Chapter 9
Metabolic Acidosis and Cardiovascular Disease

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Case

A 68-year-old man with history of diabetes mellitus is admitted with fever and decreased mental status. On examination he is found to be obtunded with a blood pressure of 100/60 mmHg, T 101.2 °F, and rales detected on physical examination of the left chest. Laboratory studies show the following: WBC count 25,000 with shift to the left; Na^+, 133 mEq/l; K^+, 5.8 mEq/l; HCO_3^-, 8 mEq/l; BUN, 50 mg/dl; creatinine, 2.5 mg/dl; pH, 7.02, PCO_2, 32 mmHg.

This patient has hypobicarbonatemia, acidemia, and hypocapnia. For this patient's degree of metabolic acidosis, his expected PCO_2 is 18–22 mmHg. Because his measured PCO_2 is 32 mmHg, his respiratory response is less robust than anticipated, indicating the presence of respiratory acidosis in addition to his apparent metabolic acidosis.

The most appropriate therapy for this patient is:

A. Supportive measures only
B. Intravenous sodium bicarbonate
C. THAM
D. Dialysis

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E. THAM and dialysis
F. C, D, or E

We will discuss the suggested approach to this case after our detailed discussion at the end of this chapter.

Introduction

Metabolic acidosis can be acute (lasting minutes to a few days) or chronic (lasting weeks to years) in nature. The adverse effects of these two forms of metabolic acidosis are distinctly different as are the benefits and complications of treatment. For example, abnormalities in cardiovascular function, including hemodynamic parameters, are prominent with acute metabolic acidosis thereby contributing to a high mortality rate [1]. By contrast, although there is an increased risk of death with chronic metabolic acidosis [2], there is no evidence that cardiovascular function is significantly compromised. There is however a link between metabolic acidosis and the stimulation of factors that could lead to cardiovascular disease, such as hypertension [3] and chronic inflammation [4]. Possibly a more focused assessment will reveal a closer relationship between metabolic acidosis and development of cardiovascular disease, but such studies have yet to be published.

In this chapter, we detail the abnormalities in cardiovascular function noted with both acute and chronic metabolic acidosis, their potential pathogenesis, and the impact of therapy.

General Differences Between Acute and Chronic Metabolic Acidosis

The distinction between acute and chronic metabolic acidosis is imprecise. In some studies, acute metabolic acidosis is defined as an acid–base disturbance lasting minutes to a few days in duration. By contrast, chronic metabolic acidosis is considered to last 3 days or more in duration. However, others define chronic metabolic acidosis as an acid–base disturbance lasting weeks to years [1]. The latter definition likely has more relevance for clinical situations and so this definition will be utilized in the present discussion.

The acidemia with acute metabolic acidosis is generally more severe than with chronic metabolic acidosis. With the former, blood pH can be as low as 6.8 but is usually above 7.3 with chronic metabolic acidosis and is never below 7.2 [5]. The less severe degree of acidemia presumably reflects the activation of body's defense mechanisms through the neutralization of acid by body buffers and the excretion of acid by the kidney. It is well accepted that the latter process requires several days to reach its maximum.

However, body buffering, which begins almost immediately, can also require several days to reach an optimal state, reflecting in part the recruitment of bone buffers [6].

The disorders producing acute and chronic metabolic acidosis are also usually different. The most common causes of acute metabolic acidosis are organic acidoses such as ketoacidosis and lactic acidosis, administration of large quantities of Cl^--rich solutions, and diarrhea [1]. By contrast, the most common cause of chronic metabolic acidosis is chronic kidney disease (CKD) or various forms of renal tubular acidosis [5]. Less frequently, chronic diarrhea or loss of bicarbonate-rich fluid from various intestinal fistulae leads to chronic metabolic acidosis.

These two critical factors, the severity of the acidemia and the duration of exposure of tissues to an acidic milieu, might account for the different clinical abnormalities observed with acute and chronic metabolic acidosis. Particularly, severity of the acidemia appears to be important in the genesis of cardiac dysfunction [7, 8] as described below. Nevertheless, there is a dearth of studies examining the impact of mild chronic metabolic acidosis on cardiac function, so that a deleterious effect of chronic metabolic acidosis on cardiac function cannot be completely ruled out.

