Sodium Bicarbonate in Different Critically Ill Conditions

From Physiology to Clinical Practice

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The goal of intensivists is to restore all of a patient's physiologic balances as soon as possible, generally by seeking and treating the cause(s) of any alteration. However, even though acute metabolic acidosis is common among critically ill patients, its mechanisms are complex, making it difficult to identify the cause. Consequently, attention often shifts from treatment of the cause to correction of the pH.

Acidemia is defined as pH less than 7.38, and severe acidemia as pH of 7.20 or lower.[1] The combination of low pH with a plasma bicarbonate concentration less than 20 mM defines metabolic acidosis, which is one of the most frequent acid–base disorders occurring in intensive care unit (ICU) patients, with an incidence ranging from 14 to 42%.[2,3] In contrast, acute severe metabolic acidemia—when plasma pH is lower than 7.20—has an incidence of 6% and related ICU mortality of 57%.[4]

Acute metabolic acidosis is considered responsible for several detrimental effects including impaired cardiac contractility, systemic vasodilatation, pulmonary vasoconstriction, arrhythmias, altered oxygen delivery, altered renal blood flow, cerebral edema, diaphragm dysfunction, energy failure with decreased adenosine triphosphate production, and immune response impairment.[4] It may also reduce the potency of catecholamine vasopressors.[4,5] In the ICU, the most common causes of metabolic acidosis are lactic acidosis, ketoacidosis, renal failure, loss of enteric fluid (*e.g.,* diarrhea and pancreatic fistula), saline administration, and poisoning.

However, independent from the cause and the underlying illness, correcting pH by intravenous bicarbonate infusion in critically ill patients with metabolic acidosis is commonly considered a key therapeutic endpoint. Although there is still debate from a physiologic point of view as to whether the acidosis itself is harmful or is just a marker of the underlying pathology, raising extracellular pH can restore cardiovascular function and oxygen delivery to tissues.[6,7]

Since acidosis is often associated with shock, bicarbonate administration is mainly intended to combat the cardiovascular effects, including myocardial dysfunction, vasopressor resistance, and ventricular arrhythmias. However, bicarbonate's potential physiologic consequences also include a sudden increase in hemoglobin–oxygen affinity, through the Bohr effect, hypercapnia,[8–10] a hyperosmolar state,[11] low plasma calcium concentration because of chelation by albumin, and increases in glycolytic pathways and lactate production. Intravenous bicarbonate also seems to have a role in preventing acute kidney injury (AKI) after the use of contrast medium, cardiac surgery, or liver transplantation.

It is clearly impossible to review every facet of this topic, so this review focuses on the rationale for the use of bicarbonate in the management of acute respiratory and metabolic acidosis and the prevention of AKI in different critically ill conditions.

Acid–Base Approaches

Two widely used approaches to understand the changes in acid–base balance are the Henderson–Hasselbach and the Stewart method. They differ only in the assessment of the metabolic component.

The Henderson–Hasselbach approach is based on the measured concentrations of bicarbonate and carbon dioxide: $CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$. Carbon dioxide and carbonic acid are considered independently regulated by the lungs (excreting carbon dioxide) and the kidneys (filtering and reclaiming bicarbonate), respectively.

The kidneys respond to acid–base equilibrium by acting on renal acid excretion as free hydrogen ions or hydrogen in the form of ammonium, and renal bicarbonate excretion. Up to 85% of the filtered bicarbonate is resorbed in the proximal tubule where cytosolic hydrogen ions are secreted into the lumen; then they combine with tubular bicarbonate to form carbon dioxide, which can readily diffuse into epithelial cells. Once inside the tubular epithelial cell, the generated carbon dioxide is reconverted to a hydron and bicarbonate ion by carbonic anhydrase. The bicarbonate is transported through the basolateral membrane and into the blood.

This is a descriptive method and cannot quantify any metabolic acid component other than carbonic acid. To assess the severity of the metabolic acidosis or alkalosis, base excess has been introduced; however, this suffers some

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inaccuracy *in vivo* and does not explain the mechanisms of the metabolic acid–base disorders. To understand how the pH and carbonic acid concentration are altered independently from partial pressure of carbon dioxide, we have to look beyond Henderson–Hasselbach.

