyperchloremia during their ICU stay.[45] Hyperchloremia was associated with lower base excess levels. The observational nature of the study does not allow mechanistic interpretations, but it is conceivable that hyperchloremia may be just the product of an aggressive saline-based resuscitation followed by acute kidney injury (which may be related to hyperchloremia[87,88]), and not that it is the cause of mortality. Similar results have been shown in cardiac surgery.[89] The potential for deleterious effects from chloride-rich solutions has been shown repeatedly in other observational studies in patients with systemic inflammatory response syndrome,[90] sepsis,[91] and in global intensive care patients.[87]

THERAPEUTIC CONSIDERATIONS

Apart from prognostic considerations, the cause and components of metabolic acidosis have important therapeutic consequences regarding treatment. Metabolic acidosis is corrected when the kidney regenerates serum SID (or, said another way, produces HCO_3^-), when organic acids are metabolized and/or when a high SID solution is infused. Besides management and treatment of the underlying cause of acidosis (e.g., restoration of cardiac output in cardiogenic shock or hemofiltration in particular poisonings[92]), practical questions arise regarding the use of buffers, mainly sodium bicarbonate and THAM (trometamol; tris-hydroxymethyl aminomethane), and use of renal replacement therapy. Four questions are extremely important:

1. **Should predominantly lactic acidosis be corrected by buffer infusion?**

There is a great controversy surrounding the use of sodium bicarbonate in lactic acidosis. Because HCO_3^- is a weak anion, the SID of a $NaHCO_3$ solution is equal to its sodium concentration. Bicarbonate is converted into CO_2, which eventually will be excreted by the lungs. Many experts, and overall consensus, recommend bicarbonate infusion when pH is less than 7.15.[93] Rationale for bicarbonate infusion is related to the correction of the deleterious hemodynamic effects of acidosis. However, such benefits are not clear, and bicarbonate infusion may even be associated with a worsening of intracellular pH[94] and noncorrection of acidosis (especially if ventilation is fixed).[95] A pivotal study in dogs has shown that bicarbonate infusion actually worsened blood pressure and was associated with a further increase in lactate when compared with saline.[96] In a pilot study in humans, Cooper et al. have shown that correcting severe acidemia in patients with lactic acidosis (mean lactate levels of 7.8 mEq/L) failed to improve hemodynamics and was associated with a decrease in serum ionized calcium levels,[97] which could be related to the activation of Na^+/H^+ exchanger (resulting in an increase in intracellular calcium up to toxic values).[98] Therefore the possible benefits of acidosis correction may be masked by profound hypocalcemia induced by abrupt pH increase, as well as by respiratory acidosis resulting from CO_2 increase.[93] It recently has been suggested in animal models that infusion of a Na^+/H^+ exchanger blocker (sabiporide) before $NaHCO_3$ during lactic acidosis may reduce inflammatory response and improve hemodynamic function.[98] Further studies are warranted.

The degree of CO_2 elevation after bicarbonate infusion depends not only on respiratory function but also on hemoglobin and albumin concentrations (i.e., the higher the hemoglobin and albumin, the greater the increase in CO_2).[99] More recently, Kim et al. have shown that bicarbonate use was independently associated with higher mortality in patients with lactic acidosis.[100] We therefore advocate against the preemptive use of bicarbonate in lactic acidosis and in favor of considering other therapies (such as renal replacement therapy) to manage acidosis in this population.

THAM (trometamol; tris-hydroxymethyl aminomethane) is another alternative for the management of critically ill patients.[101] Although most studies assessed its role in the context of mixed acid-base disturbances with increase in

CO_2 (because of THAM's capacity to buffer CO_2),[102] THAM also has been assessed in metabolic acidosis caused by other sources.[103–105] THAM has the theoretical advantages of not worsening intracellular acidosis and not inducing hypernatremia. THAM has not been assessed specifically in patients with overt lactic acidosis, but some case reports suggest it may be useful in metformin-associated lactic acidosis[106] and antiretroviral therapy lactic acidosis.[107]

2. **Should SIG acidosis be corrected by buffer infusion?**

There are scant data on the use of buffers in pure SIG acidosis. Because mixed acid-base abnormalities are the rule, it is unusual to see a pure SIG metabolic acidosis, and therefore there are no studies that assessed the role of buffering in these situations. Efforts should be made to assess osmolar gap in these situations, as discussed before.

