



Review

Severe Metabolic Acidosis in Intensive Care: Implications for Acute Kidney Injury, Bicarbonate, and Renal Replacement Therapy

Carlos Rebolledo-Maldonado ¹, Juan Solano-Ropero ² , Elber Osorio-Rodríguez ^{1,*} , Aleyda Parra-Castillo ³, Carlos Beltran-Sánchez ^{3,4}, Neil Martínez-Fontalvo ⁵ , Diego González-Betancur ⁵ , Dairo Rodelo-Barrios ^{2,5} , Manuel Cueto-Chaparro ^{5,6}, José Correa-Guerrero ^{5,7} , Alberto Polo-Barranco ⁸ and Carmelo Dueñas-Castell ^{7,9}

- ¹ Group Care Medicine, Department of Intensive Medicine, Clínica Colsanitas S.A., Clínica Iberoamérica, Barranquilla 080002, Colombia; carlos.rebolledo@unisimon.edu.co
- ² Department of Critical Medicine and Intensive Care, Faculty of Medicine, Simón Bolívar University, Barranquilla 080002, Colombia; juan.solanor@unisimon.edu.co (J.S.-R.); daiorodelo1992@gmail.com (D.R.-B.)
- ³ Grupo Investigación Interdisciplinaria en Seguridad Alimentaria y Nutricional (GRIINSAN), Faculty of Health Sciences, Universidad del Atlántico, Puerto Colombia 081001, Colombia; aleydaparra@mail.uniatlantico.edu.co (A.P.-C.); carlosbeltran@mail.uniatlantico.edu.co (C.B.-S.)
- ⁴ Grupo Investigación en Ciencias de la Salud de la Universidad del Atlántico (GICS-UA), Faculty of Basic Sciences, Universidad del Atlántico, Puerto Colombia 081001, Colombia
- ⁵ Critical and Internal Medicine Research Group (CRITIMED), Cartagena de Indias 130005, Colombia; neilmartinezf18@gmail.com (N.M.-F.); dagobuto@gmail.com (D.G.-B.); manueljkuetto@hotmail.com (M.C.-C.); josegabriel2101@gmail.com (J.C.-G.)
- ⁶ Department of Nephrology, Clínica Colsanitas S.A., Clínica Iberoamérica, Barranquilla 080002, Colombia
- ⁷ Department of Critical Medicine and Intensive Care, University of Cartagena, Cartagena de Indias 130005, Colombia; crdc2001@gmail.com
- ⁸ Group Sanitas Crea, Centros Médicos Colsanitas, Department of Internal Medicine, Clínica Colsanitas S.A., Clínica Iberoamérica, Barranquilla 080002, Colombia; dralbertopolob@gmail.com
- ⁹ Department of Internal Medicine, Hospital Serena del Mar, Cartagena de Indias 130005, Colombia
- * Correspondence: osorioelver@gmail.com; Tel.: +57-3205240376

Abstract

Severe metabolic acidosis is a frequent finding in the intensive care unit (ICU) and a critical marker of clinical severity and organ dysfunction, closely linked to acute kidney injury (AKI) due to shared physiological mechanisms and the loss of the kidney's ability to maintain acid-base homeostasis. Therefore, it represents the biochemical expression of heterogeneous pathophysiological mechanisms related to acid-base balance. These include tissue hypoperfusion, sepsis, mitochondrial dysfunction, accumulation of unmeasured anions, bicarbonate loss, and reduced renal excretion of the acid load. Its presence is associated with increased mortality, greater vasopressor and mechanical ventilation requirements, prolonged ICU stay, and a higher likelihood of renal replacement therapy (RRT). However, pH correction alone does not guarantee clinical improvement. Therefore, contemporary management prioritizes the etiology, severity of the acidemia, and hemodynamic status. In this context, sodium bicarbonate plays a limited and selective role, particularly in severe acidemia with advanced AKI or hyperkalemia, or as temporary supportive therapy while the underlying cause is corrected or extracorporeal support is arranged. Similarly, RRT should be reserved for refractory cases and should not be initiated based solely on isolated pH thresholds. This review analyzes the definition, epidemiology, clinical implications, pathophysiology, and therapeutic strategies for severe metabolic acidosis in critically ill patients, with emphasis on its interaction with AKI, the rational use of bicarbonate, and the timing of RRT initiation.



Academic Editor: Raymond Vanholder

Received: 16 June 2026

Revised: 15 July 2026

Accepted: 17 July 2026

Published: 20 July 2026

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Keywords: metabolic acidosis; intensive care unit; acute kidney injury; sodium bicarbonate; renal replacement therapy; acidemia; critically ill patient

1. Introduction

Metabolic acidosis is one of the most frequent and significant alterations in critically ill patients [1]. Its relevance in the intensive care unit (ICU) is due not only to its high prevalence but also to the complex pathophysiological network that underlies it [2]. This disorder rarely results from a single mechanism [3]; rather, it usually results from the convergence of hypoperfusion, mitochondrial dysfunction, renal inability to excrete an acid load, and sepsis [4]. Thus, acidemia represents the biochemical expression of multifactorial systemic injury [2,5]. Some series report that this alteration, alone or combined, affects up to 58% of patients upon admission to the ICU [6], and is presented in its severe form ($\text{pH} < 7.20$, of metabolic origin) in 2% and 10% of cases [7].

