Intensive Care Med (2025) 51:2418–2421
https://doi.org/10.1007/s00134-025-08200-9

WHAT'S NEW IN INTENSIVE CARE

Short piece: metabolic acidosis

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Metabolic acidosis refers to the result of any physiological disturbance or ingestion of an exogenous agent that increases the plasma proton concentration or a decrease in acid excretion, regardless of whether acidemia (pH < 7.38) is present. When the pH drops below 7.20, the condition is typically classified as severe, a disturbance observed in approximately 2–10% of ICU patients, depending on the cohort and case mix. In these patients, mortality rates can reach 60% [1–3].

While correction of the underlying disease is the primary objective of treatment, the role of adjunctive interventions, such as sodium bicarbonate infusion or kidney replacement therapy (KRT), continues to generate debate. Evidence suggests that sodium bicarbonate may confer benefits in selected patients, notably in those with both severe acidosis together with moderate to severe acute kidney injury (AKI) [2] although KRT remains the standard of care for acidosis related to toxin accumulation or in refractory cases where severe acidosis is observed despite adequate medical management [1, 4, 5].

This short piece synthesizes the latest literature on the epidemiology, physiological consequences, diagnostic strategies, and evidence-based treatment of metabolic acidosis in the ICU with a focus on sodium bicarbonate therapy and KRT.

Consequences of metabolic acidosis on organ function

Among the immediate consequences of metabolic acidosis is a reduction in catecholamine responsiveness, which complicates the management of patients with hypotension. As pH falls—particularly to within the range of 7.20–7.10—cardiac output declines, and the effects of both inotropic and vasoconstrictive agents are blunted together with an increased risk of ventricular arrhythmias [6]. Some argue that the theoretical response to an acute metabolic acidosis may be protective given that acidemia initially facilitates tissue oxygen delivery through a rightward shift of the oxyhemoglobin dissociation curve (Bohr effect). The net impact on oxygen delivery depends on both the duration and severity of acidemia [6].

Neurological symptoms, including confusion and lethargy, are frequently observed in acute acidemia and may be related to altered neuronal excitability, even when cerebrospinal fluid pH remains within the physiological range [6].

Phenotyping patients with metabolic acidosis

The approach to quantifying acid–base disorders includes the "traditional" approach, determined through the interaction of pCO_2 and HCO_3^- [7], or the physicochemical (Stewart) method.

The physicochemical method analyzes acid–base imbalances by considering three independent variables that determine hydrogen ion concentration: the strong ion difference (SID, the difference between cations (mainly Na^+, K^+, Ca^{2+}, Mg^{2+}) and anions (mainly Cl^-, lactate)), the total concentration of weak acids (Atot, mainly albumin and phosphate), and the partial pressure of carbon dioxide (pCO_2). According to Stewart, changes in these variables alter the dissociation of water, thereby affecting pH, rather than bicarbonate or hydrogen ions being independent regulators themselves [1, 8].

Furthermore, the application of methods other than the physiological response has not been translated into an outcome. A step-by-step approach has been suggested by most experts and can be summarized as follows (Fig. 1): first, careful examination of the clinical context and picture, including ingestion of drugs and toxins, should be considered. The second step is the determination of the primary disorder using the measured pH and the serum bicarbonate concentration,

