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EDITORIAL

Sodium bicarbonate application for the treatment of acute metabolic acidosis: what we know and what we still don't know

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Metabolic acidosis is common in critically ill patients and reflects a broad spectrum of underlying pathophysiological processes. Intravenous sodium bicarbonate is widely used, yet its efficacy and safety remain debated [1].

Physiological rationale and mechanistic considerations

In metabolic acidosis, e.g., lactic acidosis (Fig. 1A), the immediate defence is buffering, followed by compensatory responses from the respiratory and renal systems [2]. Increased alveolar ventilation lowers arterial partial pressure of carbon dioxide ($PaCO_2$) while the kidneys increase net acid excretion, mainly through increased glutamine metabolism, ammoniagenesis, and chloride excretion [3, 4]. From a physicochemical perspective, this results in an increased plasma strong ion difference (SID) and exerts an alkalinizing effect, mainly driven by a reduction in strong anions, while preserving plasma sodium concentration and osmolality (Fig. 1B). In a bicarbonate-centred framework, the same physiology appears as increased plasma bicarbonate at stable or even reduced $PaCO_2$, leading to an increased $HCO_3^-/PaCO_2$ ratio, thus raising pH [5].

When compensation is inadequate or rapid correction is required, intravenous sodium bicarbonate is frequently administered in clinical practice [1]. Despite its widespread use, bicarbonate therapy remains controversial. This manuscript reviews mechanisms of sodium bicarbonate therapy, current clinical evidence, and potential benefits and harms in critically ill patients.

Mechanisms of sodium bicarbonate therapy

When sodium bicarbonate is administered intravenously, it dissociates into Na^+ and HCO_3^-, increasing plasma SID by adding a strong cation (Na^+) without a corresponding strong anion. In parallel, the rise in HCO_3^- accounts for alkalinization in the traditional bicarbonate-centred approach.

The effect of sodium bicarbonate depends on its formulation, as two preparations are available: hypertonic and isotonic solutions.

On the one hand, hypertonic solutions (4.2%, 7.5%, 8.4%) contain very high sodium concentrations (up to ~ 1000 mEq/L) and exert a strong alkalinizing effect by increasing plasma sodium and, consequently, plasma SID (Fig. 1C). This comes at cost of a substantial sodium load and increased plasma osmolality [6]. Because $NaHCO_3$ delivers Na^+ and HCO_3^- in equimolar amounts, plasma bicarbonate rises in parallel to preserve electroneutrality.

On the other hand, isotonic sodium bicarbonate (typically 1.3%, ~ 154 mEq/L Na^+) also raises pH through an increase in SID [7]. In this case, however, the main driver is chloride dilution, while plasma sodium remains relatively stable. A concomitant increase in bicarbonate concentration can be observed. However, because isotonic preparations contain lower Na^+ and HCO_3^- concentrations, achieving a meaningful alkalinizing effect requires larger fluid volumes, increasing the risk of fluid overload.

Another important and often underappreciated consequence of sodium bicarbonate administration is carbon dioxide (CO_2) generation. Sodium bicarbonate buffers