Cardiovascular Effects of Acute Metabolic Acidosis

The major cardiovascular abnormalities observed in patients with acute metabolic acidosis are shown in Table 9.1. They are inferred from studies performed using cultured cells, isolated tissues, tissues perfused in vitro, whole animals, and in some cases humans [7–9].

Infusion of lactic acid or administration of phenformin to dogs with normal cardiac function designed to produce severe lactic acidosis (systemic pH < 7.2) caused a reduction in cardiac contractility and cardiac output [7, 8, 10]. Moreover, infusion of hydrochloric acid in rats produced peripheral vasodilatation and hypotension [9]. Central venoconstriction causing an increase in central blood volume has also been described. Although general vasodilatation of arterial vessels has often been reported, constriction of myocardial blood vessels, renal vessels, and pulmonary vessels has been reported with an acidic systemic pH [8].

Table 9.1 Major cardiovascular abnormalities observed in patients with acute metabolic acidosis

Adverse effects	Comments
Decreased cardiac contractility and cardiac output	Studies primarily in animals indicated decreased cardiac contractility observed when pH falls below 7.1–7.2
Cardiac arrhythmias	Frequency unknown
Hypotension	Related to decreased contractility and peripheral vasodilatation
Stimulation of inflammatory response	Noted with exposure of <24 h; major inflammatory mediators stimulated

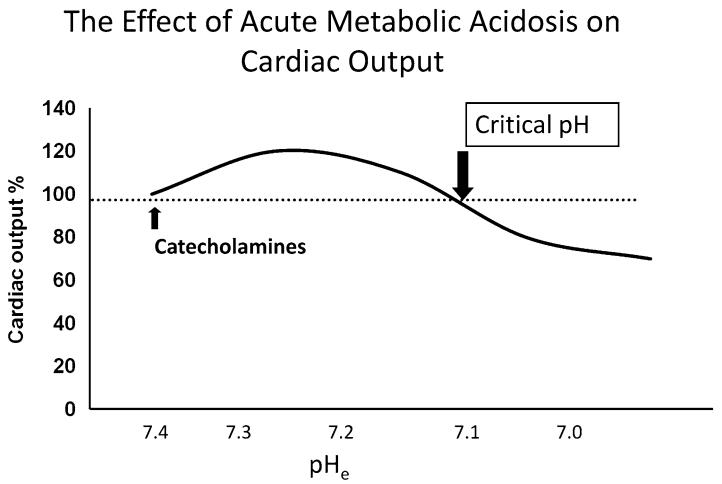

Fig. 9.1 The relationship between acute acidemia and cardiac function. As blood pH falls from 7.4 to 7.2, an increase in cardiac output can be observed. This is attributed to an influx of catecholamines, since it can be muted by administration of beta blockers. As systemic pH falls below 7.2, cardiac output falls by approximately 20 %. The fall in cardiac output might be greater in individuals with underlying cardiac disease or who are receiving beta blockers

The impairment of cardiovascular function with acute metabolic acidosis is clearly pH-dependent. As shown in Fig. 9.1, when systemic pH is reduced from 7.4 to 7.2 by the infusion of lactic acid, cardiac output actually rises [7, 10]. The rise in cardiac output is due to increased actions of catecholamines, since it was prevented by administration of beta blockers or prior removal of the adrenal glands. However, when systemic pH is reduced below 7.1–7.2, cardiac output falls, even in the presence of an intact sympathetic system. The response to endogenous or infused catecholamines is also muted thereby stemming the increment in cardiac output and peripheral resistance usually observed from the action of these hormones [8, 11]. On the other hand, vagal activity is stimulated particularly when systemic pH is reduced below <7.1 [8].

Metabolic acidosis also increases the risk for development of cardiac arrhythmias: their prevalence is higher both in the presence and absence of other factors that can provoke arrhythmias, such as changes in serum potassium or ionized calcium [12].

Oxygen delivery to tissues is also perturbed by metabolic acidosis. Experimentally induced metabolic acidosis leads to a rapid reduction in binding of oxygen to hemoglobin (Bohr effect) thereby improving tissue access to oxygen [13, 14]. Within 8 h, however, binding of oxygen to hemoglobin is enhanced somewhat by suppression of phosphofructokinase activity and resultant decreased net 2,3 diphosphoglycerate production (2,3 DPG). The final effect of acidosis on oxygen delivery depends on the sum of these counterbalancing forces, and therefore will depend on the duration of acidosis. The data support that a short duration of metabolic acidosis leads to decreased

oxygen binding to hemoglobin, but hemoglobin oxygen binding appears to increase as the duration of metabolic acidosis increases.