The Stewart approach is a physical–chemical analysis based on the concept that all cation and anion concentrations must balance according to the law of electroneutrality. There are three independent determinants of pH: the carbon dioxide produced by cell metabolism, the weak acids (mainly albumin and phosphate), and the strong ion difference ($[Na^+] + [K^+] + [Ca^{++}] + [Mg^{++}] - [Cl^-] - [\text{other anions}]$). Metabolic acidosis is produced by a decrease in the strong ion difference, which can be brought about by the generation of organic anions (*i.e.*, lactate, ketones), the loss of cations (renal tubular acidosis), or the increase of anions (addition of exogenous anions or increase in phosphate).[12] The essence of this approach is that neither hydron nor carbonic acid can change unless one of these independent variables changes. The merit of the Stewart approach is to unify the acid–base and the electrolyte equilibrium, serving as a quantitative method to understand the interactions within the body fluids.[12]

Strong ion difference refers to the difference between the strong cations and the strong anions (apparent strong ion difference) or the sum of the charge contribution of carbon dioxide, albumin, and phosphate (effective strong ion difference). In this sense, the effective strong ion difference is identical to the buffer base as the sum of bicarbonate and nonvolatile weak acid buffers[13] (fig. 1).

This holistic view can clarify conditions that are inexplicable by other methods, such as the hyperchloremic acidosis associated with saline fluid resuscitation and the hyperlactatemia at normal pH and base excess with concomitant alkalosis.[1] In our opinion, this is the only method with which one can analyze pathophysiology and plan treatment.[15]

Acute Respiratory Acidosis

In patients with acute respiratory distress syndrome, mechanical ventilation is commonly used to improve the gas exchange and reduce the work of breathing. However, the mechanical forces generated can promote ventilator-induced lung injury.[16] One way to limit ventilator-induced lung injury is to reduce the mechanical ventilation, but this causes an increase in $Paco_2$, an approach called permissive hypercapnia.[17,18] It is not clear whether hypercapnia and the associated acidemia, independent from mechanical ventilation, have beneficial or harmful effects.

Though the evidence for buffering the acidosis with sodium bicarbonate is not clear, it is common in clinical practice.[17] In a seminal randomized controlled trial on lung-protective ventilation in the presence of respiratory acidosis, sodium bicarbonate was allowed.[19] However, with reduced and constant mechanical ventilation, sodium bicarbonate did not raise the arterial blood pH but did increase carbon dioxide.[20] Furthermore, it actually reduced arterial blood pressure and cardiac output.[21,22] Respiratory acidosis is associated with intracellular and extracellular changes in pH, and the intracellular acidosis can further increase in response to sodium bicarbonate, because of a "paradoxical" acidosis due to the free diffusion into the cells of carbon dioxide generated by bicarbonate.[23,24]

Acute Metabolic Acidosis

According to the Stewart approach, the administration of sodium bicarbonate raises pH by increasing the concentration of plasma sodium relative to chloride, rather than simply adding a bicarbonate buffer to the system, since it is instead rapidly converted to carbon dioxide.[25] In aqueous solutions, fully dissociated sodium behaves as a strong ion, whereas bicarbonate behaves like a weak acid since it exists in equilibrium with dissolved carbon dioxide that rapidly diffuses across cellular membranes, increasing intracellular partial pressure of carbon dioxide, with possible worsening of the intracellular acidosis (fig. 2). Surveys and observational studies have reported that, in daily clinical practice, more than half of critical care physicians consider bicarbonate infusion for a patient with severe metabolic acidemia, whatever its cause.[7]

However, not only is the rationale for this therapy weak, but evidence from the literature is too. A prospective study that enrolled more than 1,700 patients with sepsis and acute metabolic acidosis from 2001 to 2012 reported that patients who received sodium bicarbonate during the first 48 h after ICU admission did not show any improvement in outcome.[26]

Two multicenter randomized trials evaluated the effect of intravenous bicarbonate infusion in patients with acute metabolic acidosis with different causes. The first study enrolled critically ill patients with severe metabolic or mixed acidemia treated with intravenous bicarbonate compared with those who were not, independent from the severity of the acidosis. There were no differences in the need for vasopressors, length of mechanical ventilation, or mortality.[4]

