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Review Article

Etiology and Management of Acute Metabolic Acidosis: An Update

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Acidosis · Lactate · Metformin · Bicarbonate · Balanced fluid resuscitation

Abstract
Background: The etiology of acute metabolic acidosis (aMA) is heterogeneous, and the consequences are potentially life-threatening. The aim of this article was to summarize the causes and management of aMA from a clinician's perspective. ***Summary:*** We performed a systematic search on PubMed, applying the following search terms: "acute metabolic acidosis," "lactic acidosis," "metformin" AND "acidosis," "unbalanced solutions" AND "acidosis," "bicarbonate" AND "acidosis" AND "outcome," "acute metabolic acidosis" AND "management," and "acute metabolic acidosis" AND "renal replacement therapy (RRT)/dialysis." The literature search did not consider diabetic ketoacidosis at all. Lactic acidosis evolves from various conditions, either with or without systemic hypoxia. The incidence of metformin-associated aMA is actually quite low. Unbalanced electrolyte preparations can induce hyperchloremic aMA. The latter potentially worsens kidney-related outcome parameters. Nevertheless, prospective and controlled data are missing at the moment. Recently, bicarbonate has been shown to improve clinically relevant endpoints in the critically ill, even if higher pH values (>7.3) are targeted. New therapeutics for aMA control are under development, since bicarbonate treatment can induce serious side effects. ***Key Messages:*** aMA is a frequent and potentially life-threatening complication of various conditions. Lactic acidosis might occur even in the absence of systemic hypoxia. The incidence of metformin-associated aMA is comparably low. Unbalanced electrolyte solutions induce hyperchloremic aMA, which most likely worsens the renal prognosis of critically ill patients. Bicarbonate, although potentially deleterious due to increased carbon dioxide production with subsequent intracellular acidosis, improves kidney-related endpoints in the critically ill.

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Introduction

Metabolic acidosis is a frequent acid-base disturbance in daily clinical medicine. An exact definition of "acute" metabolic acidosis (aMA) is missing. Nevertheless, the term acute may be used if acidosis or acidemia evolves within minutes to days [1]. Exact epidemiological data are difficult to provide, since many diseases/circumstances can induce aMA. Among those are accumulation of organic acids in uncontrolled diabetes mellitus, severe hypoperfusion (shock), sepsis with or without shock, ingestion of certain types of drugs, and a heterogeneous group of less common causes [2]. aMA also occurs as a result of net bicarbonate loss [3]. The latter has been observed in inflammatory intestinal diseases and after the administration of so-called carbonic anhydrase inhibitors [4]. In recent years, unbalanced electrolyte solutions have been discussed as inducing hyperchloremic metabolic acidosis. Meanwhile, this particular concept has partly been confirmed [5].

The consequences of aMA are potentially life-threatening, depending on its severity and onset. While patients with chronic MA suffer particularly from protein catabolism and impaired excretory kidney function, aMA induces hemodynamic instability and hyperkalemia [6]. In addition, hyperchloremic MA due to unbalanced electrolyte solutions has been associated with an increased risk of acute kidney injury (AKI) [5]. It needs to be emphasized that no causal relationship has been identified so far. Nevertheless, aMA should be prevented. Treatment of the respective cause is the measure of first choice. However, alkali therapy is being performed in hospitals all over the world, particularly in the intensive care unit (ICU). Recently, a prospective trial evaluated outcome parameters in critically ill subjects that received bicarbonate in a controlled manner [7]. Until then, it had been almost unknown whether bicarbonate therapy truly improved relevant endpoints or not.

The current article is intended to summarize the etiology, pathophysiology, and therapy of the following types of aMA: (1) lactic acidosis, including metformin-associated acidosis, and (2) aMA following volume resuscitation with unbalanced electrolyte solution. Ketoacidosis will not be discussed in this article. The last section focuses on bicarbonate therapy in aMA.

Definition and Pathophysiology

Metabolic acidosis occurs if an increase in extracellular hydrogen ion concentration does not result from net accumulation of carbon dioxide. Both the pH and serum bicarbonate decrease. As discussed in the Introduction, a clear definition of "acute" in aMA is missing. Two mechanisms account for the generation of metabolic acidosis: the net accumulation of organic acids or the net loss of bicarbonate. Organic acids may accumulate due to endogenous overproduction, exogenous ingestion, or impaired excretion. Respective acids/anions are, for instance, acetoacetate and beta-hydroxybutyrate in diabetic ketoacidosis, lactic acid in shock/sepsis, and formic acid after ingestion of methanol. Net loss of bicarbonate may occur in diseases that affect the upper gastrointestinal tract, followed by impaired reabsorption of bicarbonate containing pancreas secretes. Another, less frequent cause is diminished tubular reabsorption of filtered bicarbonate in the kidney. This is typically seen in renal tubular acidosis type 2 and in subjects treated with acetazolamide. The substance inhibits the activity of the enzyme carbonic anhydrase, which is required for renal bicarbonate preservation. The loss of bicarbonate results in increased de novo bicarbonate synthesis, which also increases the production of hydrogen ions. Metabolic acidosis is either diagnosed as high-anion-gap MA if organic acid accumulation is the respective cause, or as normal-anion-gap MA if bicarbonate loss accounts for the acidemia.

