Review

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

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Review

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

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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.

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

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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 (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 can shift the oxyhemoglobin dissociation curve (Bohr effect) to the right, which initially facilitates oxygen delivery to the 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]. For years, the treatment of severe acidemia relied on the idea that correcting pH alone should result in clinical improvement [16]. However, current evidence supports a selective approach focused on the disorder's etiology [10]. In this context, both sodium bicarbonate and renal replacement therapy (RRT) should be used under strict criteria, taking into account the identification of clinical subgroups that could benefit from these interventions [17].

In this context, sodium bicarbonate and RRT occupy relevant but non-universal roles in severe metabolic acidosis: bicarbonate may reduce RRT use in selected patients, although this effect has not been consistently confirmed, whereas RRT should be reserved for well-defined clinical scenarios and not initiated solely on the basis of an isolated pH threshold [18,19]. In this narrative review, we aim to integrate the most relevant clinical and pathophysiological evidence on severe metabolic acidosis in critically ill patients, with special emphasis on AKI, the use of sodium bicarbonate, and the timing of RRT initiation.

2. 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]. While the former is governed by a single, accurate, and universally accepted marker such as $PaCO_2$ [11,21], metabolic analysis offers different levels of depth. This ranges from the descriptive Henderson-Hasselbalch model, focused on pH and plasma bicarbonate [HCO_3^-] [20], to the semi-quantitative approach proposed by Singer and Hastings, which introduces the concept of a buffer base to define the sum of HCO_3^- and the anions of non-volatile weak acids [22]. Finally, Stewart's quantitative model provides a perspective based on the difference in strong ions and the concentration of volatile and weak acids [23,24].

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In clinical practice, the standardized base excess (SBE) has become established as a fundamental parameter for quantifying metabolic disorders [22]. Its conceptual evolution has allowed it to overcome the limitations of previous indicators by integrating the effect of non-carbonic buffers, such as plasma proteins [25]. Therefore, SBE is a useful parameter for quantifying the magnitude of the metabolic component of an acid–base disorder [20]. However, the SBE has diagnostic limitations: it does not identify the underlying mechanisms on its own, and, as a composite marker (influenced by chloride, lactate, and ketoacids), its components can compensate for each other [23,26]. Consequently, a normal value does not rule out underlying metabolic disorders, necessitating an integrated interpretation with other biochemical data [24].

From the Henderson-Hasselbalch perspective, metabolic acidosis is defined as a primary disorder characterized by a decrease in HCO_3^- and base excess, 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 pH < 7.35, HCO_3^- < 20–22 mmol/L, and BE ≤ −3 mmol/L [2]. Its 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 [27].

These acid-base disturbances are extremely prevalent: up to 90% of ICU patients present with some acid-base disorder in the first 24 hours [2]. Mallela et al. describe disturbances in 93.3% of patients [28]. International studies confirm that metabolic acidemia is the most common subtype, affecting 42.9% of cases [29] and associated with prolonged hospital stays and a greater need for ventilation or vasopressors [7]. Although classic studies report mortality rates of up to 60% in severe cases [30], the real impact of correcting pH alone remains a subject of debate compared to treating the underlying cause [31].

Historical evidence, such as the study by Gunnerson et al., demonstrates a 45% mortality rate in patients with acidosis compared to 25% in the control group [30]. Similarly, Jung et al. report a mortality rate close to 60% in critically ill patients with severe metabolic acidosis, with a 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 [27]. 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 [31].

3. 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 [32]. 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 [27]. 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.

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 [33]. 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 $PaCO_2$ and limit the decrease in pH; however, when ventilatory demand is sustained over time, the increased work of

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breathing can exceed the functional reserve of the critically ill patient and promote ventilatory fatigue [34]. $PaCO_2$ 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 [35]. In patients receiving mechanical ventilation, metabolic acidosis can impair ventilatory adjustment, increase respiratory drive, and contribute to failed weaning attempts [36].

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

Neurological manifestations are nonspecific and include headache, restlessness, altered mental status, drowsiness, and, in cases of severe acidemia, stupor or coma [4]. Furthermore, acidosis can potentiate the depressant effects of sedative and analgesic drugs by altering their ionization state and tissue distribution [37]. Therefore, this complicates serial neurological assessment and the application of sedation scales.