3. **Should low SID, non SIG metabolic acidosis be corrected by buffer infusion?**

Apart from the rationale of correcting acidosis, avoiding the reduction in glomerular filtration rate induced by hyperchloremia, and therefore reducing acute kidney injury, is another potential reason to control serum chloride levels in critically ill patients.[104,108] Again, few data are available to advocate for or against alkali use in this situation. In a small pilot study in renal transplant recipients, bicarbonate infusion titrated to control metabolic acidosis was associated with reduced creatinine levels after transplantation.[109] Similar studies in patients undergoing liver transplantation failed to show any benefits of sodium bicarbonate in preventing postoperative acute kidney injury.[110] In the study by Rhem et al., although correction of hyperchloremia is possible with alkali therapy, no clinical end points were assessed.[105]

4. **How does renal replacement therapy (RRT) correct metabolic acidosis?**

RRT corrects metabolic acidosis through multiple mechanisms, including reduction in SIG, increase in SID (resulting from chloride reduction), and reduction in phosphate. The effect is dependent largely upon the dialysate solution used.[111] Metabolic alkalosis that subsides after the first days of RRT is usually a consequence of the aforementioned effects coupled with hypoalbuminemia.[112] Of course, other particularities may be important, such as citrate clearance and baseline SIG levels. Some reports suggest an initial worsening in acidosis after commencement of continuous RRT because of citrate infusion.[113]

CONCLUSION

Metabolic acidosis is a common problem in critically ill patients. There are many subtleties that still demand further study. There is a lack of epidemiologic and practical intervention studies that assess specific therapies according to the predominant mechanism of acidosis. Clinical practitioners should be aware that not all forms of metabolic acidosis are equal and should tailor their treatment depending on context. Provided they are applied correctly, the traditional and physiochemical approaches to diagnosis are acceptable and lead to similar conclusions.[7]

Key Points

1. Metabolic acidosis is common and related to patient prognosis.
2. Acid-base status is dynamic, and several different profiles are found in the same patient over the course of critical illness.
3. Although the prognostic significance of lactic acidosis is clearly established, the exact association between unmeasured anions and hyperchloremia as it relates to prognosis demands further attention.
4. Understanding acid-base has practical therapeutic consequences at the bedside.

Key References

7. Dubin A, Menises MM, Masevicius FD, et al. Comparison of three different methods of evaluation of metabolic acid-base disorders. *Crit Care Med*. 2007;35(5):1264-1270.
9. Kellum JA, Song M, Li J. Science review: extracellular acidosis and the immune response: clinical and physiologic implications. *Crit Care*. 2004;8(5):331-336.
26. Kellum JA, Song M, Venkataraman R. Effects of hyperchloremic acidosis on arterial pressure and circulating inflammatory molecules in experimental sepsis. *Chest*. 2004;125(1):243-248.
30. Chowdhury AH, Cox EF, Francis ST, et al. A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and plasma-lyte® 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. *Ann Surg*. 2012;256(1):18-24.
65. Zampieri FG, Ranzani OT, Azevedo LC, et al. Lactated Ringer's is associated with reduced mortality and less acute kidney injury in critically ill patients: a retrospective cohort analysis. *Crit Care Med*. 2016;Epub ahead.

A complete reference list can be found online at ExpertConsult.com.