Lactic Acidosis Excluding Metformin

Lactate is the anion of lactic acid. Two enantiomers exist, L- and D-lactate. In most situations, lactic acidosis evolves as the result of L-lactate accumulation. Historically, two types of L-lactic acidosis are distinguished: type A, in which accumulation of lactic acid results from impaired oxygen supply, and type B, which does not necessarily run parallel with tissue hypoxia [8]. Recently, Kamel et al. [2] introduced a new concept of this particular acid-base disorder. L-Lactic acidosis either results from lactate overproduction or from impaired acid excretion. The latter occurs less frequently, although both mechanisms can evolve simultaneously. The article by Kamel et al. [2] describes the molecular mechanisms of lactic acid production and metabolism in a very detailed manner. Therefore, we omit a discussion of the biochemical processes here; they will only be mentioned if necessary. We do not intend to favor one concept over the other (type A/B vs. overproduction/impaired elimination). Nevertheless, the most important types of lactic acidosis shall be reviewed briefly.

Tissue Hypoxia in Shock

Cardiogenic, hypovolemic, and (variably) septic shock are characterized by transient or prolonged hypoperfusion of tissues/organs. Subsequently, the so-called total or global oxygen delivery declines. Oxygen is critically needed for electron acceptance at the inner mitochondrial membrane. Lower electron acceptance inhibits proton transfer through the membrane, ultimately resulting in reduced adenosine triphosphate (ATP) synthesis. Lower ATP production is partly compensated by stimulation of anaerobic glycolysis. The respective end product, pyruvate, is metabolized to lactic acid. Serum L-lactate is by no means insignificant in critically ill patients but a predictor of mortality, particularly in septic individuals [9]. Serum lactate in sepsis should be lowered as effectively as possible, although the exact target level is still a matter of debate [10].

Sepsis

Lactic acidosis in sepsis may partly result from hypoperfusion and, thus, generalized hypoxia. In addition, local hypoxia can emerge in septic patients, even if hemodynamic parameters have been optimized. Local hypoxia ensues notably from microvascular or endothelial dysfunction, resulting in impaired regional blood flow distribution and inefficient mitochondrial oxygen supply [2]. Microvasculopathy in sepsis is further aggravated by activation of the coagulation cascade and by endothelial adherence of inflammatory cells [11–13]. Recently, Kamel et al. [2] listed further mechanisms that promote lactate overproduction in sepsis, independently from tissue hypoxia.

Malignant Diseases

Hematological and solid malignancies can induce L-lactic acidosis [14]. The acid-base disorder predominantly results from acid overproduction by malignant cells. As a matter of fact, lactic acid production by cells does not require lack of oxygen. Almost 100 years ago, tumor cells were shown to consume glucose and to produce lactic acid even if oxygen is provided in sufficient quantities [15]. Nevertheless, local hypoxia in expanding tumors may perpetuate the production of acid as well [16].

Muscular Hyperactivity

L-Lactate levels often increase in patients with seizures or severe asthma [17, 18]. Extensive muscular contraction augments local ATP production via glycolysis with subsequent stimulation of local pyruvate and lactic acid production.

Substance-Associated Lactic Acidosis (Excluding Metformin)

Lactic acidosis can result from both lack and accumulation of certain substances. The former type is typically seen in thiamine and pyridoxine deficiency [19, 20]. The latter type can occur in severe ethanol and methanol intoxication, and in subjects treated with antiretroviral drugs, linezolid, or propofol. As opposed to L-lactic acidosis, D-lactic acidosis occurs significantly less frequently. D-Lactic acid is produced by certain types of bacteria in the gut. In the literature, this particular type of aMA has been proposed as "unidentified anion gap metabolic acidosis" [21]. It needs to be considered if high-anion-gap aMA is diagnosed without the identification of common causes. The diagnosis can be difficult, since D-lactic acid has been shown to undergo fast degradation [22].

Metformin-Associated Acidosis

Metformin has been established as a first-choice drug for treating type 2 diabetic patients. The substance lowers systemic glucose concentrations through inhibiting gluconeogenesis in the liver. In addition, peripheral glucose utilization is stimulated because metformin increases insulin sensitivity [23]. During gluconeogenesis, pyruvate is further metabolized by the enzyme pyruvate carboxylase. Metformin reduces the activity of the enzyme, which results in increased conversion of pyruvate in lactate [24]. The drug also uncouples oxidative phosphorylation in mitochondria [25].