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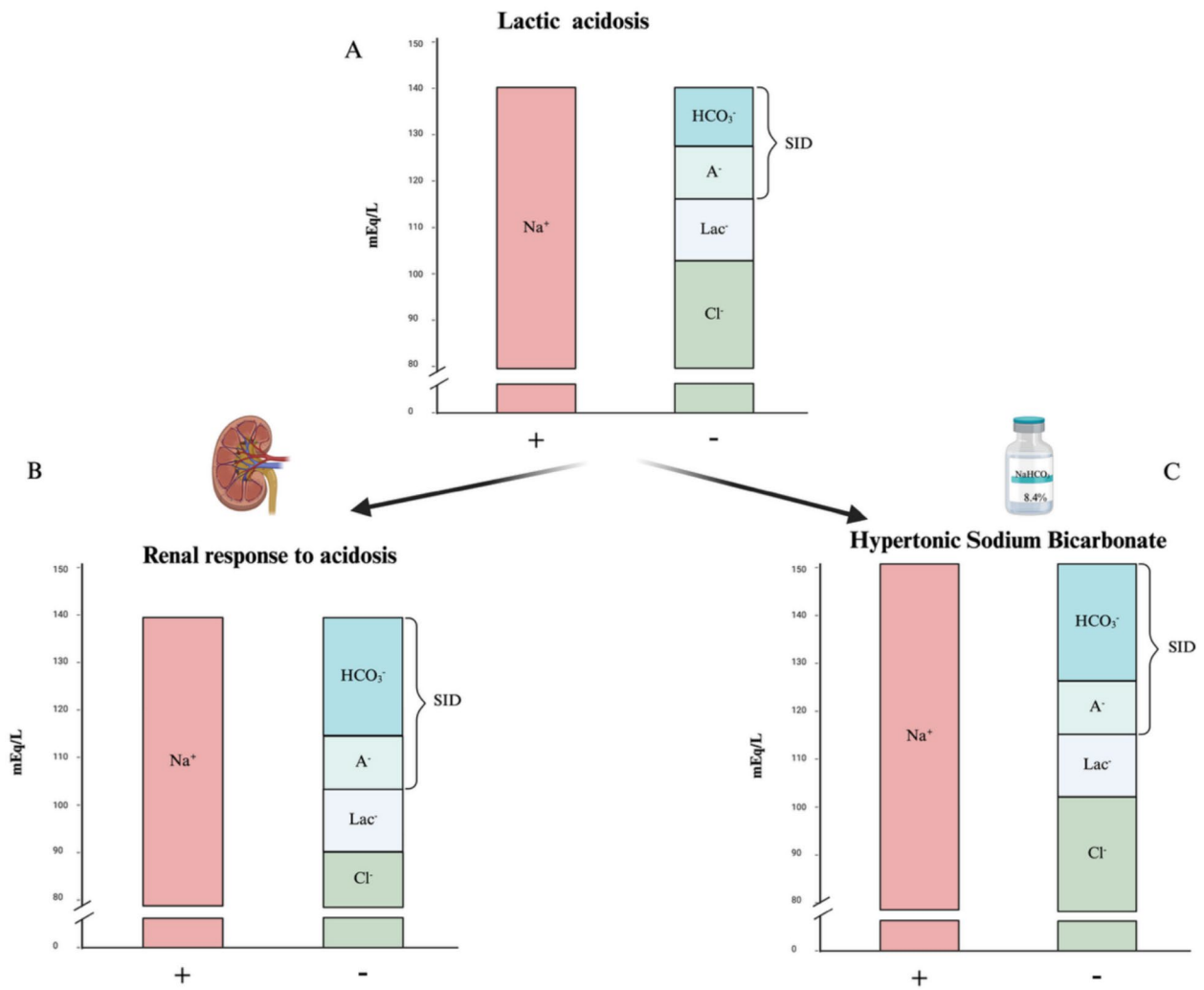

Fig. 1 Conceptual framework of stable metabolic acidosis due to lactate accumulation (**A**), and its sequential correction via renal compensation (**B**) and administration of hypertonic sodium bicarbonate (**C**). The three Gamblegrams illustrate changes in strong cations and anions across different conditions. Sodium (Na^+), the principal strong cation, is represented in red, while the main strong anions, chloride (Cl^-) and lactate (Lac^-), are shown in the opposite column. The Strong Ion Difference (SID), defined as the difference between fully dissociated cations and anions, is one of the three independent variables determining acid–base equilibrium according to the physicochemical model. SID governs the charge gap within the anionic compartment of the Gamblegram, which is usually balanced by weak non-carbonic anions (A^-) and the dependent variable bicarbonate (HCO_3^-) to maintain electroneutrality. **A** Lactic acidosis. The accumulation of Lac^- reduces SID, leading to a decrease in pH and the development of metabolic acidosis. **B** Renal compensation: As a physiologic response, the kidneys excrete acid, primarily as ammonium chloride. The selective elimination of strong anions (e.g. Cl^-) without a loss of Na^+ increases SID, exerting an alkalinizing effect without affecting osmolality. **C** Hypertonic bicarbonate therapy. Administration of hypertonic sodium bicarbonate increases plasma Na^+ concentration and SID (by increasing Na^+ without a corresponding increase in Cl^-), leading to alkalinization, while also raising osmolality and Na^+ concentration.

hydrogen ions forming carbonic acid, shifting the equilibrium towards the formation of CO_2 [8].

$$NaHCO_3 + H^+ \rightarrow Na^+ + H_2CO_3 \rightarrow Na^+ + H_2O + CO_2$$

Effective elimination of this additional CO_2 depends on a transient increase in alveolar ventilation to avoid hypercapnia.