From a clinical perspective, severe metabolic acidosis is not only a biochemical abnormality but also a key determinant of organ dysfunction [4]. Severe acidemia can rapidly reduce catecholamine responsiveness, impair myocardial contractility, and complicate the management of hypotension [8]. As the pH decreases, further hemodynamic deterioration is observed, with a poor response to inotropes and an increased risk of ventricular arrhythmias [9]. Therefore, in the critically ill patient, severe acidemia should be considered a clinical warning sign, as it can perpetuate shock and promote multiple organ failure [10].

On the other hand, metabolic acidosis stimulates a compensatory ventilatory response that increases CO_2 elimination to mitigate the drop in pH, although it does not bring it back to a normal range [11]. However, the resulting increase in the work of breathing can lead to muscle fatigue and complications during weaning, particularly in patients with limited physiological reserve [12]. Additionally, acute metabolic acidosis decreases hemoglobin oxygen affinity, shifting the oxyhemoglobin dissociation curve to the right through the Bohr effect; this increases P_{50} and may initially facilitate oxygen unloading to metabolically active, acidic tissues [13]. Beyond respiratory issues, it is associated with electrolyte imbalances, neurological deterioration, and a protein catabolic state that accelerates the progression of kidney damage, reinforcing its value as a critical marker of severity in the ICU [14].

This condition is especially critical when acute kidney injury (AKI) coexists, significantly increasing morbidity and mortality and complicating therapeutic decisions [10,15]. Historically, the treatment of severe acidemia relied on the idea that correcting pH alone should result in clinical improvement [16]. Current evidence no longer supports isolated pH correction as a universal therapeutic target; instead, management should be guided by etiology, severity, hemodynamic context, and the identification of subgroups in whom sodium bicarbonate or renal replacement therapy (RRT) may be clinically useful [10,17–19]. In this narrative review, we integrate current clinical and pathophysiological evidence on severe metabolic acidosis in critically ill patients, with particular emphasis on AKI, the selective use of sodium bicarbonate, and the timing of RRT initiation.

2. Literature Search and Scope

To guide this overview, a specific search was conducted in PubMed/MEDLINE, Scopus, and Web of Science for articles published from each database's inception through June 2026. The search used terms such as "metabolic acidosis," "acidemia," "critical care," "acute kidney injury," and "renal replacement therapy," with a focus on randomized controlled trials, international guidelines, and high-quality reviews relevant to critically ill

adult patients. Reference lists of key publications were also manually reviewed to identify additional studies. As this is a narrative review, systematic review methodologies, formal meta-analysis, and systematic risk-bias assessment were not applied.

3. Definition and Epidemiology

The assessment of a patient's acid-base status involves contrasting the simplicity of the respiratory component with the complexity of the metabolic component [20]. Although the respiratory component is primarily reflected by PaCO_2 [11,21], the metabolic component can be analyzed using complementary approaches. The Henderson–Hasselbalch model remains useful at the bedside because it focuses on pH and plasma bicarbonate [HCO_3^-], whereas Stewart's physicochemical approach provides additional insight into complex or mixed disorders through the strong-ion difference and weak-acid components [20,22]. In clinical practice, standardized base excess (SBE) is useful for quantifying the magnitude of the metabolic component of an acid–base disorder [20,23,24]. However, SBE does not independently identify the mechanism underlying a metabolic disturbance and may overlook complex acid–base disorders when concurrent changes in chloride, lactate, albumin, or unmeasured anions counterbalance one another [20,25]. Consequently, a normal value does not rule out underlying metabolic disorders, necessitating an integrated interpretation with other biochemical and clinical data [22].

From the Henderson-Hasselbalch perspective, metabolic acidosis is defined as a primary disorder characterized by a decrease in HCO_3^- and base excess, usually resulting in an arterial pH below 7.35 [4]. In a pragmatic context within the critical care setting, the current consensus establishes its diagnosis based on the coexistence of $\text{pH} < 7.35$, $\text{HCO}_3^- < 20\text{--}22\text{ mmol/L}$, and $\text{SBE} \leq -3\text{ mmol/L}$ [2]. Severity is stratified according to arterial pH as mild (7.30–7.35), moderate (7.20–7.29), and severe (≤ 7.20), with values below 7.00 associated with high mortality and a greater need for life support [26].

These acid-base disturbances are extremely prevalent: up to 90% of ICU patients present with some acid-base disorder in the first 24 h [2]. Mallela et al. describe disturbances in 93.3% of patients [27]. International studies confirm that metabolic acidemia is the most common subtype, affecting 42.9% of cases [28] and associated with prolonged hospital stays and a greater need for ventilation or vasopressors [7]. Although mortality rates of approximately 55–60% have been reported in critically ill patients with severe metabolic acidemia [29], the real impact of correcting pH alone remains a subject of debate compared to treating the underlying cause [30].

Contemporary international cohort data indicate that acidemia subtypes in critically ill patients are associated with distinct clinical profiles and adverse outcomes, with prognosis depending on the predominant underlying mechanism [28]. Similarly, Jung et al. report a mortality rate close to 60% in critically ill patients with severe metabolic acidosis, with a $\text{pH} < 7.20$ [7]. However, the prognosis depends not only on the absolute pH value but also on the underlying etiology, the rate of onset, the patient's comorbidities, the coexistence of shock, and the presence of AKI or other organ dysfunction [26]. Consequently, acidosis is emerging as a key prognostic marker of adverse outcomes, although the debate persists over whether pH correction alone offers real clinical benefits compared with treating the underlying cause [30].