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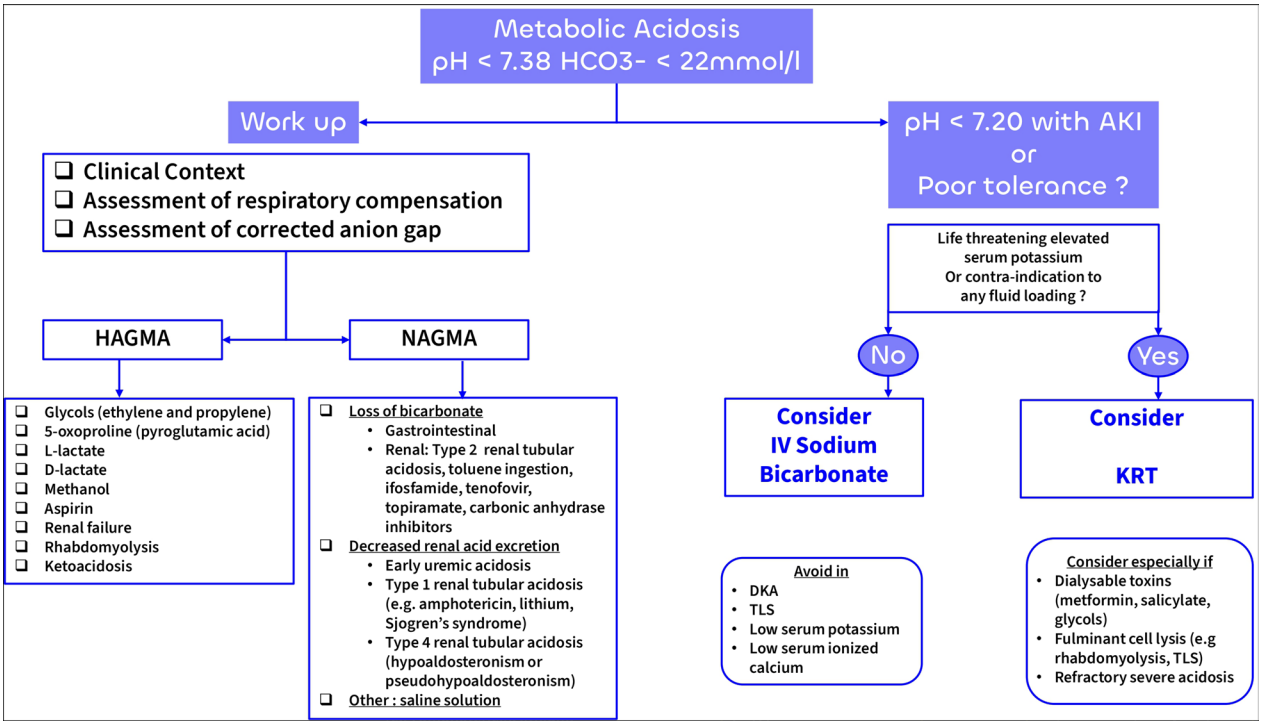

Fig. 1 Metabolic acidosis work-up and symptomatic therapy. Metabolic acidosis requires an extensive work-up, including four main steps, which allow patients to be dichotomized into two main categories. High Anion Gap Metabolic Acidosis (HAGMA) involves endogenous or exogenous anions, some of which are usually unmeasured [15]. Non-Anion Gap Metabolic Acidosis (NAGMA) includes the loss of sodium bicarbonate and renal tubular acidosis. Delta gap is the change in anion gap–the change in bicarbonate. In parallel with the diagnostic work-up, one should consider temporizing severe metabolic acidosis (pH ≤ 7.20 and poor clinical tolerance) with intravenous sodium bicarbonate. Although the dose is uncertain, we may target pH ≥ 7.30. Careful evaluation of side effects and potential contraindications of sodium bicarbonate should be performed, as well as the benefit–risk balance of early and potentially unnecessary Kidney Replacement Therapy (KRT). KRT: kidney replacement therapy; DKA: diabetic ketoacidosis; TLS: tumor lysis syndrome; AKI: acute kidney injury

followed by the third step which determines the degree of physiological compensation for the acidosis, herein referred to as respiratory compensation. The expected $PaCO_2$ is given by the following formula:

$$1.5 \times (\text{serum bicarbonate concentration}) + 8 \pm 2\,\text{mmHg}. \quad (1)$$

The calculation of the corrected anion gap follows: hypoalbuminemia is associated with a decrease in ionized plasma albumin, which leads to a decrease in anion gap (AG):

$$\text{Corrected anion gap} = Na^+ - Cl^- - HCO_3^- + [(40\text{-albumin}) \times 0.25]. \quad (2)$$

Calculating the corrected anion gap allows dichotomizing cases into High Anion Gap Metabolic Acidosis (HAGMA) and Non-Anion Gap Metabolic Acidosis (NAGMA). The main causes of HAGMA and NAGMA are summarized in Fig. 1.