Infusion of lactic acid in rats causes a decrease in cardiac cellular ATP levels [15]. This was presumed to be due to inhibition of a key enzyme involved in glycolysis, phosphofructose kinase (pH optimum of 7.2) [16, 17]. However, in this study the decreased cellular ATP levels were not associated with a significant fall in pH_i (7.13 vs 7.07 p=NS); observations suggesting that other factors might be involved in reducing ATP levels.

Metabolic acidosis alters the inflammatory response, an effect that could theoretically exacerbate or contribute to the development of cardiovascular dysfunction. Infusion of HCl to septic rats to produce severe non-anion gap (hyperchloremic acidosis) led to hypotension and an increased in the inflammatory molecules, IL-6, IL-10, and TNF [18]. Furthermore, exposure of cells to an acidic milieu increased expression of several pro-inflammatory cytokines within 24 h [4].

In summary, acute metabolic acidosis can reduce cardiac contractility and output, cause peripheral vasodilatation, and predisposes to arrhythmias, all of which favor the development of hypotension. These effects appear when blood pH is less than 7.2 in normal animals. Whether the same holds for humans has not been studied. Moreover, the aforementioned studies were performed in animals without underlying cardiovascular disease. Given the high prevalence of cardiovascular disease in the human population, it is likely that hemodynamic abnormalities would be observed more frequently in individuals with underlying cardiac disease. Even in the presence of more moderate acidosis, there will be increased outpouring of catecholamines which can increase peripheral resistance, cardiac contractility, and the threshold for appearance of arrhythmias. These observations suggest that in some cases, e.g., patients at high risk for arrhythmias, administration of base might be considered even with less severe acidemia.

Mechanisms of Cellular Dysfunction and Injury with Acute Metabolic Acidosis

Acute metabolic acidosis is associated with decreases in systemic, interstitial (pH_e), and intracellular pH (pH_i). Although cellular dysfunction with metabolic acidosis is attributed primarily to changes in pH_i, in vitro studies suggest that a reduction in pH_e can impair cellular function independent of any impact on pH_i [11]. Furthermore, administration of base to treat the acidosis might be successful in raising systemic pH while failing to raise intracellular or interstitial pH to the same extent, or paradoxically, even causing systemic and/or intracellular pH to fall transiently (particularly when base is given as sodium bicarbonate in patients with impaired tissue perfusion). Therefore, from a clinical perspective, there is some value in dividing the mechanisms underlying alterations in cellular function into those primarily related to a decrease in systemic and pH_e and those related to a decrease in pH_i, understanding that there can be significant overlap.

Effect of a Decrease in Extracellular pH (Table 9.2)

Table 9.2 Adverse effects of chronic metabolic acidosis

Adverse effect	Comments
Development or exacerbation of bone disease	Also leads to impaired growth in children
Degradation of muscle protein with muscle wasting	No evidence of effect on cardiac muscle
Reduced protein synthesis with tendency to hypoalbuminemia	Severe hypoalbuminemia could contribute to hypotension in patients particularly those on dialysis
Progression of chronic kidney disease	Related in part to increased endothelin and aldosterone levels that theoretically could affect hemodynamic function
Abnormalities of thyroid hormone synthesis	Alterations in levels could affect cardiac function
Development of hypertension	Suggestive relationship based on analysis of NHANES data
Increased production of aldosterone, endothelin, and catecholamines	Might contribute to genesis of cardiovascular disease

As discussed below, in addition to its impact on pH_i, a decrease in pH_e can theoretically impair cellular function and cause cell injury by attenuating cellular responsiveness to insulin and catecholamines. This effect of decreased pH_i and pH_e alters the opening of acid sensing ion channels (ASIC) in the brain and K channels in the heart and blood vessels, thereby activating proton-sensitive G-coupled receptors and activating transient receptor potential vanilloid 1 (TRPV1) channels in the heart and brain. Decreased pH_i and pH_e also alter activity of the CaSR receptor and increase the ionized component of intracellular and extracellular calcium concentration [19–21].

