Acid-Base and Electrolyte Teaching Case

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.

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; hypernatremia.

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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
$\Delta AG/\Delta HCO_3^-$	—	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 $Paco_2$ was less than expected for the prevailing serum bicarbonate concentration. The change in anion gap divided by change in bicarbonate ($\Delta AG/\Delta HCO_3^-$) 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, Po_2, and hemoglobin concentration. Invasive ventilation might be required to ensure adequate Po_2 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 mortality[18-19] (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

Table 2. Effect of Bicarbonate Therapy on Cardiovascular Function and Clinical Outcome in Humans

Reference	Study	Outcome	Comments
Stacpoole[59]	Placebo phase of dichloroacetate study	No improvement with base therapy	Not RCT
Fang[67]	Prospective RCT of 532 pts with sepsis and hypotension given 5% normal saline, 3.5% saline, or 5% NaHCO₃ solution	At 120 min, NaHCO₃ group had slightly greater increase in cardiac output and BP; no differences in mortality among groups	Concluded that NaHCO₃ might be reasonable resuscitation fluid in sepsis
Jung[8]	Prospective observational multicenter study of 200 pts with severe metabolic acidosis (blood pH < 7.2); ~1/3 of pts received NaHCO₃	NaHCO₃ use was heterogeneous and not associated with difference in survival	Study not designed to determine impact of NaHCO₃ on outcome; clinicians made decision about base use independently
El Solh[68]	72 pts with septic shock and increased blood lactate received either NaHCO₃ when blood pH < 7.3 or conventional therapy	NaHCO₃ did not reduce time to reversal of shock, but was associated with shorter mechanical ventilation duration and reduced length of ICU stay	Blood pH for initiation of base therapy higher than traditionally recommended (7.1-7.2)
Kim[69]	Retrospective analysis of 103 pts with lactic acidosis and serum [HCO₃⁻] < 20 mEq/L, 69 of whom received NaHCO₃	Nonsurvivors more likely to have received NaHCO₃	NaHCO₃ group had more severe disease, lower serum [HCO₃⁻], and higher lactate
Cooper[18]	Prospective randomized crossover study of NaHCO₃ vs NaCl in 14 pts with sepsis and acute lactic acidosis	No difference in cardiac output between the 2 modalities	Pts observed for only 30 min; failure of base attributed partly to increase in Paco₂ and decrease in ionized Ca²⁺
Mathieu[70]	Prospective randomized crossover study of NaHCO₃ vs NaCl in 10 pts with acute lactic acidosis	No change in cardiac output with either modality	Pts observed for only 60 min

Abbreviations: BP, blood pressure; [HCO₃⁻], bicarbonate concentration; ICU, intensive care unit; pts, patients; RCT, randomized controlled trial; NaCl, sodium chloride; NaHCO₃, sodium bicarbonate.

not generate intracellular acidification, but rather improve acid-base parameters of the critical compartments. By contrast, in individuals predisposed to develop intracellular acidification with bicarbonate, other buffers devoid of that adverse effect (such as THAM [tris-hydroxymethyl aminomethane] or buffers containing disodium carbonate) should be considered. Central venous blood gases or measurement of cardiac index might aid in making this distinction.[23-25]

Second, an increase in pH increases binding of calcium to circulating protein, thereby reducing the ionized fraction and depressing cardiovascular function.[18] This alteration should occur with any base that increases the pH of critical compartments and is compounded by evidence that calcium concentration can be decreased in lactic acidosis itself.[26]

Both these adverse effects can be minimized. Hyperventilation to reduce carbon dioxide accumulation and infusion of calcium to stabilize calcium concentration increased intracellular pH and blood pH, improved myocardial function, and reduced the quantity of vasopressors necessary to maintain blood pressure in rats with hemorrhage-induced lactic acidosis administered bicarbonate.[16,27]

When base is given, the clinician should try to maintain blood pH at ~7.2. This pH was chosen because lower values depressed cardiac contractility

in animals,[28] suppressed the contraction of myocardial fibrils isolated from failing hearts of humans,[27] and was associated with increased mortality.[8] Increasing blood pH to ~7.2 should improve cardiac contractility and restore responsiveness of the myocardium and peripheral vessels to endogenous and infused catecholamines.[16,29,30]

To calculate the quantity of bicarbonate required to increase serum bicarbonate concentration to a given amount, we assume that administered bicarbonate is distributed in 50% body weight expressed in kilograms (bicarbonate space). This is only an estimate, and monitoring of acid-base parameters every few hours is required for potential dose adjustment. Given our patient's hypernatremia, bicarbonate should be administered as an isotonic solution.

Alternatively, administration of bases that do not generate substantial quantities of carbon dioxide (or preferably consume it) during the buffering process might be more likely to improve cellular function. Table 3 shows the benefits and limitations of buffers that might be used for this purpose.

