



Lactic Acidosis: Current Treatments and Future Directions

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Mortality rates associated with severe lactic acidosis (blood pH < 7.2) due to sepsis or low-flow states are high. Eliminating the triggering conditions remains the most effective therapy. Although recommended by some, administration of sodium bicarbonate does not improve cardiovascular function or reduce mortality. This failure has been attributed to both reduction in serum calcium concentration and generation of excess carbon dioxide with intracellular acidification. In animal studies, hyperventilation and infusion of calcium during sodium bicarbonate administration improves cardiovascular function, suggesting that this approach could allow expression of the positive aspects of sodium bicarbonate. Other buffers, such as THAM or Carbicarb, or dialysis might also provide base with fewer untoward effects. Examination of these therapies in humans is warranted. The cellular injury associated with lactic acidosis is partly due to activation of NHE1, a cell-membrane Na⁺/H⁺ exchanger. In animal studies, selective NHE1 inhibitors improve cardiovascular function, ameliorate lactic acidosis, and reduce mortality, supporting future research into their possible use in humans. Two main mechanisms contribute to lactic acid accumulation in sepsis and low-flow states: tissue hypoxia and epinephrine-induced stimulation of aerobic glycolysis. Targeting these mechanisms could allow for more specific therapy. This Acid-Base and Electrolyte Teaching Case presents a patient with acute lactic acidosis and describes current and future approaches to treatment.

Am J Kidney Dis. 68(3):473-482. Published by Elsevier Inc. on behalf of the National Kidney Foundation, Inc. This is a US Government Work. There are no restrictions on its use.

INDEX WORDS: Lactic acidosis; lactate; bicarbonate; base; metabolic acidosis; THAM; Carbicarb; sepsis; hypoxia; aerobic glycolysis; dialysis; NHE1.

Note from the editors: This article is part of a series of invited case discussions highlighting either the diagnosis or treatment of acid-base and electrolyte disorders.

INTRODUCTION

Acute lactic acidosis occurring in patients with sepsis or low-flow states is associated with cellular dysfunction and heightened mortality.¹ Elimination or control of the triggering conditions remains the only effective therapy. Often base is prescribed, but its utility remains unproven.² Because management of the triggering conditions can be challenging, effective treatment remains elusive.

In this Acid-Base and Electrolyte Teaching Case, a patient with severe sepsis and lactic acidosis is presented. We discuss advances in the pathophysiology of lactic acidosis,³ thus providing a framework for a future targeted approach to treatment.

CASE REPORT

Clinical History and Initial Laboratory Data

A 54-year-old white man with a history of alcohol abuse, alcoholic cirrhosis, depression, polysubstance abuse, and pancreatitis-induced diabetes mellitus was admitted to the hospital with palpitations, hyperventilation, and altered mental status. He reported no recent alcohol or drug use. Medications included insulin, simvastatin, and fish oil. Physical examination revealed blood pressure of 162/95 mm Hg without orthostatic changes, temperature of 99°F, pulse rate of 85 beats/min, and respirations of 18 breaths/min. Six hours later, he became tachycardic, blood pressure decreased to 105/50 mm Hg, and he developed a temperature of 101°F.

Subsequently, he developed oliguria and severe acidemia with a marked elevation in blood lactate concentration. Admission and subsequent laboratory findings are shown in [Table 1](#).

Additional Investigations

Blood cultures were negative. Computed tomography of the chest and abdomen was unremarkable. An exploratory laparotomy revealed no evidence of intestinal ischemia.

Diagnosis

Severe sepsis; acute kidney injury; acute lactic acidosis; alcoholic cirrhosis; hyponatremia.

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Received December 8, 2015. Accepted in revised form April 1, 2016. Originally published online June 10, 2016.

Because an author of this article is the editor for this feature, the peer-review and decision-making processes were handled without his participation. Details of the journal's procedures for potential editor conflicts are given in the Information for Authors & Journal Policies.

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0272-6386

<http://dx.doi.org/10.1053/j.ajkd.2016.04.020>

Table 1. Laboratory Data During the Hospital Course

Parameter	On Admission	10 h Later	Day 4
pH	NA	7.15	7.43
Paco ₂ , mm Hg	NA	30	38
HCO ₃ ⁻ , mEq/L	25	10	24
Na ⁺ , mEq/L	140	150	148
K ⁺ , mEq/L	3.5	3.3	3.3
Cl ⁻ , mEq/L	105	110	110
Ca ²⁺ , mEq/L	NA	2.26	2.4
Lactate, mEq/L	1.0	20.0	5.0
Scr, mg/dL	1.2	2.2	2.8
Albumin, g/dL	2.3	NA	2.3
eGFR, mL/min/1.73 m ²	66	—	—
Anion gap, mEq/L	10	30	14
ΔAG/ΔHCO ₃ ⁻	—	20/15	—

Note: Conversion factor for Scr in mg/dL to μmol/L, ×88.4.