Acute metabolic acidosis is associated with impaired glucose tolerance and increased insulin resistance [19]; effects that can be reversed by correction of the acidosis. Although this might be related in part to a reduction in receptor number, binding of insulin to individual receptors is also impaired. The latter effect is related to the fall in interstitial pH, since exposure of isolated adipocytes to an extracellular $pH \leq 7.2$ reduced receptor binding of I^{125} insulin [22]. The magnitude of this decrease was correlated with the severity of the reduction in extracellular pH: receptor binding falling to 30–70 % of control values when extracellular pH was reduced to 6.7.

The blunted response of the cardiovascular system to catecholamines is due to a decrease in pH_i and pH_e. Prior exposure of neutrophil beta-adrenergic receptors to a low pH (7.1) leads to a striking reduction in isoproterenol-stimulated cAMP accumulation associated with decreased binding of catecholamine to its receptor [11].

The Ca^{2+}-sensing receptor is present in the heart and its sensitivity to Ca^{2+} and response to PTH were depressed by an acidic milieu. Activation of the calcium sensing receptor has been postulated to play a role in the magnitude of ischemia-reperfusion injury [23, 24].

Acid sensing ion channels (ASIC) ASIC1a, are pH-sensitive channels permeable to both calcium and sodium (half maximal activation at an external pH of 6.2–6.8) which are expressed at extremely high levels on dorsal root ganglion sensory neurons of the heart. They have been implicated in the transmission of ischemic pain. Since these channels are absent in cardiomyocytes, they presumably play no role in the cardiovascular response to acidosis [25]

Transient receptor potential vanilloid 1 (TRPV1) channels are Ca^{2+}-permeable channels expressed also in the heart that are activated by an external pH < 6.0. It has been postulated these channels might contribute to myocardial cell death and development of cardiac arrhythmias, particularly with severe metabolic acidosis [26].

Proton-sensing G-protein-coupled receptors such as OGR1 and G2A present in vascular tissue (half maximal activation at a pH_e of 7.17) cause release of Ca^{2+} from intracellular stores with subsequent IP_3 production. Their presence in vascular smooth muscle has led to speculation that their activation contributes to the arterial vasodilatation observed with metabolic acidosis, but this requires further examination [27].

Several potassium channels in the heart and vascular tissues are pH-sensitive [28]. Alterations of potassium flux thorough the channels might contribute to development of cardiac arrhythmias and hypotension with acute acidosis.

Finally, a reduction in systemic pH increases the concentration of ionized calcium by reducing its binding to albumin. The increase in Ca^{2+} has been postulated to counteract the depressive effect of a reduced pH on cardiac contractility.

Intracellular pH

A reduction in pH_i of the heart is postulated to play a dominant role in myocardial dysfunction. Decreased binding of Ca^{2+} to troponin and impaired enzyme activity reducing ATP production are major factors [29]. Activation of the Na^+-H^+ exchanger, NHE1 by acidosis might also contribute to cardiac dysfunction and development of arrhythmias, particularly with acute lactic acidosis [30]. Activation of NHE1 increases intracellular sodium and secondarily intracellular calcium leading to marked elevation of the concentration of both cations in myocardial cells [30]. Inhibition of NHE1 attenuates the increase in sodium and calcium and lessens the impact of acute lactic acidosis on cardiovascular function. Several studies have also demonstrated that administration of a selective inhibitor to animals with various models of lactic acidosis strikingly reduces mortality presumably related to improvement in cardiovascular function [31].

Response of the Heart to Administration of Base

Theoretically, administration of base would be expected to improve disturbed cardiovascular function through amelioration of the accompanying acidemia. However, administration of sodium bicarbonate depresses cardiovascular

function in animal studies [32]. Moreover, although administration of base did not depress cardiac function in humans, its administration did not increase cardiac output more than an equivalent quantity of normal saline, despite significant increase in systemic pH induced by the administered base [33, 34]. The failure of bicarbonate to improve cardiac function despite an improvement of systemic pH has been attributed to two possible factors: (1) generation of carbon dioxide during the buffering process with rapid entry of carbon dioxide into myocardial cells and a decrease in pH_i [1]; and/or (2) a reduction in ionized calcium because of increased binding to albumin [33].