4. Clinical Implications

The clinical presentation of metabolic acidosis in the ICU depends on the rapidity of onset, the severity of the acidemia, the underlying etiology, and the patient's physiological reserve [31]. Generally speaking, acute acidosis is associated with cardiovascular dysfunction, respiratory disturbances, neurological compromise, and metabolic-renal changes [14].

However, in critically ill patients, many of these manifestations can be masked by sedation, mechanical ventilation, vasopressor use, and the coexistence of multiple organ dysfunction [26]. Therefore, its clinical recognition should not rely solely on subjective symptoms, but rather on the integration of arterial blood gas analysis, lactate levels, base deficit, electrolytes, renal function, and support requirements. Table 1 summarizes the main clinical implications of metabolic acidosis in the ICU by system.

Table 1. Clinical manifestations of metabolic acidosis in the ICU.

System	Manifestations
Cardiovascular	Tachycardia; hypotension; arrhythmias; hemodynamic instability
Respiratory	Tachypnea; hyperventilation; deep breathing/Kussmaul pattern; ventilatory fatigue
Neurological	Headache; drowsiness; altered mental status; stupor; coma
Gastrointestinal	Nausea; vomiting; abdominal pain
Metabolic-electrolyte	Hyperkalemia; insulin resistance; disturbances in glycemic control
Muscular/skeletal	Weakness: loss of lean body mass; bone resorption
Sedated/intubated patient	Elevated lactate; base deficit; increased vasopressor requirement; renal dysfunction; difficulty in ventilator weaning; delirium

From a hemodynamic standpoint, acute acidemia can manifest as tachycardia, hypotension, circulatory instability, and an increased need for vasopressor support [8]. This effect is particularly relevant in patients with sepsis or shock, in whom decreased cardiovascular reserve reduces tolerance to abrupt changes in pH and can exacerbate tissue hypoperfusion [32]. Furthermore, acidemia can impair myocardial performance and attenuate the response to catecholamines, making metabolic acidosis not only a marker of severity but also a potential amplifier of hemodynamic instability.

In the respiratory system, the characteristic compensatory response is an increase in alveolar ventilation, clinically expressed as tachypnea, hyperventilation, or deep breathing, provided the patient maintains spontaneous ventilation [12]. This compensation aims to reduce PaCO₂ and limit the decrease in pH; however, when ventilatory demand is sustained over time, the increased work of breathing can exceed the functional reserve of the critically ill patient and promote ventilatory fatigue [33]. PaCO₂ should be interpreted in conjunction with pH and the magnitude of the metabolic disturbance, as hypercapnia may indicate insufficient compensation or an associated respiratory disorder [34]. In mechanically ventilated patients, acidemia may increase respiratory demand and has been associated with adverse post-extubation outcomes, potentially complicating ventilator weaning [35,36].

Neurological and systemic manifestations of metabolic acidosis are often nonspecific and may be difficult to interpret in critically ill patients. Neurological involvement can range from headache, restlessness, and altered mental status to stupor or coma in severe acidemia [4]. In addition, acidosis may potentiate the depressant effects of sedative and analgesic drugs by altering their ionization state and tissue distribution, thereby complicating serial neurological assessment and the application of sedation scales [37]. Systemically, it is frequently accompanied by hyperkalemia, insulin resistance, impaired glycemic control, and increased protein and bone catabolism [38–40]. Metabolic acidosis can promote muscle proteolysis, interfere with protein synthesis, and contribute to negative nitrogen balance, favoring loss of lean mass and functional decline [41,42]. Bone may also act as an extracellular buffer against acid load, but this occurs at the expense of mineral release, increased resorption, and deterioration of bone quality [43].

Finally, in the sedated and intubated patient, the clinical impact of metabolic acidosis rarely manifests as subjective symptoms, such as dyspnea, which are often difficult to assess in non-communicative patients [44]. In this scenario, the progression of acidosis is recognized mainly through objective parameters: increased vasopressor requirements, persistent elevation of lactate and worsening of base deficit, as well as deterioration of renal function requiring renal replacement therapy and repeated failure of ventilatory weaning attempts [2,10,45].

5. Pathophysiology

Metabolic acidosis in the ICU should not be viewed as a single entity, but rather as the end result of the loss of acid-base homeostasis [10]. This originates from three main mechanisms: net acid accumulation, loss of HCO_3^- , or impaired renal excretion of acid load [2]. In critically ill patients, these mechanisms often coexist and potentiate each other, particularly in settings of sepsis, shock, AKI, and intensive resuscitation [2,46]. This interaction can also be observed in severe tropical infections, such as dengue and leptospirosis, in which hemodynamic, inflammatory, and tubular mechanisms favor the development of AKI, metabolic disturbances, and, in the most severe cases, the need for RRT [47,48]. In this context, Table 2 summarizes the main mechanisms of metabolic acidosis in the ICU.

Table 2. Clinical scenarios associated with metabolic acidosis in the ICU and their pathophysiological interpretation.

Clinical Scenario/Pattern	Predominant Pathophysiological Mechanism
High anion gap	
Sepsis/shock	Multifactorial hyperlactatemia; unmeasured anions may coexist and, after resuscitation, a hyperchloremic component may emerge
Ketoacidosis	Accumulation of acetoacetate and β -hydroxybutyrate due to insulin deficiency and counterregulatory hormone predominance
Acute kidney injury or advanced CKD	Reduced NH_4^+ generation, decreased HCO_3^- regeneration, and retention of uremic anions
Selected intoxications	Unmeasured acid load due to toxic alcohols, salicylates, or other toxins.
Normal anion gap/hyperchloremic	
Diarrhea, fistulas, or drainage losses	Gastrointestinal bicarbonate loss with a relative increase in chloride
Renal tubular acidosis	Renal bicarbonate loss or a defect in distal H^+ secretion
Large-volume 0.9% saline administration	Reduction in the strong ion difference due to a relative chloride excess
Acetazolamide	Renal bicarbonate loss associated with carbonic anhydrase inhibition

Abbreviations: CKD: chronic kidney disease; H^+ : hydrogen ion; HCO_3^- : plasma bicarbonate; NH_4^+ : ammonium.