The second study, a multicenter randomized controlled trial (Sodium Bicarbonate Therapy for Patients with Severe Metabolic Acidaemia in the Intensive Care Unit),[27] in 400 critically ill patients with severe acidemia (pH less than 7.2; $Paco_2$, 45 mmHg; lactate greater than 2 mM), found that early bicarbonate infusion, with a target pH of 7.30, did not reduce 28-day mortality and the incidence of at least one organ failure by day 7, except for a decrease in the need for renal replacement therapy.[27] However, up to 16% of the patients in the bicarbonate group had at least one blood pH greater than 7.45 during the study, which may explain several side effects such as increased lactic acid production and hypocalcemia, as well as a decrease in cardiac contractility.[28]

These data suggest the importance of strict laboratory and blood gas monitoring during bicarbonate infusion to

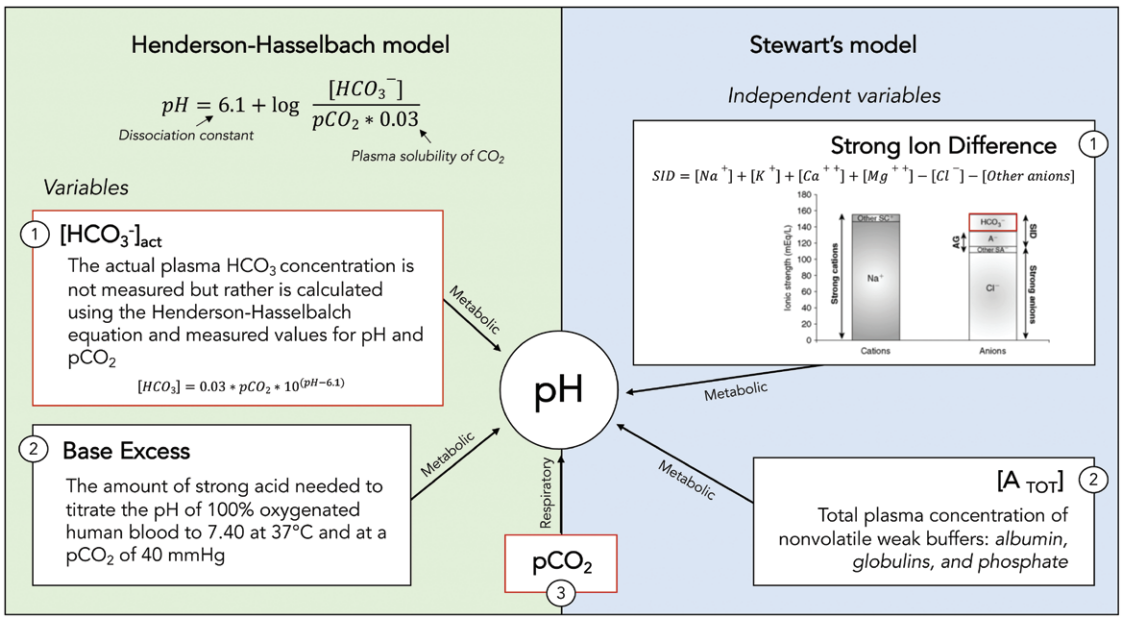

Fig. 1. Differences between the conventional and Stewart approach. According to the Stewart model, variables independently determine the pH in order to maintain electrical neutrality: (1) strong ion difference (SID); (2) total concentration of weak acids; and (3) partial pressure of carbon dioxide of the solution. Thus, with the Stewart approach, metabolic disorders are the results of changes in strong ion difference or total concentration of weak acids. According to the Henderson–Hasselbach equation, pH is proportionate to the ratio of bicarbonate (HCO_3) to $Paco_2$. This considers bicarbonate one of the strongest buffers and determinants of pH in our physiologic system. To separate the metabolic and respiratory components in acid–base disorders, the concept of base excess was first introduced by Siggaard-Andersen.[14] Base excess represents the amount of acid or alkali that must be added to 1 liter of oxygenated blood, exposed *in vitro* to a partial pressure of carbon dioxide of 40 mmHg, to achieve the average normal pH of 7.40. Blood base excess measures the metabolic component that is independent from the respiratory component and incorporates the effect of hemoglobin as a buffer. A_{TOT}, concentration of nonvolatile weak buffers.