Clinical evidence

Management of metabolic acidosis must primarily address the underlying cause. Although severe acidosis might impair myocardial contractility and reduce catecholamine responsiveness, available studies have not consistently shown haemodynamic improvement following sodium bicarbonate administration [9]. Accordingly, increasing arterial pH through sodium-bicarbonate administration does not

necessarily translate into improved perfusion or cellular function.

In specific cases of metabolic acidosis, such as lactic acidosis or diabetic ketoacidosis, pharmacological buffering cannot replace benefits of causal therapy [10]. Current guidelines also discourage the use of sodium bicarbonate in cardiac arrest, where extremely low cardiac output and inadequate ventilation compromise effective transport and elimination of CO_2 [11].

The role of sodium bicarbonate remains controversial in metabolic acidosis associated with acute kidney injury (AKI) and in multifactorial metabolic acidosis (e.g. septic shock). Accordingly, several clinical studies investigated this issue: The BICAR-ICU trial did not demonstrate an overall mortality benefit from sodium bicarbonate administration in all metabolic acidosis causes. However, a predefined subgroup of AKI patients appeared to benefit, showing a reduced need for renal replacement therapy (RRT) [12]. These findings were subsequently supported by a target-trial emulation study which suggested improved outcomes, particularly in patients with AKI [13]. The BICARICU-2 trial, focusing exclusively on AKI patients, confirmed a reduction in RRT use, although it did not show a survival benefit [14].Taken together, the most consistent signal is reduced RRT utilization, whereas a mortality benefit remains unproven. In patients with AKI, who are particularly susceptible to severe metabolic acidosis due to impaired renal compensatory function, sodium bicarbonate may be used as a bridge to stabilization until renal recovery occurs or RRT is initiated, balancing potential benefits against predictable risks.

Practical considerations

Assessment of a patient's compensatory capacity is essential before administering sodium bicarbonate. This includes (i) the ability to augment alveolar ventilation to eliminate the additional CO_2 generated by buffering, along with (ii) renal function, which influences both the severity and persistence of metabolic acidosis and the extent to which bicarbonate therapy acts merely as a temporary measure. Clinical decisions should be individualized based on acidosis severity, comorbidities, and the risk of complications. In patients with very severe acidemia (e.g. $pH \leq 7.1$) and haemodynamic instability or shock, cautious administration of sodium bicarbonate may be considered as a pragmatic, temporary measure to mitigate the deleterious effects of profound acidemia, while definitive treatment of the underlying cause is pursued.

Dosing practices vary widely: observational data report median administered doses of ~ 110 mEq over 24 h [1], whereas randomized trials used substantially higher mean daily doses (≈ 250–375 mEq/day) [12, 14]. Ideally, any decision to treat should be anchored to a predefined clinical target and accompanied by close monitoring of predictable adverse effects, including sodium/volume load and hyperosmolality, and hypercapnia when ventilatory reserve is limited.

Alternative buffers (e.g. tromethamine) and extracorporeal approaches such as selective chloride removal by electrodialysis, remain investigational and require further evidence [15].

Management of metabolic acidosis should prioritize correction of the underlying cause rather than routine pharmacologic alkalinization. Current evidence suggests a reduction in the need for RRT with sodium bicarbonate administration in selected patients with AKI, whereas survival benefit remains unproven. When administered, predictable harms, including sodium and volume load, hyperosmolality, and CO_2 generation, should be anticipated and closely monitored, particularly in patients with limited ventilatory reserve, hypercapnia, or cardiac arrest.

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Conflicts of interest
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