Clinically, metabolic acidosis is categorized into two patterns: high anion gap acidosis, due to the accumulation of unmeasured anions, and hyperchloremic acidosis, due to the loss of HCO_3^- or the relative increase in chloride [31,49]. This distinction is vital for guiding the etiology and detecting mixed disorders in critically ill patients. High anion gap acidosis usually reflects an overload of organic acids, with hyperlactatemia being the most prevalent finding in the ICU [50,51]. Ketoacidosis, on the other hand, follows a different dynamic: insulin deficiency and increased counterregulatory hormone levels activate hepatic lipolysis and ketogenesis [52]. This results in the expansion of acetoacetate and β -hydroxybutyrate, anions that consume HCO_3^- and precipitate acidemia [53].

Renal function plays a crucial role in metabolic acidosis, as the kidney not only reabsorbs HCO_3^- but also serves as an essential urinary buffer [54]. In the proximal tubule,

glutamine generates NH_4^+ and produces new bicarbonate that returns to the circulation, while ammonium facilitates the excretion of the acid load [55]. At the level of the distal nephron, NH_3 secretion through ammonia transport pathways facilitates proton buffering and urinary NH_4^+ excretion, a process that is upregulated during metabolic acidosis [56]. This process is optimized by the recycling of ammonium in the renal medulla, which maximizes the net elimination of acid [57]. However, in AKI or advanced chronic kidney disease (CKD), impaired ammoniogenesis and reduced net acid excretion limit the kidney's ability to eliminate protons, thereby perpetuating acidemia [58,59].

Hyperchloremic metabolic acidosis, on the other hand, follows a different dynamic: instead of an overproduction of acids, it is characterized by the loss of HCO_3^- in the face of a relative increase in plasma chloride [60]. Because bicarbonate is a major extracellular anion and a central component of the bicarbonate- CO_2 buffer system, its reduction decreases extracellular buffering capacity and is accompanied by reciprocal changes in other ions or unmeasured anions to preserve electroneutrality [61]. A similar pattern may develop after large-volume administration of chloride-rich fluids, in which the rise in plasma chloride reduces the strong-ion difference and shifts acid-base equilibrium toward acidemia [62,63]. Renal tubular dysfunction may contribute to hyperchloremic acidosis when bicarbonate reclamation or chloride handling is altered [54]. Bicarbonate loss or chloride loading reduces the strong-ion difference, making chloride the predominant extracellular anion to preserve electroneutrality [60].

In contrast, high anion-gap metabolic acidosis usually reflects the accumulation of unmeasured anions and should prompt an active search for the underlying source [31,49]. In the ICU, the most frequent mechanism is lactate accumulation related to shock, sepsis, tissue hypoperfusion, impaired oxygen utilization, or reduced lactate clearance [50,51]. Ketoacidosis represents another major pathway, driven by the accumulation of acetoacetate and β -hydroxybutyrate in the setting of insulin deficiency and counterregulatory hormone excess [52,53]. In AKI or advanced CKD, impaired renal excretion favors the retention of uremic anions, while toxic alcohols and salicylates generate organic acids that may cause severe acidemia and require early antidotal or extracorporeal therapy [11,54,56].

Once established, acidemia can amplify organ dysfunction beyond its biochemical expression [8]. Its clinical impact depends on etiology, speed of onset, severity, and the patient's physiological reserve [8,64]. At the myocardial level, excess protons reduce myofilament sensitivity to calcium and attenuate the β -adrenergic responsiveness, compromising contractility and promoting hemodynamic instability [65]. In the respiratory system, acidemia activates carotid body chemoreceptors, increasing respiratory drive to reduce PaCO_2 ; however, sustained ventilatory demand increases respiratory muscle energy expenditure and may contribute to diaphragmatic fatigue [66,67]. At the level of the central nervous system, acidemia can alter extracellular pH and neuronal excitability by affecting ion channels and neurotransmission [68]. Therefore, the relevance of metabolic acidosis in the ICU lies not only in the magnitude of the pH decrease, but also in its ability to signal hypoperfusion, metabolic failure, renal impairment, or severe systemic injury, all of which require rapid etiological evaluation and targeted intervention [10].

6. Medical Management of Metabolic Acidosis

The management of metabolic acidosis in the ICU has evolved from isolated pH correction to a physiological strategy grounded in etiology and clinical context [2]. In practice, this involves discerning whether the disorder is mediated by acid gain, bicarbonate loss, or impaired renal excretion of the acid load, as each mechanism dictates different therapeutic priorities [69]. Following this logic, the current debate focuses on identifying which patients truly benefit from specific interventions, such as sodium bicarbonate or renal

replacement therapy, to optimize their outcomes [10]. Figure 1 summarizes the practical approach in critically ill patients.