THAM buffers protons by virtue of its amine group. In contrast to sodium bicarbonate, it does not generate carbon dioxide. It might lower Pco₂.[31] It is as effective as sodium bicarbonate in increasing serum bicarbonate concentration[32] and when given to

Table 3. Bases and Base Delivery Systems for Treatment of Acute Metabolic Acidosis

Base or Base Delivery System	Formulation	Mechanism of Action	Complications	Comments
$NaHCO_3$	7.5%, 1,784 mOsm/kg 8.4%, 2,000 mOsm/kg Isotonic solution, prepared in house by pharmacy	HCO_3^- binds protons	Intracellular acidification with severe impairment of cardiac function; depression of ionized Ca^{2+}; volume overload; possible posttreatment metabolic alkalosis	Hypertonic solutions associated with greater depression of cardiac function, so isotonic solution preferred; adverse effects of HCO_3^- might be minimized with hyperventilation and Ca^{2+} infusion
THAM	0.3 mol/L solution, pH 8.6, osmolality 386 mOsm/kg	Amine group binds protons; must be excreted from body to generate base; THAM can also consume CO_2	Hyperkalemia; suppression of ventilation; liver necrosis in babies	Exact prevalence of adverse effects not well known; should be used cautiously with decreased kidney function and consideration given to concomitant dialysis to expedite removal of THAM
Ringer lactate	275 mOsm/kg Lactate 28 mEq/L Ca^{2+} 4 mEq/L	Lactate converted to HCO_3^- in the body	Elevation of blood lactate in patients with impaired liver function	Appears preferable to saline solution as resuscitation fluid; presence of Ca^{2+} prevents depression of Ca^{2+}; use as source of base in ongoing lactic acidosis not rigorously examined
Plasma-Lyte	294 mOsm/kg Acetate 27 mEq/L	Acetate converted to HCO_3^- in the body	Potential increase in blood acetate levels in patients with severe impairment of liver function	In contrast to Ringer lactate, Ca^{2+} is absent
Intermittent hemodialysis	HCO_3^- in dialysate of 35-40 mEq/L; also can be given by infusion	HCO_3^- delivered to patient by diffusion and intravenously	Theoretically has similar complications as intravenous administration of $NaHCO_3$	In contrast to $NaHCO_3$ administration, volume overload can be more easily minimized; quantity and rate of delivery can be controlled
CVVH	HCO_3^- in IV replacement solutions; if citrate used as anticoagulant, it will be metabolized to HCO_3^-	HCO_3^- only delivered IV or from citrate metabolism	Complications similar to those noted with HCO_3^- administration by other means; however, usually less severe because of potential for slow rate of HCO_3^- delivery	Quantity and rate of HCO_3^- administration can be carefully controlled
CVVHD	HCO_3^- in dialysate solutions; if citrate used as anticoagulant, it will be metabolized to HCO_3^-	HCO_3^- delivered primarily by diffusion or from citrate metabolism	Complications similar to those noted with HCO_3^- administration by other means; however, usually less severe because of potential for slow rate of HCO_3^- delivery	Quantity and rate of HCO_3^- administration can be carefully controlled; hyperosmolality and volume overload can be minimized
CVVHDF	HCO_3^- in IV solution and in dialysate; if citrate used as anticoagulant, it will be metabolized to HCO_3^-	HCO_3^- delivered in IV solutions, by diffusion, or from citrate metabolism	Complications similar to those noted with HCO_3^- administration by other means; however, usually less severe because of potential for slow rate of HCO_3^- delivery	Quantity and rate of HCO_3^- administration can be carefully controlled; hyperosmolality and volume overload can be minimized
Carbicarb	1:1 Na_2CO_3 $NaHCO_3$	Buffers protons	Possible posttreatment metabolic alkalosis	Minimal generation or even consumption of CO_2; not available for clinical use; further study of its value indicated

Abbreviations: CO_2, carbon dioxide; CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration; IV, intravenous; Na_2CO_3, disodium carbonate; $NaHCO_3$, sodium bicarbonate; THAM, tris-hydroxymethyl aminomethane.

individuals with carbon dioxide retention, improves cardiac contractility in parallel with improvement in acid-base balance.[33] To eliminate acid, THAM has to be removed from the body. This is easily accomplished when kidney function is normal, but is limited as kidney function declines. As a small molecule, THAM is dialyzable. Therefore, decreased kidney function might not prevent its use. Because it is the only other base approved for treatment of acid-base disorders, further studies of the benefits and complications of THAM are warranted.