At a systemic level, it is frequently accompanied by hyperkalemia, insulin resistance, impaired glycemic control, and increased protein and bone catabolism [38–40]. Furthermore, metabolic acidosis promotes muscle proteolysis by activating protein degradation pathways and interfering with protein synthesis; it has also been associated with a negative nitrogen balance, changes that can accelerate the loss of lean mass and increase functional decline in critically ill patients [41,42]. In parallel, bone acts as an extracellular buffer against acid load; however, this buffering effect occurs at the expense of bone 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].

4. 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.

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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 NH4+ 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; NH4+: 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 [32,49]. 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 [50–52]. Ketoacidosis, on the other hand, follows a different dynamic: insulin deficiency and increased counterregulatory hormone levels activate hepatic lipolysis and ketogenesis [53]. This results in the expansion of acetoacetate and β-hydroxybutyrate, anions that consume HCO_3^- and precipitate acidemia [54].

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 [55]. In the proximal tubule, glutamine generates NH4+ and produces new bicarbonate that returns to the circulation, while ammonium facilitates the excretion of the acid load [56]. At the level of the distal nephron, NH3 buffers protons by transforming into NH4+, which is trapped in the tubular lumen for subsequent elimination [57]. This process is optimized by the recycling of ammonium in the renal medulla, which maximizes the net elimination of acid [58]. However, in AKI or advanced CKD, impaired ammoniagenesis and reduced net acid excretion limit the kidney's ability to eliminate protons, thereby perpetuating acidemia [59,60].

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 [61]. In the ICU setting, this disorder is usually due to well-defined clinical scenarios, such as diarrhea, gastrointestinal drainage, renal tubular acidosis, or the administration of high-chloride solutions [2]. The end result is a reduction in extracellular buffering capacity due to the decrease in the concentration of available HCO_3^- [62]. From a physicochemical perspective, this phenomenon results in a reduction in the strong ion difference (SID), thereby shifting acid–base equilibrium toward acidemia [63].

Once established, acidemia transcends a mere biochemical change to become a factor that amplifies organ dysfunction [8]. However, its clinical impact depends on the etiology, the speed of

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its development, and the patient's physiological reserve [8]. At the myocardial level, excess protons reduce myofilament sensitivity to calcium and attenuate the β-adrenergic response; this mechanism compromises contractility and promotes hemodynamic instability [64]. 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, or renal impairment—elements that necessitate rapid etiological evaluation and targeted intervention [10].

In the respiratory system, acidemia activates the compensatory ventilatory response, mediated primarily by chemoreceptors in the carotid bodies. This process increases respiratory drive to reduce $PaCO_2$ [65]. However, if this demand is prolonged, the increase in minute ventilation raises the energy expenditure of the respiratory muscles, which can lead to diaphragmatic fatigue [66]. Simultaneously, in the central nervous system, acidemia alters extracellular pH and neuronal excitability by affecting ion channels and neurotransmission [67]. It is important to note that the clinical impact lies not only in the magnitude of the pH, but also in the speed of its onset, its etiology, and the severity of the associated systemic aggression [68].

5. 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.