Abbreviations: AG, anion gap; eGFR, estimated glomerular filtration rate; HCO₃⁻, bicarbonate; NA, not available; Scr, serum creatinine.

Clinical Follow-up

Antibiotics were administered to treat the suspected infection, and crystalloids and vasopressors were given to support the circulation. Because of kidney failure and the accompanying lactic acidosis, continuous venovenous hemodialysis therapy was initiated. Blood pressure remained stable at 120/70 mm Hg, and blood lactate level decreased to 5 mEq/L and then remained between 4 and 6 mEq/L for the rest of the hospitalization. He was evaluated for a liver transplant, but was rejected owing to serious comorbid conditions. On hospital day 8, he died.

DISCUSSION

This patient with severe sepsis and liver disease had a precipitous decrease in serum bicarbonate concentration to 10 mEq/L and blood pH to 7.15 and an increase in blood lactate level to 20 mEq/L. These findings fulfill the classic definition of acute lactic acidosis: blood lactate level ≥ 5 mEq/L, blood pH ≤ 7.35, and serum bicarbonate concentration ≤ 20 mEq/L.⁴ He also had coexisting respiratory acidosis because the decrease in Paco₂ was less than expected for the prevailing serum bicarbonate concentration. The change in anion gap divided by change in bicarbonate (ΔAG/ΔHCO₃⁻) of 1.3 is consistent with acute lactic acidosis alone or a combined metabolic alkalosis and metabolic acidosis.^{5,6} The former diagnosis seemed most likely because no conditions promoting the development of metabolic alkalosis were present (diuretics, vomiting, or gastric drainage).

Although both acidemia and hypobicarbonatemia were present, these abnormalities are sometimes absent in hyperlactatemic patients because of coexisting acid-base disorders, such as metabolic alkalosis or respiratory alkalosis.³ Nonetheless, hyperlactatemia implies the presence of lactic acidosis, in which there is net addition of lactate and protons to the body fluids.^{3,7} Limited data suggest that at a given blood lactate level, acidemia is

associated with worse clinical outcomes^{8,9}; however, further work is required on this important issue.

Sustained hyperlactatemia in sepsis or low-flow states carries mortality ≥ 60%.^{1,10} Next, we first provide a brief description of the current therapy of lactic acidosis and then suggest potential future therapies that derive from advances in our understanding of the pathophysiology of the disorder.

Resuscitative efforts to support the circulation and ventilation are the first steps in treating lactic acidosis. The optimal crystalloid solution for fluid resuscitation remains under investigation, with proponents of both saline and balanced-salt solutions.^{11,12} Using central venous pressure and oxygen saturation to guide therapy is controversial.^{13,14} Vasopressors and inotropic agents should be administered, as required, but excessive use should be avoided to prevent aggravation of hyperlactatemia from reduction in tissue perfusion or overstimulation of the β₂-adrenoceptor. Optimized delivery of oxygen to tissues depends on the adequacy of cardiac output, Po₂, and hemoglobin concentration. Invasive ventilation might be required to ensure adequate Po₂ and prevention of hypercapnia.

Swift initiation of cause-specific measures is key to effective management of acute lactic acidosis. In sepsis, early administration of appropriate antibiotics and control of the infection source are paramount.¹²⁻¹⁵ An exploratory laparotomy was performed in our patient because of concerns about intestinal ischemia.

When present, severe acidemia (blood pH < 7.2) might impair cardiovascular function and blood flow.^{6,16} Therefore, many clinicians will administer base to increase blood pH to a presumed safe level (pH ~ 7.2).⁶ Because reductions in intracellular pH and interstitial pH are considered the key effectors of cellular dysfunction in acute metabolic acidosis, base therapy aims at increasing intracellular pH and interstitial pH, along with blood pH.¹⁷

Sodium bicarbonate has been the most commonly used base (hypertonic or preferably isotonic solution). However, in the majority of studies, it does not improve cardiac function or reduce mortality¹⁸⁻¹⁹ (Table 2). This failure has largely been ascribed to 2 adverse effects. First, carbon dioxide is generated as protons are buffered by bicarbonate. The carbon dioxide rapidly traverses the cell membrane, whereas bicarbonate movement into the cell is hindered, with the potential for producing an intracellular respiratory acidosis.^{20,21} Importantly, not all studies showed intracellular acidification after bicarbonate administration.²² This is most likely to occur when large amounts of bicarbonate are given rapidly, particularly to patients with severe circulatory failure, promoting carbon dioxide accumulation in tissues. Perhaps the use of bicarbonate should be individualized. If the circulation is adequate or only moderately impaired, bicarbonate administration might

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