rapidly detect any side effects. A recent systematic review highlighted the lack of data on the effects of intravenous sodium bicarbonate in critically ill patients with metabolic acidosis and called for further studies.[29]

Gastrointestinal Losses

In normal conditions ,the gastrointestinal tract can maintain a physiologic acid–base balance by exchange of the strong ions in the different parts. According to the traditional approach, during acute colonic diarrhea, metabolic acidosis can result from gastrointestinal bicarbonate excretion while, according to the Stewart approach, intestinal fluids pass through too fast to be properly processed, so water and sodium are no longer reabsorbed, promoting metabolic acidosis.[30] It has therefore been suggested that sodium bicarbonate could be used to compensate gastrointestinal losses in case of poor clinical tolerance.[1]

Lactic Acidosis

Lactic acidosis is the consequence of the increase of strong anions in the Stewart approach or the decrease of the bicarbonate as buffer. Kellum argued against treating lactic metabolic acidosis with intravenous bicarbonate,[31] while the Surviving Sepsis Campaign suggested not infusing bicarbonate for lactic acidosis when plasma pH is greater than 7.15 but gave no recommendations for pH below this threshold.[32]

Some studies have set out to assess the effect of sodium bicarbonate for lactic acidosis on hemodynamics, electrolyte changes, and mortality.[33–35] In a single-center retrospective study of 36 septic patients with lactic acidosis, when pH was less than 7.3, the bicarbonate infusion did not affect the median time until reversal of shock or hospital mortality, but did significantly shorten the length of the intensive care stay compared to standard therapy.[36]

Cooper *et al.* reported that raising the pH to 7.36 after bicarbonate infusion in 14 patients with lactic acidosis did not improve cardiac output or their cardiovascular response to circulating catecholamines, although it did lower ionized calcium and raise $Paco_2$.[33] Similarly, Mathieu *et al.* found no differences in hemodynamic variables in patients with lactic acidosis receiving sodium bicarbonate or an equal volume of sodium chloride, in random order, while the oxygen extraction ratio rose significantly.[34]

None of these studies could draw any conclusions in terms of morbidity and mortality. However, in a

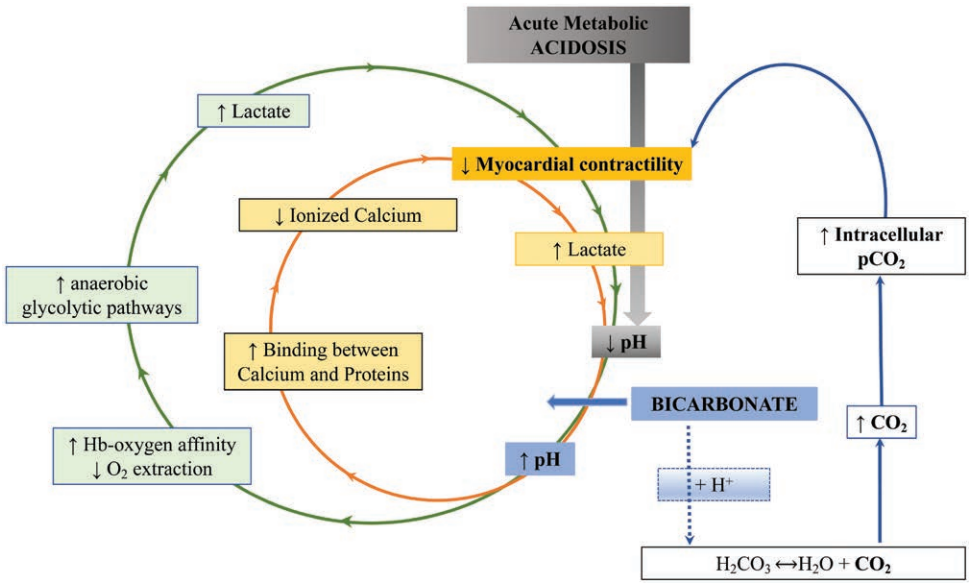

Fig. 2. The vicious or virtuous circle of sodium bicarbonate infusion and acute metabolic acidosis. The physiologic effects of bicarbonate during metabolic acidosis can further enhance the effects of the metabolic acidosis *per se*. The sudden rise of pH after bicarbonate can, on one hand, lead to an increase in hemoglobin–oxygen affinity by the Bohr effect in glycolytic pathways and lactate production, and on the other, a decrease in plasma Ca^{2+} because of chelation by albumin with consequent impaired myocardial contractility and increased lactate production. Moreover, bicarbonate behaves like a weak acid since it exists in equilibrium with dissolved carbon dioxide that rapidly diffuses across cell membranes, raising intracellular partial pressure of carbon dioxide (pCO_2), with possible worsening of the intracellular acidosis.