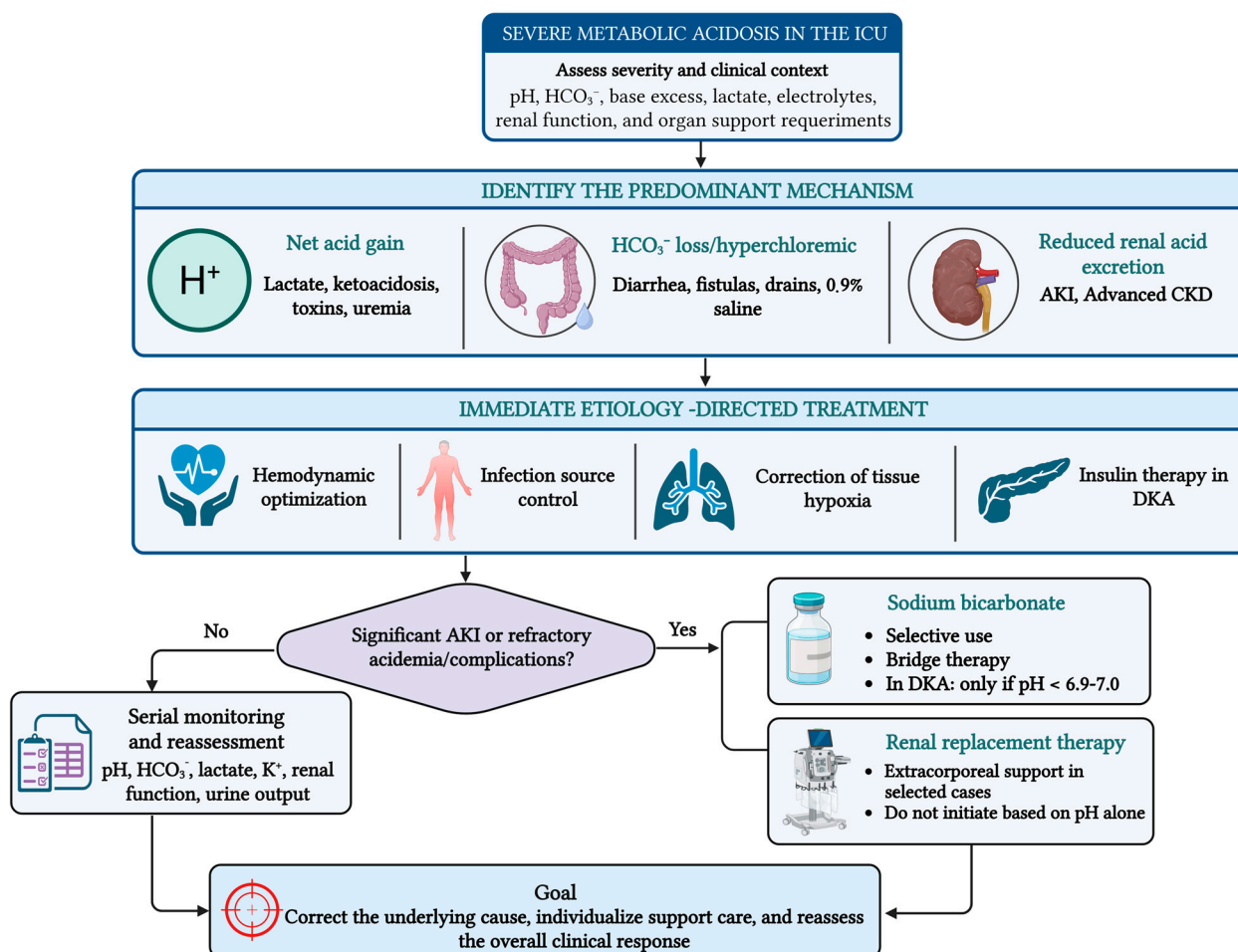


Figure 1. Practical approach to severe metabolic acidosis in the ICU. This figure summarizes the initial assessment, identification of the predominant mechanism, etiology-directed treatment, and the role of adjunctive therapies in selected patients. Abbreviations: AKI: acute kidney injury; CKD: chronic kidney disease; DKA: diabetic ketoacidosis; HCO_3^- : plasma bicarbonate; ICU: intensive care unit; K^+ : potassium. Created in BioRender. Osorio, E. (2026) <https://BioRender.com/sb6wzrb>; figure preparation was completed in June 2026.

6.1. Sodium Bicarbonate: Physiological Basis and Risks

In this context, contemporary debate has focused on the role of sodium bicarbonate as a therapeutic intervention [2]. Bicarbonate can transiently raise extracellular pH [8]. However, increased CO_2 production and reduced ionized calcium can limit its benefit and negatively affect cardiovascular function [70]. Nevertheless, in critically ill patients, metabolic acidosis should not be addressed as an isolated entity, but rather as a reflection of complex pathophysiological processes [24]. Therefore, chemical pH correction using bicarbonate does not always translate into a real improvement in clinical outcomes [10]. Consequently, its use should be individualized and reserved for specific scenarios, such as severe acidemia associated with AKI, while prioritizing the correction of the underlying cause [17].

Current evidence supports that treatment should be directed primarily at the etiology of metabolic acidosis, including hemodynamic optimization, control of the infectious focus, correction of tissue hypoxia, insulin therapy in diabetic ketoacidosis (DKA), and RRT when indicated [2,10,71]. In this context, intravenous bicarbonate should be considered a selective

adjunctive therapy and not the cornerstone of treatment [72]. The use of bicarbonate requires caution because of the risks of sodium and volume overload, reduced ionized calcium, increased CO₂ generation with possible retention when alveolar ventilation is insufficient, rebound alkalosis, and a false perception of correction while the underlying cause persists [2,73]. In patients with impaired cardiac or renal function, these effects may worsen congestion or hemodynamic instability, while rapid CO₂ diffusion may contribute to paradoxical intracellular acidosis if ventilation and tissue perfusion are inadequate [74]. Therefore, serial monitoring of blood gases and electrolytes is essential to prevent iatrogenic alkalosis once the acidemia has resolved [75].