Balanced-salt solutions containing organic acid anions as the source of base, such as lactated Ringer solution and Plasma-Lyte (Baxter Healthcare), have been recommended for fluid resuscitation,[11] but their use in the treatment of metabolic acidosis has not been examined rigorously. Also, their use in individuals with severe liver disease might not be appropriate because of the limited metabolism of the organic acid anion. Thus, although infusion of 1 L of lactated Ringer solution produces only a minor increment in blood lactate level in individuals with normal liver function,[34] the impact is likely to be magnified in patients with severe liver disease. This could be important because in vitro studies suggest that lactate could have a depressant effect on cardiovascular function.[35]

Disodium carbonate also consumes carbon dioxide in the process of buffering. Therefore, a 1:1 mixture of sodium bicarbonate and disodium carbonate, termed Carbicarb, was developed in the 1980s.[36] In animal experiments, it improved acid-base parameters of blood and the intracellular compartment while generating little or no carbon dioxide.[37] A single study of patients with mild metabolic acidosis failed to demonstrate a significant advantage of Carbicarb compared to sodium bicarbonate,[38] and it has never been introduced into clinical practice. Given its overall profile, further examination of this base seems warranted.

Dialysis is an effective method of delivering large quantities of base. During dialysis, base in the dialysate diffuses into the patient's blood. In addition, base can be administered intravenously during the dialysis procedure. Dialysis has the advantage that extracellular fluid volume and serum osmolality, 2 parameters that can be perturbed by administering hypertonic sodium bicarbonate, can be readily controlled. Also, by using a dialysate calcium concentration ≥ 3.0 mEq/L,[39] sufficient calcium can be delivered to stabilize serum calcium concentration. Although intermittent dialysis can be used, we prefer continuous renal replacement therapy (particularly continuous venovenous hemodialysis). With this modality, the quantity and rate of base delivered can be modulated to minimize any rapid changes in carbon dioxide generation and acid-base parameters.[40] To be sure, even relative alkalinization of body fluids by

administered base, including by dialysis, augments lactic acid production by stimulating 6-phosphofructokinase. Nonetheless, dialysis can decrease hyperlactatemia and ameliorate acidemia.[41]

Dialysis removes substances that can produce severe metabolic acidosis, such as toxic alcohols and metformin, and has been effective in the treatment of both disorders.[42,43] Lactate is also removed by dialysis, although the quantity is relatively small compared to the amount produced.[44] We have a low threshold for initiating dialysis therapy in patients with lactic acidosis and decreased kidney function, but controlled studies to determine its risk to benefit ratio are warranted.

The therapies discussed heretofore have not decreased morbidity and mortality in patients with lactic acidosis. However, measures based on a deeper understanding of the pathogenesis of lactic acidosis and cellular injury might improve the clinical outcomes.

As shown in Fig 1, hyperlactatemia occurs when lactate production exceeds its consumption. In low-flow states and sepsis, excess net production of lactic acid can be driven by 2 distinctly different mechanisms: First, tissue hypoxia impairs mitochondrial oxidation and causes both overproduction and underutilization of lactate. When acidemia coexists with hypoxia, the liver can be converted into a net lactate-producing organ. Even if systemic oxygen delivery is not sufficiently low to induce global hypoxia, associated microcirculatory dysfunction can reduce oxygen extraction, causing regional tissue hypoxia and hyperlactatemia. Tissue hypoxia is often considered the leading mechanism of increased net lactic acid production.

The second mechanism is aerobic glycolysis (stimulation of glycolysis by factors other than tissue hypoxia or impaired oxidative phosphorylation by chemical agents or drugs) stimulated by high levels of circulating epinephrine. By binding to the β_2-adrenoceptor on the plasma membrane, epinephrine increases the glycolytic flux both directly and by stimulation of the ubiquitous adenosine triphosphatase sodium/potassium pump (Na^+/K^+-ATPase) and the resultant consumption of ATP.[45] An increase in lactate utilization also occurs, but falls short of the abundant production. This is considered the primary mechanism of hyperlactatemia in the hyperdynamic stage of sepsis.[46] However, both aerobic glycolysis and tissue hypoxia often contribute to the hyperlactatemia in sepsis and low-flow states.[47]