retrospective study of patients with lactic acidosis, sodium bicarbonate infusion was independently associated with increased mortality.[37]

In 2015, Lee *et al.* compared survivors and nonsurvivors in a retrospective analysis of 109 septic patients with lactic acidosis who received bicarbonate. Patients had similar pH, arterial carbon dioxide, and bicarbonate at ICU admission, while after 48 h, nonsurvivors had lower pH, higher carbon dioxide, and similar bicarbonate, despite similar infusions of sodium bicarbonate.[35]

Among the causes of lactic acidosis, metformin accumulation and overdosage is one of the most frequent.[38] Although theoretically sodium bicarbonate might have a role, no studies have reported a positive effect.[39] In conclusion, the utility of bicarbonate therapy for reducing mortality or improving hemodynamics in patients with lactic acidosis, even if pH less than 7.2, remains to be proved (table 1).

AKI

Acute kidney injury is a heterogeneous clinical syndrome with several definitions and causes in ICU patients. The traditional approach has it that the associated metabolic acidosis results from an increase in urinary bicarbonate excretion or a decrease in renal bicarbonate synthesis. The Stewart approach, on the other hand, suggests that the acidosis secondary to AKI is multifactorial and depends on the balance of acidifying and alkalinizing forces such as hyperchloremia, the retention of other daily unmeasured anions (citrate, acetate, sulfate), and hyperphosphatemia.

Independent from the pathogenesis and despite the controversy on intravenous sodium bicarbonate as supportive therapy to neutralize metabolic acidosis, it is still often employed.[40] A Cochrane meta-analysis published in 2017 concluded there were no randomized clinical trials to support the use of sodium bicarbonate in patients with AKI.[41] However, more recently, in an *a priori* defined stratum of patients with AKI enrolled in the Sodium Bicarbonate Therapy for Patients with Severe Metabolic Acidaemia in the Intensive Care Unit trial to assess the effect of sodium bicarbonate, 28-day survival was better in patients treated with bicarbonate than in the control group (54% *vs.* 37%).[27] This improvement in the outcome might be explained by a lower chloride load in the sodium bicarbonate group, since it is associated with several negative effects.[42–44] Subsequently, in an observational study of 836 patients receiving bicarbonate therapy to correct acidosis due to AKI, Zhang *et al.* found no evidence that this treatment was beneficial in terms of expected mortality in subgroups with severe acidemia (pH less than 7.15) and pancreatitis.[45] These authors also reported that the infusion of sodium bicarbonate improved survival only in patients with sepsis and AKI.[26] Finally, the guidelines from a French expert panel suggested

Table 1. Positive, Negative, and Unknown Effects of Bicarbonate Infusion in Different Clinical Conditions

Respiratory acidosis in acute respiratory distress syndrome[21–24]
- • Bicarbonate is associated with paradoxical acidosis due to the free diffusion into the cells of carbon dioxide generated by bicarbonate.
- • It reduces arterial blood pressure and cardiac output.

Gastrointestinal losses[1]
- • Bicarbonate can be suggested to compensate the losses and limit the physiologic effect of metabolic acidosis in case of poor clinically tolerance.

Lactic acidosis[37,38,78,79]
- • It might contrast the cardiovascular effects of acidemia without any effect on outcome.
- • Bicarbonate therapy is not suggested to improve hemodynamics or to reduce vasopressor requirements in patients with hypoperfusion-induced lactic acidemia with pH < 7.2.
- • Increase in hemoglobin–oxygen affinity reducing oxygen extraction particularly where Po_2 is lower and oxygen uptake is influenced by pH
- • Increase in $Paco_2$ → intracellular paradoxical acidosis
- • Potential hypernatremia and hyperosmolar state
- • Reduced plasmatic [Ca^{2+}] because of chelation by albumin
- • Increase in anaerobic glycolytic pathways mediated by pH sensitive enzyme phosphofructokinase with lactate production

Acute kidney injury[40]
- • Bicarbonate can be suggested to compensate the losses and limit the physiologic effect of metabolic acidosis in case of poor clinically tolerance.