Based on these findings, it might be expected that administration of a base that did not generate significant quantities of carbon dioxide, and stabilization of ionized calcium by administration of calcium might allow expression of positive effects of correction of the acidosis. The latter possibility has been investigated with carbicarb, a 1:1 mixture of sodium bicarbonate and disodium carbonate [35]. In vitro studies involving addition of carbicarb to acidified blood led to a reduction in carbon dioxide [36]. Moreover, administration of carbicarb to dogs with metabolic acidosis improved cardiac function and pH_i [37]. Studies in humans were less impressive with only a subset of individuals having a positive response to carbicarb [38]. Further studies examining potential of carbicarb or other bases which consume carbon dioxide are under investigation.

At this juncture, the decision about what buffer to administer and what level of blood pH to target has not been resolved. It appears reasonable to target a blood pH of 7.2 as a goal since many of the adverse effects on the cardiovascular system are detected at this level as described above. If sodium bicarbonate is given, it should be administered as an isotonic solution at a slow rate. Since this can cause ionized Ca^{2+} to fall, administration of calcium is reasonable although this strategy has not been subject to rigorous examination. Utilization of THAM as an alternative needs to be examined more closely as does the use of dialysis. Furthermore, administration of NHE1 inhibitor as an adjunct to base therapy should be examined. Only with intense clinical investigation of different modalities of treatment will evidence-based guidelines be made available.

Chronic Metabolic Acidosis

The major adverse effects of chronic metabolic acidosis are shown in Table 9.2. Noticeable by their absence are abnormalities in cardiovascular function. In contrast to acute metabolic acidosis, no direct impact of chronic metabolic acidosis on cardiovascular function has been documented. It is not clear how meticulously investigators have approached this issue and it is possible that a relationship could be found. However, the less severe degree of acidemia in patients with chronic acidosis could explain, at least in part, the absence of cardiovascular abnormalities. As noted, no change in cardiac contractility is noted

as blood pH is reduced from 7.4 to 7.2, and in vitro studies have predominately examined both increases and decreases at extreme levels of pH to determine the effect of pH changes in cellular function. Thus, the failure to observe cardiovascular abnormalities is not surprising.

One potential link between metabolic acidosis and abnormalities in cardiovascular function is the increase production of beta 2 microglobulin in dialysis patients with acidosis [39]. In patients with excess beta 2 microglobulin, there is greater deposition of amyloid in tissues, including the heart.

Also, recent studies suggest that metabolic acidosis is a risk factor for development of hypertension [3]. Among non-obese adult women, higher plasma bicarbonate was modestly associated with lower odds of developing hypertension after adjusting for matching factors. Also, hypertension was positively correlated with an increased dietary acid load [40]. Thus, either metabolic acidosis or an increase in an acid load, conditions theoretically characterized by increased tissue acidity were associated with a risk of hypertension; data consistent with acidosis or acid retention being a contributory factor for development of hypertension. On the other hand, in a separate large study there was no association between acid load and the risk for hypertension [41]. Further studies will be required to resolve this controversy. It is intriguing to think that increased tissue acidity contributes to hypertension, and if so it could represent an indirect link to development of cardiovascular disease.

Many investigators consider inflammation as a factor in the development of ischemic cardiovascular disease. Exposure of individual epithelial cell or macrophages to reductions in pH elicits an increase in the production and release of pro-inflammatory cytokines [4, 42]. These effects could contribute to the development of atherosclerotic cardiovascular disease.

Finally, in addition to enhanced production of catecholamines, investigators have documented an increase production of endothelin-1 and aldosterone [43]. All three hormones could affect cardiac remodeling or injury by various mechanisms. More intense investigations of these and other potential factors that might promote the development of cardiovascular disease are warranted.

Further evidence that metabolic acidosis might contribute to cardiovascular disease can be inferred from the increase in mortality of individuals with metabolic acidosis serum bicarbonate <17 mEq/l [2]. Since cardiovascular disease is the most common cause of mortality in patients with CKD both prior to and after initiation of chronic dialysis, it is reasonable to infer that chronic acidosis might contribute to development of cardiovascular disease with an eventual increase in mortality. Figure 9.2 presents a hypothetical model demonstrating how chronic acidosis might lead to cardiovascular disease and eventual increase in mortality.

In summary, chronic metabolic acidosis does not appear to produce acute cardiac dysfunction. However, it could promote the development of cardiovascular disease through its stimulation of key hormones that affect the cardiovascular system, and the development of hypertension.