6.2. Clinical Evidence: BICAR-ICU, BICARICU-2 and SODa-BIC

Historically, severe acidemia was considered inherently harmful, leading to the assumption that sodium bicarbonate should improve outcomes by correcting pH [76]. However, randomized evidence does not support its routine use as a universal strategy [2,10]. In BICAR-ICU, bicarbonate therapy did not improve the composite primary outcome in the overall population, but a prespecified subgroup analysis suggested lower RRT use and improved 28-day survival among patients with KDIGO stage 2–3 AKI [17]. This finding generated the hypothesis that bicarbonate might be useful in patients in whom acidemia reflects both systemic illness and impaired renal acid excretion. BICAR-ICU-2 did not reduce 90-day mortality, although it was associated with less RRT utilization [19]. More recently, SODa-BIC evaluated critically ill patients with metabolic acidosis and vasopressor support and showed faster correction of acidemia, but no reduction in major adverse kidney events at 30 days, mortality, vasopressor-free days, or other patient-centered outcomes [77]. Taken together, these trials suggest that sodium bicarbonate can improve acid–base variables and may reduce or delay RRT in selected patients, but this biochemical effect does not consistently translate into improved survival or durable kidney outcomes [17,19,77].

Several factors may explain these apparently discordant findings, including differences in inclusion criteria, AKI severity, vasopressor dependence, bicarbonate protocols, timing of intervention, and selected endpoints. Thus, bicarbonate should not be interpreted as a disease-modifying therapy for metabolic acidosis as a syndrome, but rather as a selective adjunct that may be reasonable in severe acidemia with AKI or hyperkalemia, or as temporary support while the underlying cause is corrected or RRT is arranged [10,17–19]. These findings are described in Table 3.

Table 3. Clinical evidence and potential subgroups for sodium bicarbonate use in severe metabolic acidosis.

Clinical Subgroup or Scenario	Participants/Evidence Base	Relevant Finding	Clinical Interpretation	Citation
General population with severe metabolic acidemia	BICAR-ICU: 389; HCO ₃ [−] <i>n</i> = 194, control <i>n</i> = 195	No significant improvement in the overall primary outcome in BICAR-ICU	Routine use solely to normalize pH is not recommended	Jaber S et al., [17]
Severe acidemia with KDIGO stage 2–3 AKI	BICAR-ICU AKI subgroup: 182; HCO ₃ [−] <i>n</i> = 92, control <i>n</i> = 90; BICARICU-2: 627 analyzed; HCO ₃ [−] <i>n</i> = 314, control <i>n</i> = 313; SODa-BIC: 498 analyzed; HCO ₃ [−] <i>n</i> = 244, placebo <i>n</i> = 254	BICAR-ICU and BICARICU-2 suggested lower RRT use, but no consistent survival benefit. SODa-BIC did not show benefit in the AKI stage 2–3 subgroup	Consider selectively; renal benefit remains uncertain	Jaber S et al., [17]; Jung B et al., [19]; SODa-BIC Investigators et al., [77]

Table 3. Cont.

Clinical Subgroup or Scenario	Participants/Evidence Base	Relevant Finding	Clinical Interpretation	Citation
Metabolic acidosis with vasopressor-dependent or septic shock	SODa-BIC: 498 analyzed; HCO_3^- $n = 244$, placebo $n = 254$	Faster acidemia correction without reduction in major adverse kidney events, mortality, or vasopressor-free days	Do not use routinely to improve renal, hemodynamic, or survival outcomes	SODa-BIC Investigators et al., [77]; Prescott H et al., [78]
Hyperkalemia with metabolic acidemia	Not trial-specific; based on pathophysiological reviews/guidance	Variable effect on serum potassium concentration	Use only as an adjunctive intervention	Kraut J et al., [9]; Yagi K et al., [10]
Gastrointestinal or renal bicarbonate loss	Not trial-specific; based on physiological rationale and expert guidance	Represents a true bicarbonate deficit	Bicarbonate replacement may be appropriate	Achanti A et al., [2]; Adrogué HJ et al., [16]
Severe diabetic ketoacidosis	Not trial-specific in ICU bicarbonate trials; based on diabetes guidelines and clinical evidence	No benefit from routine use and potential risk of hypokalemia	Reserve for extreme acidemia, generally $\text{pH} < 6.9$ – 7.0	Umpierrez GE et al., [79]; Correa-Guerrero J et al., [80]
Selected poisonings	Not trial-specific; evidence depends on toxic agent and EXTRIP/toxicology guidance	Clinical usefulness depends on the specific toxic agent	Individualize treatment according to the substance involved	Barceloux D et al., [81]; Palmer BF et al., [82]; Ghannoum M et al., [83]; Ghannoum M et al., [84]; Roberts D et al., [85]
Bridge to RRT	Trial interpretation: BICAR-ICU/BICARICU-2/SODa-BIC	Produces transient correction of acidemia without proven improvement in patient-centered outcomes	May be considered as temporary supportive therapy while correcting the cause or arranging RRT, without assuming improved clinical outcomes	Yagi K et al., [10]; SODa-BIC Investigators et al., [77]

Abbreviations: AKI: acute kidney injury; KDIGO: Kidney Disease: Improving Global Outcomes; HCO_3^- : Plasma bicarbonate; RRT: renal replacement therapy. Note: Sodium bicarbonate improves acid–base variables, but current randomized evidence does not demonstrate a consistent benefit in survival or major adverse kidney events. Its use should therefore remain selective and guided by the cause of acidosis, severity of acidemia, renal function, and accompanying complications.