The risk of metformin-induced lactic acidosis has most likely been overestimated in recent years. It has been reported at 0.03–0.06 per 1,000 patient-years [26]. However, it might significantly increase in the following situations: systemic hypoxia (stimulation of anaerobic glycolysis), liver insufficiency (reduced gluconeogenesis), and/or impaired excretory kidney function (diminished metformin excretion). Recently, Rajasurya et al. [27] proposed a clinical approach to the syndrome. Lactic acidosis should only be considered as metformin induced if either no other plausible cause can be identified or systemic levels of metformin suggest a pathogenetic role for the drug.

Acidosis due to Administration of Unbalanced Electrolyte Solutions

The concept of crystalloid-induced aMA is based on the following pathophysiological considerations. Chloride and bicarbonate are distributed between the extra- and intracellular space in a dynamic manner. According to the necessity to preserve electroneutrality in the extracellular space, every net addition of one anion modulates the availability of the other anion diametrically. Expanding the extracellular chloride load results in higher glomerular filtration and tubular elimination of bicarbonate, and in reduced proton net excretion by the kidney. Thus, hyperchloremic metabolic acidosis ensues, where the anion gap remains unchanged [28].

The chloride content in 0.9% saline solution is above the range of the human extracellular fluid (154 vs. 95 mmol/L). The fact that these preparations can induce aMA has been discussed for many years [5, 29]. Quite early (in 2012), animal experiments indicated that unbalanced (chloride-enriched) crystalloids might affect kidney function in an unfavorable manner [29]. Meanwhile, this concept has partly been confirmed by clinical observations. However, prospective *and* randomized trials are rare at the moment. In 2012, Yunos et al. [30] published a prospective, open-label, sequential-period trial. During a control phase of 6 months, ICU patients received crystalloids in a liberal manner (unbalanced and balanced solutions). During the intervention phase, unbalanced solutions were only applied if a specialist had

Table 1. Etiology of aMA

Type	Mechanism
Lactic acidosis excluding metformin	
Tissue hypoxia	Systemic oxygen supply ↓ → oxidative phosphorylation → anaerobic glycolysis ↑ → pyruvate synthesis ↑ → pyruvate conversion into lactic acid ↑
Sepsis	Systemic oxygen supply ↓ (see above)
	Endothelial dysfunction and leukocyte adhesion → microvasculopathy → local oxygen supply ↓
	Increased lactic acid production, independently of tissue oxygenation
Malignant diseases	Increased lactic acid production, independently of oxygen supply Local hypoxia in solid tumors
Muscular hyperactivity	Local (intramuscular) ATP synthesis via anaerobic glycolysis ↑ → pyruvate synthesis ↑ → pyruvate conversion into lactic acid ↑
Substances	Thiamine deficiency: pyruvate decarboxylase activity ↓ → pyruvate accumulation and conversion into lactic acid ↑
	Pyridoxine deficiency: gamma-aminobutyric acid (GABA) synthesis ↓ → risk of seizures ↑ → muscular hyperactivity → lactic acid →
	Ethanol: hepatic NADH + H^+ synthesis ↑ → pyruvate conversion into lactic acid ↑
	Methanol: formic acid ↑ → inhibition of complex IV of the respiratory chain → anaerobic glycolysis ↑ (see above)
	Antiretroviral drugs: mitochondrial damage → oxidative phosphorylation → anaerobic glycolysis ↑ (see above)
	Linezolid: inhibition of complex IV of the respiratory chain → anaerobic glycolysis ↑ (see above)
	Propofol: see linezolid
Metformin-associated acidosis	
Lactic acidosis	Inhibition of pyruvate carboxylase → pyruvate conversion into lactic acid ↑
	Uncoupling of oxidative phosphorylation → ATP synthesis via anaerobic glycolysis ↑
aMA due to unbalanced electrolyte solutions	
Hyperchloremic metabolic acidosis with normal anion gap	Glomerular und tubular bicarbonate elimination ↑
	Renal proton excretion ↓

aMA, acute metabolic acidosis.

decided that way. It became apparent that the incidence of AKI lowered during phase 2, which was indicative of deleterious effects of more chloride-rich preparations.

Shaw et al. [31] published a retrospective cohort study and extracted data from the Premier Perspective Comparative Database. Almost 32,000 subjects were included. Administration of saline worsened almost all outcome variables including mortality, rate of postoperative infection, and AKI incidence. Another retrospective cohort study included septic ICU patients. Out of 53,448 included individuals, 3,396 had been treated with balanced fluids. The subjects that received the latter showed better survival, but AKI incidence rates did not differ

between the "balanced" and the "unbalanced" group. Comparable observations were reported from another retrospective trial, published in 2014 [32]. The randomized SALT trial from 2017, however, failed to show beneficial effects of balanced solutions on AKI incidence or renal replacement therapy (RRT) [33]. Nevertheless, updated recommendations for the prevention of acute kidney injury in critically ill patients from 2018 [34] favored balanced crystalloids. Table 1 summarizes the etiology of aMA.