Prevention of acute kidney injury[52]
- • Both in the prevention of contrast-induced acute kidney injury and cardiac surgery–associated acute kidney injury bicarbonate could be used with reasonable benefits even if yet unproven.
- • By urinary alkalinization, it reduces the Haber–Weiss radical production, preventing the renal damage.
- • Slowing the Haber–Weiss production of free radicals, it reduces the conversion of hemoglobin to methemoglobin and the consequent production of tubular casts responsible of pigment nephropathy.

Liver transplantation[73–75]
- • Nephroprotective effects
- • It could increase risk of central pontine myelinolysis due to rapid correction of chronic hyponatremia.
- • Intraoperative bicarbonate administration does not provide any benefits, while the harm is likely.
- • It does not correct the lactic acidosis during the intraoperative anhepatic phase.

The table shows whether bicarbonate is suggested with reasonable benefits (indicated by •), limited to unproven benefits with negligible harm (indicated by •), or more harmful than benefits (indicated by •) for each clinical scenario.

giving bicarbonate to intensive care patients with severe metabolic acidemia (pH less than or equal to 7.20; $Paco_2$ less than 45 mmHg) and moderate to severe renal failure, with a moderate level of evidence.[1]

Prevention of AKI

Contrast Medium

The incidence of contrast-induced nephropathy ranges between 1 and 50% depending on each patient's risk factors and the amount of contrast medium employed.[46–48] Critically ill patients are usually exposed to several, often unavoidable, risk factors for contrast-induced nephropathy including sepsis, anemia, hypotension, potentially nephrotoxic drugs, and shock, with an incidence between 17 and 19%.[49]

The pathophysiology of this condition is not completely clear but is probably caused by the combination of renal ischemia and direct tubular epithelial cell toxicity. High-osmolar contrast agents seem more nephrotoxic than iso-osmolar or low-osmolar agents[50,51] because they induce tubular-glomerular feedback that causes the endogenous production of adenosine with renal vasoconstriction and decreased renal blood flow with local hypoxia. The hypoxia promotes a mitochondrial generation of superoxide that drives the Haber–Weiss reaction with further production of free radicals.[52] This reaction is most active at acidic pH, while at neutral pH, ferric ions precipitate, reducing the production of hydroxyl radicals.[53,54] Therefore, bicarbonate, by raising pH, might reduce the radical production and prevent the renal damage.

In noncritically ill patients, several studies have found no differences with regards to contrast-induced nephropathy prevention between those treated with and without buffer solutions.[55–58] In critically ill patients, according to the International Consensus Conference on the Prevention and Management of AKI, bicarbonate infusion may be considered, but without any strong recommendation.[59] The Sodium Bicarbonate Versus Sodium Chloride for Preventing Contrast-associated Acute Kidney Injury in Critically Ill Patients study by Valette *et al.*,[49] a multicenter randomized controlled trial investigating the safety and efficacy of sodium bicarbonate *versus* sodium chloride in 320 critically ill patients who underwent imaging with intravascular contrast medium, did not find any differences in the need for renal replacement therapy, ICU stay, and mortality.[49] Similarly, in a retrospective study, intravenous infusion of sodium bicarbonate before and after computed tomography with contrast agent did not lead to any reduction in the incidence of contrast-induced nephropathy.[47]

Cardiac Surgery

Cardiac surgery is associated with AKI, with an incidence of 3 to 52%,[60,61] increasing the requirements for renal replacement therapy and mortality.[62,63] Causative factors may be hypoperfusion, ischemia-reperfusion injury, erythrocyte damage, and hemolysis, with the generation of oxygen free radicals and free hemoglobin.[64,65] In addition, cardiopulmonary bypass (CPB) may induce hemolysis, leading to the release of free hemoglobin, which is converted to methemoglobin that precipitates in the distal tubule in an acid environment, with consequent renal impairment. Therefore, bicarbonate might have different effects, slowing the Haber–Weiss production of free radicals, reducing the conversion of hemoglobin to methemoglobin and the consequent production of tubular casts.[57,66]