References

1. Morgan TJ. The Stewart approach–one clinician's perspective. *Clin Biochem Rev*. 2009;30(2):41-54.
2. Singer RB, Hastings AB. An improved clinical method for the estimation of disturbances of the acid-base balance of human blood. *Medicine (Baltimore)*. 1948;27(2):223-242.
3. Gomez H, Kellum JA. Understanding Acid Base Disorders. *Crit Care Clin*. 2015;31(4):849-860.
4. Zampieri FG, Park M, Ranzani OT, et al. Anion gap corrected for albumin, phosphate and lactate is a good predictor of strong ion gap in critically ill patients: a nested cohort study. *Rev Bras Ter intensiva*. 2013;25(3):205-211.
5. Moviat M, van Haren F, van der Hoeven H. Conventional or physicochemical approach in intensive care unit patients with metabolic acidosis. *Crit Care*. 2003;7(3):R41-R45.
6. Moviat M, van den Boogaard M, Intven F, et al. Stewart analysis of apparently normal acid-base state in the critically ill. *J Crit Care*. 2013;28(6):1048-1054.
7. Dubin A, Menises MM, Masevicius FD, et al. Comparison of three different methods of evaluation of metabolic acid-base disorders. *Crit Care Med*. 2007;35(5):1264-1270.
8. Farwell WR, Taylor EN. Serum anion gap, bicarbonate and biomarkers of inflammation in healthy individuals in a national survey. *CMAJ*. 2010;182(2):137-141.
9. Kellum JA, Song M, Li J. Science review: extracellular acidosis and the immune response: clinical and physiologic implications. *Crit Care*. 2004;8(5):331-336.
10. Zampieri FG, Kellum JA, Park M, et al. Relationship between acid-base status and inflammation in the critically ill. *Crit Care*. 2014;18(4):R154.
11. Lardner A. The effects of extracellular pH on immune function. *J Leukoc Biol*. 2001;69(4):522-530.
12. Torres IM, Patankar YR, Shabaneh TB, et al. Acidosis potentiates the host proinflammatory interleukin-1β response to Pseudomonas aeruginosa infection. *Infect Immun*. 2014;82(11):4689-4697.
13. Huang C-J, Haque IU, Slovin PN, et al. Environmental pH regulates LPS-induced nitric oxide formation in murine macrophages. *Nitric Oxide*. 2002;6(1):73-78.
14. Mitchell JH, Wildenthal K, Johnson RL. The effects of acid-base disturbances on cardiovascular and pulmonary function. *Kidney Int*. 1972;1(5):375-389.
15. Stringer W, Wasserman K, Casaburi R, et al. Lactic acidosis as a facilitator of oxyhemoglobin dissociation during exercise. *J Appl Physiol*. 1994;76(4):1462-1467.
16. Wimberley PD, Whitehead MD, Huehns ER. The effect of acidosis on red cell 2,3-DPG and oxygen affinity of whole foetal blood. *Adv Exp Med Biol*. 1977;94:463-467.
17. Lejeune P, Brimioulle S, Leeman M, et al. Enhancement of hypoxic pulmonary vasoconstriction by metabolic acidosis in dogs. *Anesthesiology*. 1990;73(2):256-264.
18. Farber MO, Szwed JJ, Dowell AR, et al. The acute effects of respiratory and metabolic acidosis on renal function in the dog. *Clin Sci Mol Med*. 1976;50(3):165-169.
19. Bullivant EM, Wilcox CS, Welch WJ. Intrarenal vasoconstriction during hyperchloremia: role of thromboxane. *Am J Physiol*. 1989;256(1 Pt 2):F152-F157.
20. Tournadre JP, Allaouchiche B, Malbert CH, et al. Metabolic acidosis and respiratory acidosis impair gastro-pyloric motility in anesthetized pigs. *Anesth Analg*. 2000;90(1):74-79.
21. Perez GO, Oster JR, Katz FH, et al. The effect of acute metabolic acidosis on plasma cortisol, renin activity and aldosterone. *Horm Res*. 1979;11(1):12-21.
22. Engström M, Schött U, Romner B, et al. Acidosis impairs the coagulation: a thromboelastographic study. *J Trauma*. 2006;61(3):624-628.
23. Blinks JR, Koch-Weser J. Physical factors in the analysis of the actions of drugs on myocardial contractility. *Pharmacol Rev*. 1963;15:531-599.
24. Morris ME, Millar RA. Blood pH/plasma catecholamine relationships: non-respiratory acidosis. *Br J Anaesth*. 1962;34(10):682-689.
25. Kimmoun A, Novy E, Auchet T, et al. Hemodynamic consequences of severe lactic acidosis in shock states: from bench to bedside. *Crit Care*. 2015;19:175.