Lactic acidosis

Lactic acidosis is a HAGMA caused by excess lactate and proton accumulation. Type A is linked to tissue hypoxia (e.g., heart failure, sepsis). Type B, occurring without hypoxia (e.g., liver dysfunction, medications, or metabolic disorders), is due to a combination of microcirculatory dysfunction, increased aerobic glycolysis, mitochondrial dysfunction, and reduced lactate clearance [6, 8]. Although lactate reduction has been associated with improved survival, targeting lactate normalization may lead to excessive fluid or vasopressor administration in type B lactic acidosis [9]. Combining lactate reduction with other perfusion markers (e.g., capillary refill time,

ScvO2) is, therefore, recommended to better individualize resuscitation [10].

Treatment of patients with metabolic acidosis

Treatment of the underlying cause of the metabolic acidosis remains the cornerstone of patient management; two main therapeutic strategies are available to increase the blood pH in critically ill patients: sodium bicarbonate infusion and renal replacement therapy (KRT) (Fig. 1).

Severe metabolic acidosis is a "classical indication" for starting KRT with a threshold of 7.20–7.15 when refractory to medical management although this has not been subject to scientific rigor [1, 11]. Specific KRT indications, along with severe acidosis, include dialyzable toxin ingestion (metformin, salicylate, methanol, ethylene glycol, propylene glycol), severe acute kidney injury with tumor lysis syndrome, refractory volume overload, and life-threatening hyperkalemia or hypercalcemia. Adjuncts to KRT such as hemoadsorption may also be applied in cases of specific poisoning or rhabdomyolysis. Although efficient in correcting plasma pH and normalizing electrolytes, KRT is not without complications including complications secondary to deep venous access, infection, rapid volume or electrolyte shifts, altered drug pharmacokinetics, and possibly delayed renal recovery [11].

Sodium bicarbonate infusion may be used as a temporary measure in patients with severe metabolic acidosis. In 2025, four large randomized trials are examining sodium bicarbonate as a bridge to recovery from severe metabolic acidosis in critically ill populations ([2, 12], ISRCTN14027629 and NCT05697770). Only one trial has so far been published and showed that in 389 critically ill patients with pH $\leq$7.20 and bicarbonate $\leq$20 mmol/L, intravenous sodium bicarbonate infusion targeting the arterial pH >7.30 did not significantly affect the primary outcome (all-cause mortality at day 28 and/or the presence of at least one organ failure on day 7). However, in a pre-specified subgroup of patients with moderate to severe AKI, bicarbonate therapy was associated with a reduction in both the primary outcome and 28-day mortality (46% in the bicarbonate group and 63% in the control group), implying a potential benefit in this population. Three multicenter randomized trials are ongoing to assess whether sodium bicarbonate may be beneficial for these patients [2]. In a recent target trial emulation, bicarbonate administration was associated with a small but statistically significant reduction in mortality for patients with metabolic acidosis [13].

However, sodium bicarbonate administration is not benign and may be associated with potential side effects including substantial fluid loading owing to its high osmolarity and sodium load. Correction of acidosis may also promote an intracellular shift of potassium and should be avoided in patients with low serum potassium unless the potassium is corrected prior to therapy. Also, through increasing the affinity of albumin for calcium and directly binding calcium, the risk of ionized hypocalcemia is important and should be corrected before infusing hypertonic sodium bicarbonate. In patients with diabetic ketoacidosis and a pH above 7.0, the administration of sodium bicarbonate is likely detrimental, as it may delay the resolution of ketosis and increase the risk of hypokalemia as well as rebound alkalosis. In patients presenting with tumor lysis syndrome, there is a risk of calcium phosphate precipitation and further kidney injury [14].

In conclusion, management of metabolic acidosis mandates identification of the underlying cause. In patients presenting with severe metabolic acidosis, sodium bicarbonate infusion may be used as a temporizing measure, with KRT indicated in patients refractory to medical management or with specific indications.

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Declarations

Conflicts of interest

SJ is the Editor in Chief of Intensive Care Medicine. He has not taken part in the review or selection process of this article.

Publisher's Note

Received: 4 September 2025 Accepted: 30 October 2025
Published: 17 November 2025

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