In patients treated with bicarbonate during 24 h, Haase *et al.* found a smaller increase (from 52% to 32%) of postoperative serum creatinine in patients at increased risk of cardiac surgery–related AKI who underwent CPB.[67] Similarly, in an observational study involving 342 patients, the group that

received perioperative bicarbonate had a lower incidence of postoperative AKI than the group that did not receive perioperative bicarbonate (36.5% *vs.* 50%).[68] However, several randomized trials have shown that bicarbonate did not reduce the rate of AKI.[59,69,70] Furthermore, two meta-analyses and an individual patient data meta-analysis reported that urinary alkalinization with intravenous sodium bicarbonate did not lower the incidence of cardiac surgery–related AKI.[60,71,72]

Currently, routine use of sodium bicarbonate is not recommended to prevent cardiac surgery–related AKI because of wide differences in the studies' patient characteristics and CPB time, as well as different amounts of free hemoglobin release. Consequently, the effect of sodium bicarbonate can differ depending on the levels of free hemoglobin.

Liver Transplantation

Acute kidney injury has been reported in 17 to 95% of patients after orthotopic liver transplantation. The main risk factors include long graft ischemia time, intraoperative massive transfusion, immunosuppressants, and preexisting diseases.[73] In a randomized trial, Weinberg *et al.* investigated the possible role of intraoperative bicarbonate compared to normal saline to prevent AKI after orthotopic liver transplantation, but did not find any difference in the first 48 h.[73]

However, during orthotopic liver transplantation, major alterations in the acid–base equilibrium are not infrequent,[74,75] and bicarbonate also seems to have a role in the intraoperative management of metabolic acidosis. The main causes of this acidosis are the large infusions of crystalloid fluids that contain high concentrations of chloride, as well as the accumulation of lactates during the anhepatic phase. Using the Stewart approach, complex acidosis was detected, due to both the low strong ion difference and the high total concentrations of weak acids.[75] In fact, compared with a restricted normal saline strategy, bicarbonate did not make any difference in hemodynamic parameters or pH after reperfusion.[76] Similarly, in a single-center randomized trial, it attenuated the degree of postoperative metabolic acidosis, but without any difference at 48 h.[73]

However, intraoperative bicarbonate can—within a few minutes—have an effect on hemodynamics because of its impact on intravascular volume. At low pH, the bicarbonate is used up as a buffer, the change in bicarbonate concentration is small, and sodium remains extracellular, increasing the intravascular serum osmolality that provides volume shift.

Despite the lack of robust clinical data, some physiologic studies in mechanically ventilated animals or patients have shown that the immediate effects 5 min after the rapid infusion of 100 mmol of bicarbonate include transient rises of pH, $Paco_2$, and sodium; however, after 30 min from stabilization, much of the bicarbonate has been either converted into carbon dioxide or excreted renally. There is a loss of about 60% of the dose due to the rapid buffering and conversion into carbon dioxide and water, and interstitial and intracellular redistribution of body water, with only a slight rise in serum osmolality, and then any bicarbonate greater than 26 mM is excreted more slowly renally.[20,77]

Conclusions

Acidemia is common in critically ill patients, and sodium bicarbonate is widely infused to correct metabolic acidosis in clinical practice. However, there is a lack of firm evidence in the literature because of the heterogeneity of patients studied, their severity and type of acidemia (mixed or metabolic), and the timing, dosage, and duration of the sodium bicarbonate infusion. In addition, several studies were not powered to detect differences in areas such as mortality or length of stay. Future studies should evaluate the main pathophysiological outcomes such as the hemodynamic effects and the acid–base status; the amount of sodium bicarbonate should be infused depending on the severity of metabolic acidosis and not according to anthropometric data.

At this time, acidosis therapy needs to include treatment of the underlying mechanism, because it is not acidemia *per se* but the underlying state that can be mainly addressed as responsible for differences in mortality rates. Clinicians should consider sodium bicarbonate as a drug with side effects, not just something that always does good and does no harm. Therefore, while its domestic utility is undeniable, at the moment the evidence regarding its clinical application is poor.

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Competing Interests

The authors declare no competing interests.

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