26. Kellum JA, Song M, Venkataraman R. Effects of hyperchloremic acidosis on arterial pressure and circulating inflammatory molecules in experimental sepsis. *Chest*. 2004;125(1):243-248.
27. Celotto AC, Ferreira LG, Capellini VK, et al. Acute but not chronic metabolic acidosis potentiates the acetylcholine-induced reduction in blood pressure: an endothelium-dependent effect. *Braz J Med Biol Res*. 2016;49(2):e5007.
28. Imig JD, Passmore JC, Anderson GL, et al. Chloride alters renal blood flow autoregulation in deoxycorticosterone-treated rats. *J Lab Clin Med*. 1993;121(4):608-613.
29. Wilcox CS. Regulation of renal blood flow by plasma chloride. *J Clin Invest*. 1983;71(3):726-735.
30. Chowdhury AH, Cox EF, Francis ST, et al. A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and plasma-lyte® 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. *Ann Surg*. 2012;256(1):18-24.
31. Alberti KG, Cuthbert C. The hydrogen ion in normal metabolism: a review. *Ciba Found Symp*. 1982;87:1-19.
32. Morris CG, Low J. Metabolic acidosis in the critically ill: part 1. Classification and pathophysiology. *Anaesthesia*. 2008;63(3):294-301.
33. Gladden LB. Lactate metabolism: a new paradigm for the third millennium. *J Physiol*. 2004;558(1):5-30.
34. James JH, Luchette FA, McCarter FD, et al. Lactate is an unreliable indicator of tissue hypoxia in injury or sepsis. *Lancet*. 1999;354(9177):505-508.
35. Gore DC, Jahoor F, Hibbert JM, et al. Lactic acidosis during sepsis is related to increased pyruvate production, not deficits in tissue oxygen availability. *Ann Surg*. 1996;224(1):97-102.
36. Gunnerson KJ, Saul M, He S, et al. Lactate versus non-lactate metabolic acidosis: a retrospective outcome evaluation of critically ill patients. *Crit Care*. 2006;10(1):R22.
37. Khosravani H, Shahpori R, Stelfox HT, et al. Occurrence and adverse effect on outcome of hyperlactatemia in the critically ill. *Crit Care*. 2009;13(3):R90.
38. Morgan TJ, Venkatesh B, Hall J. Crystalloid strong ion difference determines metabolic acid-base change during in vitro hemodilution. *Crit Care Med*. 2002;30(1):157-160.
39. Dietl K, Renner K, Dettmer K, et al. Lactic acid and acidification inhibit TNF secretion and glycolysis of human monocytes. *J Immunol*. 2010;184(3):1200-1209.
40. Noritomi DT, Soriano FG, Kellum JA, et al. Metabolic acidosis in patients with severe sepsis and septic shock: a longitudinal quantitative study. *Crit Care Med*. 2009;37(10).
41. Maciel AT, Park M, Macedo E. Physicochemical analysis of blood and urine in the course of acute kidney injury in critically ill patients: a prospective, observational study. *BMC Anesthesiol*. 2013;13(1):31.
42. Masevicius FD, Vazquez AR, Enrico C, et al. Urinary strong ion difference is a major determinant of plasma chloride concentration changes in postoperative patients. *Rev Bras Ter intensiva*. 2013;25(3):197-204.
43. Anderson RJ, Gabow PA, Gross PA. Urinary chloride concentration in acute renal failure. *Miner Electrolyte Metab*. 1984;10(2):92-97.
44. Kellum JA, Bellomo R, Kramer DJ, et al. Etiology of metabolic acidosis during saline resuscitation in endotoxemia. *Shock*. 1998;9(5):364-368.
45. Neyra JA, Canepa-Escaro F, Li X, et al. Association of Hyperchloremia With Hospital Mortality in Critically Ill Septic Patients. *Crit Care Med*. 2015;43(9):1938-1944.
46. Forni LG, McKinnon W, Hilton PJ. Unmeasured anions in metabolic acidosis: unravelling the mystery. *Crit Care*. 2006;10(4):220.
47. Moviat M, Terpstra AM, Ruitenbeek W, et al. Contribution of various metabolites to the "unmeasured" anions in critically ill patients with metabolic acidosis. *Crit Care Med*. 2008;36(3):752-758.
48. Gossett KA, Cleghorn B, Adams R, et al. Contribution of whole blood L-lactate, pyruvate, D-lactate, acetoacetate, and 3-hydroxybutyrate concentrations to the plasma anion gap in horses with intestinal disorders. *Am J Vet Res*. 1987;48(1):72-75.