Management Including Bicarbonate

The management of aMA requires the control of the respective cause: hemodynamic stabilization including volume therapy and vasopressors in cardiogenic, hypovolemic or septic shock, renal replacement therapy in certain types of intoxication if required, and other measures depending on the etiology. Regarding sepsis and septic shock, firm recommendations are given in the current guidelines [35, 36].

However, causal treatment often does not result in a rapid correction of serious pH abnormalities. In many patients, additional measures must be initiated in order to prevent hemodynamic and proarrhythmogenic consequences of acidemia. Therefore, alkali therapy is performed in hospitals all over the world. Before we review the modalities and outcomes of bicarbonate treatment in detail, we would like to discuss some lesser-known procedures for aMA control.

First, RRT has been successfully initiated in severe cases of metformin-associated acidosis. Moioli et al. [24] reported on 16 subjects receiving dialysis. They concluded that RRT is more effective in aMA control than buffer therapy alone. The feasibility and efficacy of RRT in this situation was also reported by Kinoshita et al. [37]. In 2015, the Extracorporeal Treatments in Poisoning Workgroup evaluated 175 articles reporting on RRT in metformin intoxication [38]. It concluded that RRT "appears to be amendable" in aMA, although the data published so far were mostly extracted from case reports.

Another and lesser-known therapeutic approach is the administration of pyruvate. The concept behind its usage is the substance's ability to activate the enzyme pyruvate dehydrogenase (PDH). Simultaneously, pyruvate acts as a PDH substrate. Under hypoxic conditions, PDH activity decreases, followed by enhanced metabolization of pyruvate in lactic acid. PDH activation in contrast augments pyruvate conversion into acetyl-CoA [39]. Initially, antiacidotic effects of pyruvate were exclusively shown in animal models (swine [40] and rats [41]). Hu et al. [42] showed pyruvate-based Ringer's solution to act in a superior way on blood loss-associated aMA in rats. Comparisons were made with lactate-containing Ringer's solution. However, substantial clinical data are missing at the moment. For further reading, we would like to refer to the excellent article by Wang et al. [39]. This article also contains information about other buffer substances such as tromethamine (THAM) and spermidine, as well as on pharmacological NHE1 inhibition.

Bicarbonate is metabolized into carbon dioxide (CO_2) and water. This process consumes protons. Although the pH and serum bicarbonate level subsequently increase, several problems are unavoidable. Firstly, increased CO_2 production requires ventilatory compensation. Secondly, bicarbonate administration lowers the intracellular pH [43], most likely as a result of increased CO_2 transfer into the intracellular compartment. Finally, bicarbonate infusion has been shown to even elevate systemic lactate levels [44]. For many years, it has not been known exactly whether bicarbonate truly improves clinically relevant endpoints or not. In 2018, Jaber et al. [7] published a multicenter, open-label, randomized controlled phase III trial. A total of 26 ICUs participated. The inclusion criteria were: ICU transfer within the last 48 h; age ≥18 years; pH ≤7.2 with serum bicarbonate ≤20 mmol/L; a SOFA score of ≥4;

and serum lactate ≥2 mmol/L. The patients in the treatment group received 2% bicarbonate up to 4 times daily; the target pH was >7.3. The primary endpoint was a composite of death until day 28 and failure of 1 or more organs until day 7. One-hundred and thirty-two subjects were included in the control group, 179 were included in the treatment group. The survival rates did not differ between the total of patients in the two groups ($p = 0.09$). Nevertheless, the AKI patients showed higher survival rates if treated with the buffer ($p = 0.028$). In addition, bicarbonate lowered the probability of receiving RRT once AKI had been diagnosed ($p < 0.0001$). The results impressively document a substantial clinical benefit from bicarbonate for the management of aMA, particularly in AKI patients. It needs to be noted that the target pH was defined at ≥7.3.

Conclusions

aMA is a frequent and potentially life-threatening complication of various conditions. Lactic acidosis might occur even in the absence of systemic hypoxia. The incidence of metformin-associated aMA is comparably low. Unbalanced electrolyte solutions induce hyperchloremic aMA, which most likely worsens the renal prognosis of critically ill patients. Bicarbonate, although potentially deleterious due to increased CO_2 production with subsequent intracellular acidosis, improves kidney-related endpoints in the critically ill.

Conflict of Interest Statement

The authors have nothing to disclose.

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Author Contributions

I.M. wrote the manuscript, S.P. corrected the article, O.R. corrected the article, and D.P. assisted in writing and corrected the article.

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