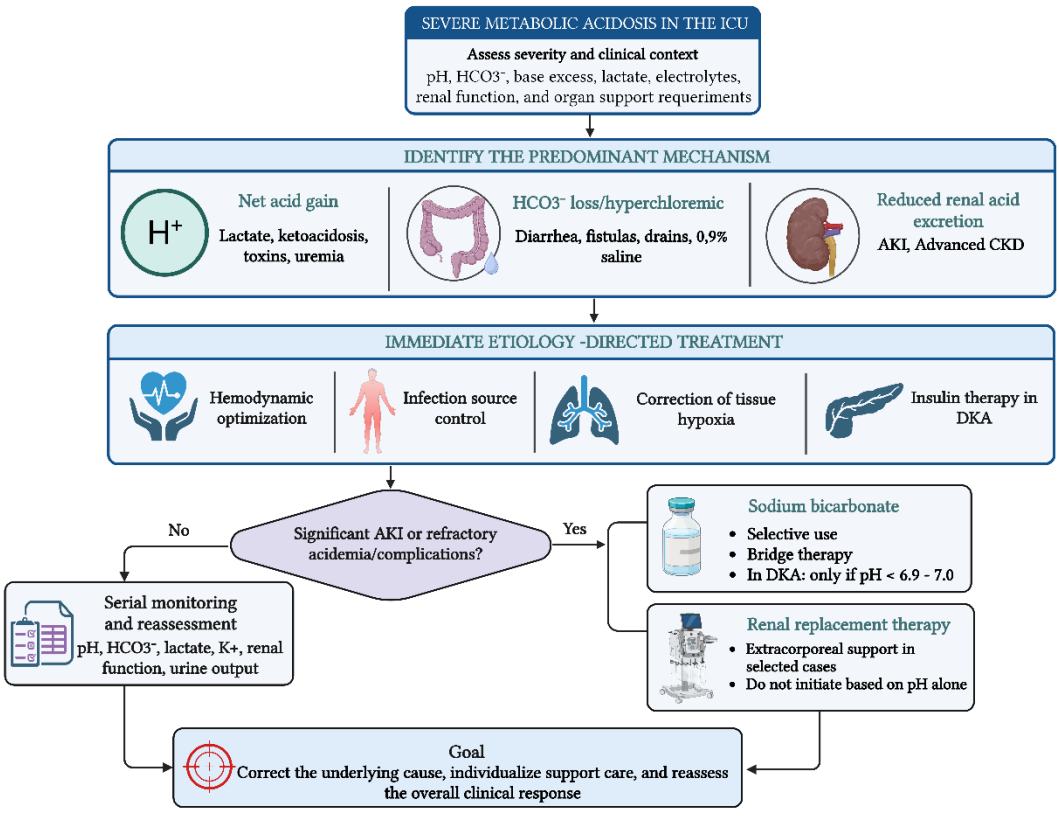

Figure 1. Practical approach to severe metabolic acidosis in the ICU. This figure summarizes the initial assessment, identification of the predominant mechanism, etiology-directed treatment, and the role of adjunctive therapies in selected patients. Abbreviations: AKI: acute kidney injury; CKD: chronic kidney disease; DKA:

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diabetic ketoacidosis; HCO_3^-: plasma bicarbonate; ICU: intensive care unit; K+: potassium; RRT: renal replacement therapy. BioRender https://BioRender.com/sb6wzrb; figure preparation was completed in June 2026.

5.1. 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 [25]. 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 [18].

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, 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 CO_2 generation with possible retention when alveolar ventilation is insufficient, rebound alkalosis, and a false perception of correction while the underlying cause persists [2,73]. Therefore, serial monitoring of blood gases and electrolytes is essential to prevent iatrogenic alkalosis once the acidemia has resolved [74].

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

Historically, acidemia was considered inherently harmful; however, current evidence has challenged the use of sodium bicarbonate as a universal therapeutic strategy [2]. The BICAR-ICU trial did not improve the primary outcome in the overall population, although a prespecified subgroup analysis suggested lower RRT use and improved 28-day survival among patients with KDIGO stage 2–3 AKI [18]. However, BICAR-ICU-2 did not reduce 90-day mortality, although it was associated with less RRT utilization. The protocol used 4.2% sodium bicarbonate in 125–250 mL boluses over 30 minutes, repeated to achieve a pH ≥7.30, with a maximum of 1000 mL in 24 hours [17]. More recently, the SODa-BIC trial, which included 500 patients with metabolic acidosis and vasopressor support, showed that bicarbonate corrected acidemia more rapidly but did not reduce major adverse kidney events at 30 days or improve other relevant clinical outcomes [75]. Taken together, these trials indicate that sodium bicarbonate improves acid–base variables but does not provide a consistent benefit in survival or patient-centered kidney outcomes [17,18,75]. Thus, the evidence suggests limiting its use to patients with severe acidemia (pH ≤ 7.2), associated with AKI or hyperkalemia, or as a temporary measure while the underlying cause is corrected or RRT is initiated [10]. 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	Relevant finding	Clinical interpretation	Citation
General population with severe metabolic acidemia	No significant improvement in the overall primary outcome in BICAR-ICU	Routine use solely to normalize pH is not recommended	Jaber S et al., [18]
Severe acidemia with KDIGO stage 2–3 AKI	BICAR-ICU and BICARICU-2 suggested lower RRT use, but no consistent survival benefit.	Consider selectively; renal benefit remains uncertain	Jaber S et al., [18]; Jung B et al., [17]; SODa-BIC