49. Kellum JA, Bellomo R, Kramer DJ, et al. Hepatic anion flux during acute endotoxemia. *J Appl Physiol*. 1995;78(6):2212-2217.
50. Mizock BA, Belyaev S, Mecher C. Unexplained metabolic acidosis in critically ill patients: the role of pyroglutamic acid. *Intensive Care Med*. 2004;30(3):502-505.
51. Maciel AT, Park M. Unmeasured anions account for most of the metabolic acidosis in patients with hyperlactatemia. *Clinics (Sao Paulo)*. Faculdade de Medicina / USP; 2007;62(1):55-62.
52. Kellum JA. Metabolic acidosis in patients with sepsis: epiphenomenon or part of the pathophysiology? *Crit Care Resusc*. 2004;6(3):197-203.
53. Mikkelsen ME, Miltiades AN, Gaieski DF, et al. Serum lactate is associated with mortality in severe sepsis independent of organ failure and shock. *Crit Care Med*. 2009;37(5):1670-1677.
54. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA*. 2016;315(8):801.
55. Day NP, Phu NH, Mai NT, et al. The pathophysiologic and prognostic significance of acidosis in severe adult malaria. *Crit Care Med*. 2000;28(6):1833-1840.
56. Dondorp AM, Chau TTH, Phu NH, et al. Unidentified acids of strong prognostic significance in severe malaria. *Crit Care Med*. 2004;32(8):1683-1688.
57. Herdman MT, Sriboonvorakul N, Leopold SJ, et al. The role of previously unmeasured organic acids in the pathogenesis of severe malaria. *Crit Care*. 2015;19:317.
58. O'Dell E, Tibby SM, Durward A, et al. Hyperchloremia is the dominant cause of metabolic acidosis in the postresuscitation phase of pediatric meningococcal sepsis. *Crit Care Med*. 2007;35(10):2390-2394.
59. Bruegger D, Kemming GI, Jacob M, et al. Causes of metabolic acidosis in canine hemorrhagic shock: role of unmeasured ions. *Crit Care*. 2007;11(6):R130.
60. Martin M, Murray J, Berne T, et al. Diagnosis of acid-base derangements and mortality prediction in the trauma intensive care unit: the physiochemical approach. *J Trauma*. 2005;58(2):238-243.
61. Kaplan LJ, Kellum JA. Initial pH, base deficit, lactate, anion gap, strong ion difference, and strong ion gap predict outcome from major vascular injury. *Crit Care Med*. 2004;32(5):1120-1124.
62. Kaplan LJ, Kellum JA. Comparison of acid-base models for prediction of hospital mortality after trauma. *Shock*. 2008;29(6):662-666.
63. Scheingraber S, Rehm M, Sehmisch C, et al. Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. *Anesthesiology*. 1999;90(5):1265-1270.
64. Reddy S, Weinberg L, Young P. Crystalloid fluid therapy. *Crit Care*. 2016;20(1):59.
65. Zampieri FG, Ranzani OT, Azevedo LC, et al. Lactated Ringer's is associated with reduced mortality and less acute kidney injury in critically ill patients: a retrospective cohort analysisitle. *Crit Care Med*. 2016;Epub ahead.
66. Saeed M, Villarroel M, Reisner AT, et al. Multiparameter Intelligent Monitoring in Intensive Care II: a public-access intensive care unit database. *Crit Care Med*. 2011;39(5):952-960.
67. Bruegger D, Jacob M, Scheingraber S, et al. Changes in acid-base balance following bolus infusion of 20% albumin solution in humans. *Intensive Care Med*. 2005;31(8):1123-1127.
68. Rehm M, Orth V, Scheingraber S, et al. Acid-base changes caused by 5% albumin versus 6% hydroxyethyl starch solution in patients undergoing acute normovolemic hemodilution: a randomized prospective study. *Anesthesiology*. 2000;93(5):1174-1183.
69. Peters JP. Acid-Base Equilibrium and Salt and Water Exchange. *Yale J Biol Med*. 1930;2(3):183-221.
70. Gamble JL, McIver MA. ACID-BASE COMPOSITION OF PANCREATIC JUICE AND BILE. *J Exp Med*. 1928;48(6):849-857.
71. Wang F, Butler T, Rabbani GH, et al. The acidosis of cholera. Contributions of hyperproteinemia, lactic acidemia, and hyperphosphatemia to an increased serum anion gap. *N Engl J Med*. 1986;315(25):1591-1595.
72. Cytryn E, Futeral B. Lactate accumulation in methanol poisoning. *Lancet*. 1983;2(8340):56.