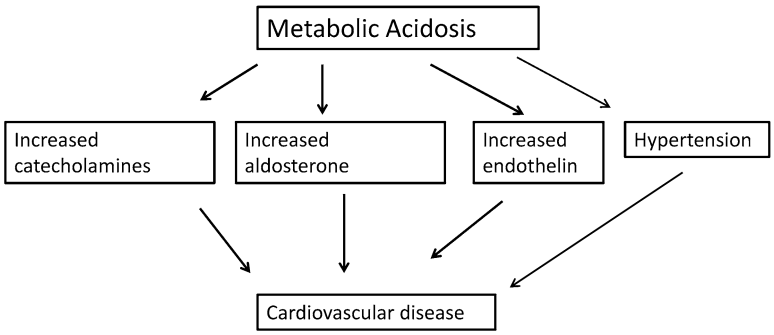

Fig. 9.2 Hypothetical relationship between chronic metabolic acidosis and cardiovascular disease. Chronic metabolic acidosis can be associated with stimulation of catecholamines, endothelin, and aldosterone. In addition to stimulation of these hormones, it can promote inflammation and the development of hypertension. The sum of these factors can lead to ischemic cardiovascular disease or cardiomyopathy

The Impact of Base on Cardiovascular Function with Chronic Metabolic Acidosis

Although metabolic acidosis itself appears not to be associated with cardiovascular dysfunction, some of its treatment strategies have been associated with adverse cardiovascular outcomes. A recent study found that in patients with CKD not on dialysis, a serum bicarbonate above 24 mEq/l due to diuretic administration or base therapy was associated with a marked increase in the prevalence of congestive heart failure [44, 45]

These findings suggest either that mild hypobicarbonatemia is protective against cardiovascular disease or, more likely, that an elevated plasma bicarbonate and pH is associated with cardiovascular dysfunction. Possibly, a more alkaline pH predisposes to calcifications which could contribute both to ischemic disease or cardiomyopathy [46]. Further studies to examine this issue are warranted, particularly since the elegant studies of Wesson's group [47–49] suggest that early base therapy is beneficial in slowing progression of CKD.

It appears very clear that administration of base is beneficial in patients with metabolic associated with CKD. Presently, recommendations are to administer base when serum [HCO_3^-] is less than 22 mEq/l [50, 51]. The precise goal is not clear although it seems reasonable to keep it less than 24 mEq/l. Base can be given as sodium bicarbonate, or sodium citrate. The former is associated with gas production in the stomach which can be bothersome for some patients. In both instances it is worthwhile estimating the base deficit by multiplying the difference between the prevailing serum [HCO_3^-] and the desired serum [HCO_3^-] × the space of distribution usually given as 50 % body weight (kg). The total base required can be given over several days. Once a serum [HCO_3^-] has been reached, the quantity of base should be reduced. In lieu of base, some investigators have demonstrated increasing the

intake of fruits and vegetables is also effective [52]. There is, of course, the potential risk of hyperkalemia but this can be avoided by choosing patients who are at low risk for hyperkalemia and by careful observation of patients treated in this way. A reduction in animal-sourced protein intake will also reduce the net endogenous acid production and is an ancillary measure that is useful.

Returning to Our Case

Answers: F. C, D, or E

The treatment of acute metabolic acidosis is one of the most controversial issues in clinical medicine today [53]. Although it is well accepted that an acidic environment is associated with compromise of the cardiovascular system, the use of base to improve it has not been successful [1]. Sodium bicarbonate is associated with generation of carbon dioxide which exacerbates intracellular acidosis. Therefore, administration of bicarbonate in this patient with incipient carbon dioxide retention would theoretically be deleterious. Indeed, in a recent animal study, hyperventilation to prevent carbon dioxide retention was associated with improved cardiovascular response [54]. THAM can raise blood and intracellular pH without generating carbon dioxide. It is cleared by the kidney and therefore might have to be used cautiously in this case. Combining THAM administration and dialysis to remove THAM might be used. Dialysis alone which provides base in the form of sodium bicarbonate but can control volume and changes in osmolality might also be considered. Other measures such as administration of an NHE1 (Na^+-H^+ exchange) inhibitor are also under investigation [55]. In summary, the treatment of acute metabolic acidosis remains under investigation and individualized care will be necessary in the treatment of patients.

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