6.3. Specific Clinical Situations

In the management of specific clinical scenarios, the use of bicarbonate should be individualized according to the underlying pathophysiology. In septic shock with hypoperfusion-induced lactic acidemia, sodium bicarbonate is not recommended solely to improve hemodynamics but may be considered when severe metabolic acidemia ($\text{pH} \leq 7.2$) coexists with AKI classified as Acute Kidney Injury Network (AKIN) stage 2 or 3 [78]. In DKA, bicarbonate is not routinely recommended and is usually reserved for extreme acidemia ($\text{pH} < 6.9$, or < 7.0 depending on the clinical guideline and context), due to the lack of demonstrated benefit and the risk of cerebral edema, hypokalemia, and delayed resolution of ketosis [79]. Fluid therapy, insulin therapy, and correction of electrolyte imbalances are a central focus [80]. Euglycemic DKA should be considered in patients receiving SGLT2 inhibitors when metabolic acidosis and ketonemia occur despite normal or only mildly elevated glucose levels; management follows the same principles as conventional DKA [86]. Finally, bicarbonate may have a specific role in selected causes of bicarbonate loss, such as diarrhea, fistulas, and renal tubular acidosis, as well as in certain toxic expo-

tures, depending on the underlying mechanism and clinical context [9,10,16,81]. These scenarios are summarized in Table 3.

In selected poisonings, the role of sodium bicarbonate depends on the toxic agent and the predominant mechanism of toxicity [87]. In salicylate poisoning, serum and urinary alkalinization reduces tissue penetration and promotes renal elimination, whereas in toxicity from tricyclic antidepressants or other sodium channel blockers, bicarbonate is primarily used in the presence of QRS widening, ventricular arrhythmias, or hemodynamic instability [74,82]. In methanol and ethylene glycol poisoning, bicarbonate can be used to correct severe acidemia; however, definitive treatment is based on inhibiting alcohol dehydrogenase and, when indicated, on extracorporeal elimination of the original compound and its toxic metabolites [83,84].

6.4. Renal Replacement Therapy

Current evidence indicates that the initiation of RRT should not be based solely on pH [88]. Although the ELAIN trial suggested a reduction in mortality with early RRT initiation, its results are limited by its single-center design and the comparison between KDIGO stages 2 and 3; it does not constitute a truly expectant management strategy [89]. In contrast, large pivotal trials such as AKIKI, IDEAL-ICU, and STARRT-AKI confirm that an accelerated strategy does not improve survival, supporting a delayed approach under close monitoring [90–92]. However, AKIKI-2 cautions that excessive delay in initiating RRT in the face of clinical or metabolic deterioration may be associated with worse outcomes [93]. Therefore, the decision should be based on the overall metabolic evolution, balancing the risk of unnecessary intervention against the risks of delaying treatment in the face of multiple organ failure, and reserving RRT for classic indications such as refractory acidosis, hyperkalemia, or volume overload [94]. The pH thresholds used in the trials should be interpreted as operational criteria rather than universal indicators independent of the clinical context. These findings are described in Table 4.

Table 4. Clinical evidence and patient subgroups for renal replacement therapy initiation in severe metabolic acidosis.

Clinical Subgroup or Scenario	Participants/Evidence Base	Relevant Finding	Clinical Interpretation	Citation
Severe AKI without urgent indications for RRT	AKIKI: 620 patients; early $n = 311$, delayed $n = 309$; IDEAL-ICU: 488 patients; early $n = 246$, delayed $n = 242$; STARRT-AKI: 3019 randomized; analyzed population $n = 2927$, accelerated $n = 1465$, standard $n = 1462$	Accelerated initiation did not improve survival	Use a delayed strategy with close monitoring	Gaudry S et al., [90]; Barbar S et al., [91]; STARRT-AKI Investigators et al., [92]
Early RRT initiation in selected surgical patients	ELAIN: 231 patients; early $n = 112$, delayed $n = 119$	ELAIN reported lower mortality with early initiation	Findings have limited generalizability	Zarbock A et al., [89]

Table 4. Cont.

Clinical Subgroup or Scenario	Participants/Evidence Base	Relevant Finding	Clinical Interpretation	Citation
KDIGO stage 3 AKI under close surveillance	AKIKI: 620 patients; early $n = 311$, delayed $n = 309$; STARRT-AKI: 3019 randomized; analyzed population $n = 2927$, accelerated $n = 1465$, standard $n = 1462$	Many patients assigned to delayed strategies avoided RRT	Do not initiate RRT solely because of AKI stage	Gaudry S et al., [90]; STARRT-AKI Investigators et al., [92]
Prolonged delay despite persistent severe AKI	AKIKI-2: 278 patients; delayed $n = 137$, more-delayed $n = 141$	Further postponement showed no benefit and possible harm	Delayed initiation should not become indefinite	Gaudry S et al., [93]
Refractory severe metabolic acidemia	Trial rescue criterion in AKIKI and STARRT-AKI; not a separate randomized subgroup	Persistent or worsening acidemia was used as a rescue criterion	Initiate RRT when medical and etiologic treatment fails	Cove M et al., [88]; Gaudry S et al., [90]; STARRT-AKI Investigators et al., [92]
Refractory hyperkalemia	Trial rescue criterion in AKIKI and STARRT-AKI; not a separate randomized subgroup	Severe hyperkalemia represents an urgent indication for RRT	Initiate promptly when medical treatment is ineffective	Cove M et al., [88]; Gaudry S et al., [90]
Refractory fluid overload	Trial rescue criterion in IDEAL-ICU and STARRT-AKI; not a separate randomized subgroup	Pulmonary edema or severe volume overload were rescue indications	Initiate RRT when oxygenation or hemodynamics are compromised	Barbar S et al., [91]; STARRT-AKI Investigators et al., [92]
Metabolic acidemia based only on an isolated pH value	Not trial-specific; based on interpretation of RRT timing trials and expert guidance	An isolated pH threshold does not identify patients who benefit from early RRT	Integrate pH with clinical course and other urgent indications	Cove M et al., [88]