73. Kajbaf F, Lalau J-D. Mortality rate in so-called "metformin-associated lactic acidosis": a review of the data since the 1960s. *Pharmacoepidemiol Drug Saf*. 2014;23(11):1123-1127.
74. Allyn J, Vandroux D, Jabot J, et al. Prognosis of patients presenting extreme acidosis (pH <7) on admission to intensive care unit. *J Crit Care*. 2016;31(1):243-248.
75. Ranzani OT, Monteiro MB, Ferreira EM, et al. Reclassifying the spectrum of septic patients using lactate: severe sepsis, cryptic shock, vasoplegic shock and dysoxic shock. *Rev Bras Ter Intensiva*. 2013;25(4):270-278.
76. Lee S-W, Hong Y-S, Park D-W, et al. Lactic acidosis not hyperlactatemia as a predictor of in hospital mortality in septic emergency patients. *Emerg Med J*. 2008;25(10):659-665.
77. Vernon C, Letourneau JL. Lactic acidosis: recognition, kinetics, and associated prognosis. *Crit Care Clin*. 2010;26(2):255-283, table of contents.
78. Jung B, Rimmele T, Le Goff C, et al. Severe metabolic or mixed acidemia on intensive care unit admission: incidence, prognosis and administration of buffer therapy. A prospective, multiple-center study. *Crit Care*. 2011;15(5):R238.
79. Rocktaeschel J, Morimatsu H, Uchino S, et al. Unmeasured anions in critically ill patients: can they predict mortality? *Crit Care Med*. 2003;31(8):2131-2136.
80. Balasubramanyan N, Havens PL, Hoffman GM. Unmeasured anions identified by the Fencl-Stewart method predict mortality better than base excess, anion gap, and lactate in patients in the pediatric intensive care unit. *Crit Care Med*. 1999;27(8):1577-1581.
81. Berndtson AE, Palmieri TL, Greenhalgh DG, et al. Strong ion difference and gap predict outcomes after adult burn injury. *J Trauma Acute Care Surg*. 2013;75(4):555-60-1.
82. Sen S, Wiktor A, Berndtson A, et al. Strong ion gap is associated with mortality in pediatric burn injuries. *J Burn Care Res*. 2014;35(4):337-341.
83. Zheng C-M, Liu W-C, Zheng J-Q, et al. Metabolic acidosis and strong ion gap in critically ill patients with acute kidney injury. *Biomed Res Int*. 2014;2014:819528.
84. Glasmacher SA, Stones W. Anion gap as a prognostic tool for risk stratification in critically ill patients - a systematic review and meta-analysis. *BMC Anesthesiol*. 2016;16(1):68.
85. Young P, Bailey M, Beasley R, et al. Effect of a buffered crystalloid solution vs saline on acute kidney injury among patients in the intensive care unit. *JAMA*. 2015;314:1701-1710.
86. Boniatti MM, Cardoso PRC, Castilho RK, et al. Is hyperchloremia associated with mortality in critically ill patients? A prospective cohort study. *J Crit Care*. 2011;26(2):175-179.
87. Yunos NM, Bellomo R, Hegarty C, et al. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. *JAMA*. 2012;308(15):1566-1572.
88. Zhang Z, Xu X, Fan H, et al. Higher serum chloride concentrations are associated with acute kidney injury in unselected critically ill patients. *BMC Nephrol*. 2013;14(1):235.
89. McCluskey SA, Karkouti K, Wijeysundera D, et al. Hyperchloremia after noncardiac surgery is independently associated with increased morbidity and mortality: a propensity-matched cohort study. *Anesth Analg*. 2013;117(2):412-421.
90. Shaw AD, Raghunathan K, Peyerl FW, et al. Association between intravenous chloride load during resuscitation and in-hospital mortality among patients with SIRS. *Intensive Care Med*. 2014;40(12):1897-1905.
91. Raghunathan K, Shaw A, Nathanson B, et al. Association Between the Choice of IV Crystalloid and In-Hospital Mortality Among Critically Ill Adults With Sepsis. *Crit Care Med*. 2014;42(7):1585-1591.
92. Holubek WJ, Hoffman RS, Goldfarb DS, et al. Use of hemodialysis and hemoperfusion in poisoned patients. *Kidney Int*. 2008;74(10):1327-1334.
93. Boyd JH, Walley KR. Is there a role for sodium bicarbonate in treating lactic acidosis from shock? *Curr Opin Crit Care*. 2008;14(4):379-383.
94. Kraut JA, Madias NE. Treatment of acute metabolic acidosis: a pathophysiologic approach. *Nat Rev Nephrol*. 2012;8(10):589-601.