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	SODa-BIC did not show benefit in the AKI stage 2–3 subgroup		Investigators et al., [75]
Metabolic acidosis with vasopressor-dependent or septic shock	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., [75]; Prescott H et al., [76]
Hyperkalemia with metabolic acidemia	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	Represents a true bicarbonate deficit	Bicarbonate replacement may be appropriate	Achanti A et al., [2]; Adrogué HJ et al., [16]
Severe diabetic ketoacidosis	No benefit from routine use and potential risk of hypokalemia	Reserve for extreme acidemia, generally pH < 6.9–7.0	Umpierrez GE et al., [77]; Correa-Guerrero J et al., [78]
Selected poisonings	Clinical usefulness depends on the specific toxic agent	Individualize treatment according to the substance involved	Barceloux D et al., [79]; Palmer BF et al., [80]; Ghannoum M et al., [81]; Ghannoum M et al., [82]; Roberts D et al., [83]
Bridge to RRT	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., [75]

Abbreviations: AKI: acute kidney injury; KDIGO: Kidney Disease: Improving Global Outcomes; 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.

5.3. 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 (pH ≤ 7.2) coexists with AKI classified as Acute Kidney Injury Network (AKIN) stage 2 or 3 [76]. In diabetic ketoacidosis, bicarbonate is not routinely recommended and is usually reserved for extreme acidemia (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 [77]. Fluid therapy, insulin therapy, and correction of electrolyte imbalances are a central focus [78]. 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 exposures, depending on the underlying mechanism and clinical context [9,10,16,79]. 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 [84]. In salicylate poisoning, serum and urinary alkalinization reduces tissue penetration and promotes renal elimination, whereas in toxicity from tricyclic

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antidepressants or other sodium channel blockers, bicarbonate is primarily used in the presence of QRS widening, ventricular arrhythmias, or hemodynamic instability [80,85]. 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 [81,82].

5.4. Renal Replacement Therapy

Current evidence indicates that the initiation of RRT should not be based solely on pH [86]. 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 [87]. 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 [88–90]. However, AKIKI-2 cautions that excessive delay in initiating RRT in the face of clinical or metabolic deterioration may be associated with worse outcomes [91]. 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 [92]. 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	Relevant finding	Clinical interpretation	Citation
Severe AKI without urgent indications for RRT	Accelerated initiation did not improve survival	Use a delayed strategy with close monitoring	Gaudry S et al., [88]; Barbar S et al., [89]; STARRT-AKI Investigators et al., [90]
Early RRT initiation in selected surgical patients	ELAIN reported lower mortality with early initiation	Findings have limited generalizability	Zarbock A et al., [87]
KDIGO stage 3 AKI under close surveillance	Many patients assigned to delayed strategies avoided RRT	Do not initiate RRT solely because of AKI stage	Gaudry S et al., [88]; STARRT-AKI Investigators et al., [90]
Prolonged delay despite persistent severe AKI	Further postponement showed no benefit and possible harm	Delayed initiation should not become indefinite	Gaudry S et al., [91]
Refractory severe metabolic acidemia	Persistent or worsening acidemia was used as a rescue criterion	Initiate RRT when medical and etiologic treatment fails	Cove M et al., [86]; Gaudry S et al., [88]; STARRT-AKI Investigators et al., [90]
Refractory hyperkalemia	Severe hyperkalemia represents an urgent indication for RRT	Initiate promptly when medical treatment is ineffective	Cove M et al., [86]; Gaudry S et al., [88]
Refractory fluid overload	Pulmonary edema or severe volume overload were rescue indications	Initiate RRT when oxygenation or	Barbar S et al., [89]; STARRT-AKI

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		hemodynamics are compromised	Investigators et al., [90]
Metabolic acidemia based only on an isolated pH value	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., [86]

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 [93]. 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 osmolarity and sodium [94,95]. 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 [95,96]. On the other hand, hybrid therapies are emerging as a versatile alternative during the transition or in the face of logistical limitations [97]. Ultimately, the modality should be dynamically reassessed as metabolic requirements and cardiovascular stability change [94].

6. 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.

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Abbreviations

The following abbreviations are used in this manuscript:

AKI	Acute kidney injury
AKIN	Acute Kidney Injury Network
BE	Base excess
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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