Abbreviations: AKI: acute kidney injury; KDIGO: Kidney Disease: Improving Global Outcomes; RRT: renal replacement therapy. Note: RRT initiation should be guided by the overall clinical and metabolic trajectory rather than by an isolated pH threshold. Evidence from AKIKI, IDEAL-ICU, and STARRT-AKI supports a delayed strategy in the absence of urgent indications, whereas AKIKI-2 suggests that excessive postponement may be harmful.

When indicating RRT, the choice of modality should be individualized according to hemodynamic stability, fluid overload, and metabolic urgency [95]. Continuous therapies are preferable in unstable or vasopressor-dependent patients, as they allow gradual solute removal and sustained acid-base control, avoiding abrupt fluctuations in osmolality and sodium [96,97]. However, given the lack of demonstrated prognostic superiority in terms of mortality, intermittent modalities are an efficient option in stable patients, facilitating their rapid mobilization and clearance [97,98]. On the other hand, hybrid therapies are emerging as a versatile alternative during the transition or in the face of logistical limitations [99]. Ultimately, the modality should be dynamically reassessed as metabolic requirements and cardiovascular stability change [96].

7. Clinical Take-Home Messages

Severe metabolic acidosis in the ICU should prompt immediate assessment of the underlying cause, rather than the isolated correction of pH. Interpretation at the bedside should combine arterial blood gas analysis with lactate, anion gap, chloride, albumin, renal function, hemodynamic status, and the patient's recent clinical trajectory.

The first therapeutic step is always etiological: restore perfusion, control infection, correct hypoxia, treat ketoacidosis or toxic exposures, and dynamically reassess renal function. Sodium bicarbonate should not be used routinely to normalize pH. Its role is better understood as selective supportive therapy in severe acidemia with AKI, hyperkalemia, true bicarbonate loss, selected poisonings, or as a temporary bridge while definitive treatment or RRT is arranged.

RRT should not be initiated solely because the pH is below a predefined threshold. The decision should integrate the persistence of acidemia despite medical treatment, refractory hyperkalemia, fluid overload, uremic complications, hemodynamic tolerance, and the overall direction of organ dysfunction.

8. Conclusions

Metabolic acidosis is a common finding in the intensive care unit and should not be interpreted as a uniform disorder, but rather as the biochemical expression of various pathophysiological processes. Its prognostic implications depend largely on the underlying etiology, the magnitude of the acidemia, and the associated organ dysfunction. Its therapeutic approach continues to rely primarily on the early identification of the predominant mechanism and the correction of the triggering cause. Although adjuvant strategies exist, such as sodium bicarbonate and renal replacement therapy, their use should be individualized and not based solely on pH normalization, since improved acid-base parameters do not always translate into better clinical outcomes. Areas of uncertainty remain regarding the subgroups of patients who might benefit most from these interventions, justifying the continued expansion of evidence in this field.

Author Contributions: Conceptualization, C.R.-M., J.S.-R., E.O.-R. and D.R.-B.; data curation, J.S.-R., D.R.-B. and J.C.-G.; formal analysis, E.O.-R.; methodology, D.R.-B. and E.O.-R.; project administration, D.R.-B., J.S.-R. and E.O.-R.; visualization, J.S.-R. and E.O.-R.; writing—original draft preparation, C.R.-M., J.S.-R., E.O.-R., A.P.-C., C.B.-S., N.M.-F., D.G.-B., D.R.-B., M.C.-C., J.C.-G., A.P.-B. and C.D.-C.; writing—review and editing, C.R.-M., J.S.-R., E.O.-R., A.P.-C., C.B.-S., N.M.-F., D.G.-B., D.R.-B., M.C.-C., J.C.-G., A.P.-B. and C.D.-C. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new primary data were generated in this study. All data analyzed were derived from previously published studies included in this review.

Acknowledgments: During the preparation of this manuscript, the authors used AI to assist with language editing (Grammarly 2026). The authors reviewed and edited the output and take full responsibility for the content of this publication.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

AKI	Acute kidney injury
AKIN	Acute Kidney Injury Network
CKD	Chronic kidney disease
CO ₂	Carbon dioxide
DKA	Diabetic ketoacidosis
H ⁺	Hydrogen ion
HCO ₃ [−]	Plasma bicarbonate
ICU	Intensive care unit
K ⁺	Potassium
KDIGO	Kidney Disease: Improving Global Outcomes
NH ₃	Ammonia
NH ₄ ⁺	Ammonium
PaCO ₂	Partial pressure of arterial carbon dioxide
RRT	Renal replacement therapy
SBE	Standard base excess
SID	Strong ion difference

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