95. Gehlbach BK, Schmidt GA. Bench-to-bedside review: treating acid-base abnormalities in the intensive care unit - the role of buffers. *Crit Care*. 2004;8(4):259-265.
96. Graf H, Leach W, Arieff A. Evidence for a detrimental effect of bicarbonate therapy in hypoxic lactic acidosis. *Science*. 1985;227(4688):754-756.
97. Cooper DJ. Bicarbonate does not improve hemodynamics in critically ill patients who have lactic acidosis. *Ann Intern Med*. 1990;112(7):492.
98. Lin X, More AS, Kraut JA, et al. Interaction of sodium bicarbonate and Na+/H+ exchanger inhibition in the treatment of acute metabolic acidosis in pigs. *Crit Care Med*. 2015;43(6): e160-e169.
99. Levraut J, Garcia P, Giunti C, et al. The increase in CO2 production induced by NaHCO3 depends on blood albumin and hemoglobin concentrations. *Intensive Care Med*. 2000;26(5): 558-564.
100. Kim HJ, Son YK, An WS. Effect of sodium bicarbonate administration on mortality in patients with lactic acidosis: a retrospective analysis. *PLoS ONE*. 2013;8(6):e65283.
101. Nahas GG, Sutin KM, Fermon C, et al. Guidelines for the treatment of acidaemia with THAM. *Drugs*. 1998;55(2):191-224.
102. Kallet RH, Jasmer RM, Luce JM, et al. The treatment of acidosis in acute lung injury with tris-hydroxymethyl aminomethane (THAM). *Am J Respir Crit Care Med*. American Thoracic SocietyNew York, NY; 2000;161(4 Pt 1):1149-1153.
103. Hoste EA, Colpaert K, Vanholder RC, et al. Sodium bicarbonate versus THAM in ICU patients with mild metabolic acidosis. *J Nephrol*. 2005;18(3):303-307.
104. Kraut JA, Kurtz I. Treatment of acute non-anion gap metabolic acidosis. *Clin Kidney J*. 2015;8(1):93-99.
105. Rehm M, Finsterer U. Treating intraoperative hyperchloremic acidosis with sodium bicarbonate or tris-hydroxymethyl aminomethane: a randomized prospective study. *Anesth Analg*. 2003;96(4):1201-1208, table of contents.
106. Lam N, Sekhon G, House AA. Metformin-associated lactic acidosis following intentional overdose successfully treated with tris-hydroxymethyl aminomethane and renal replacement therapy. *Case Rep Nephrol*. 2012;2012:671595.
107. Marfo K, Garala M, Kvetan V, et al. Use of Tris-hydroxymethyl aminomethane in severe lactic acidosis due to highly active antiretroviral therapy: a case report. *J Clin Pharm Ther*. 2009;34(1): 119-123.
108. Adeva-Andany MM, Fernández-Fernández C, Mouriño-Bayolo D, et al. Sodium bicarbonate therapy in patients with metabolic acidosis. *Sci World J*. 2014;2014:627673.
109. Etezadi F, Pourfakhr P, Mojtahedzade M, et al. Effects of tight versus non tight control of metabolic acidosis on early renal function after kidney transplantation. *Daru*. 2012;20(1):36.
110. Weinberg L, Broad J, Pillai P, et al. Sodium bicarbonate infusion in patients undergoing orthotopic liver transplantation: a single centre randomized controlled pilot trial. *Clin Transplant*. 2016;Feb 23.
111. Naka T, Bellomo R. Bench-to-bedside review: treating acid-base abnormalities in the intensive care unit–the role of renal replacement therapy. *Crit Care*. 2004;8(2):108-114.
112. Rocktäschel J, Morimatsu H, Uchino S, et al. Impact of continuous veno-venous hemofiltration on acid-base balance. *Int J Artif Organs*. 2003;26(1):19-25.
113. Naka T, Egi M, Bellomo R, et al. Low-dose citrate continuous veno-venous hemofiltration (CVVH) and acid-base balance. *Int J Artif Organs*. 2005;28(3):222-228.