Finally, in hemodynamically stable patients with sepsis, lactate clearance by the liver can be decreased, possibly through pyruvate dehydrogenase inhibition. In sepsis and low-flow states, chronic liver disease further compromises lactate clearance. However, chronic liver disease alone causes only minimal hyperlactatemia.[48,49] Kidney failure adds to the impairment in lactate clearance.
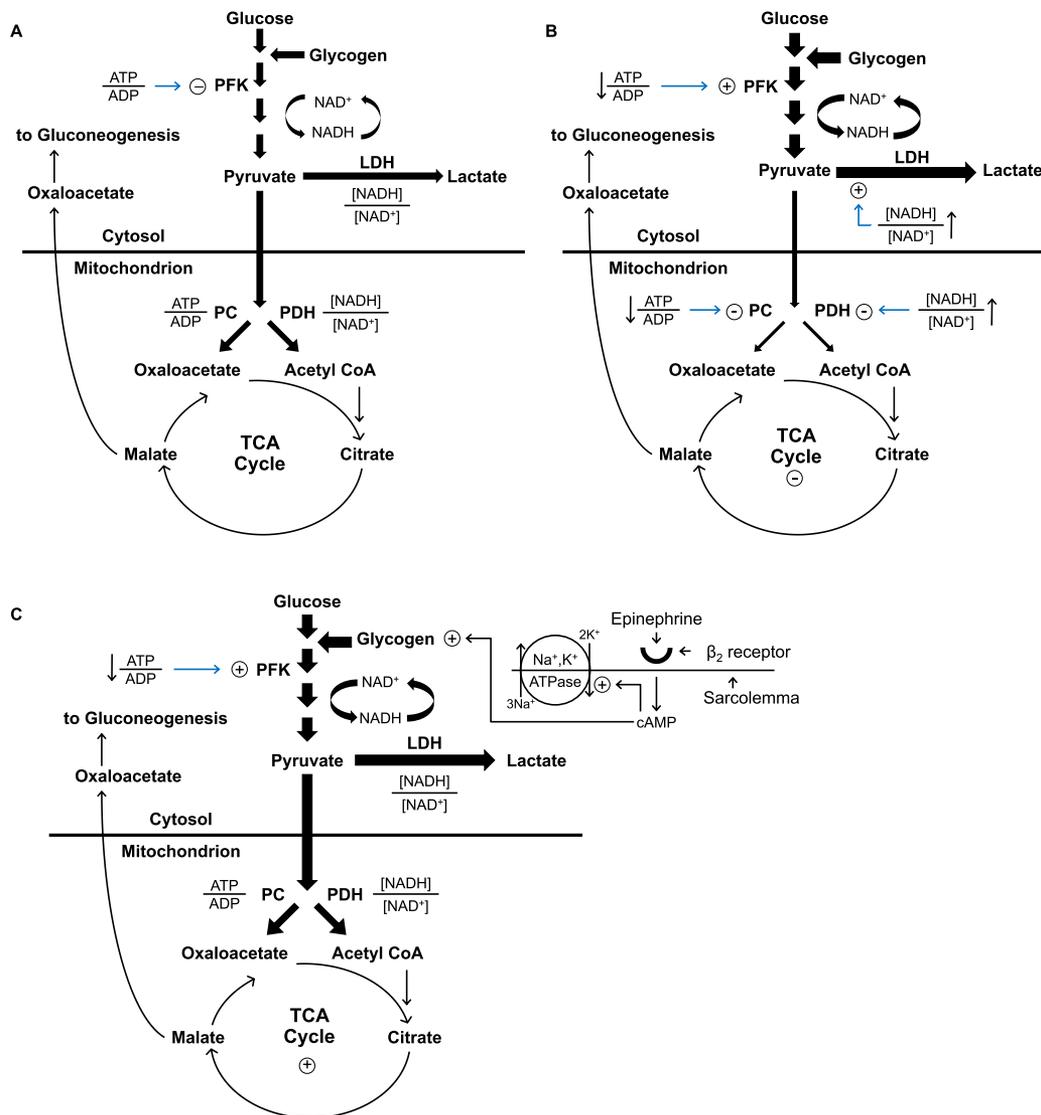
Figure 1. Putative mechanisms underlying accumulation of lactate in body fluids. Change in arrow width in panels B and C indicates directional changes in metabolic flux. (A) The normal state. Adenosine triphosphate (ATP) is an allosteric inhibitor of the rate-limiting 6-phosphofructokinase (PFK) reaction of anaerobic glycolysis. The 2 mitochondrial pathways of metabolic processing of pyruvate depend on intact oxidative phosphorylation. (B) Lactate accumulation in tissue hypoxia originates from pyruvate accumulation and reflects both overproduction and underutilization. The reduced ATP supply disinhibits the PFK reaction, stimulating anaerobic glycolysis. Hypoxia-induced decrease in ATP and increase in [NADH]/[NAD$^+$] (reduced nicotinamide adenine dinucleotide to nicotinamide adenine dinucleotide) ratio inhibit both oxidative pathways of pyruvate utilization. The increased [NADH]/[NAD$^+$] ratio shifts the equilibrium of the lactate dehydrogenase (LDH) reaction toward lactate. (C) Lactate accumulation in the hyperdynamic stage of sepsis. Glycolysis acceleration is linked to increased activity of the sarcolemmal adenosine triphosphatase sodium/potassium pump (Na$^+$/K$^+$-ATPase) consequent to β_2-adrenoceptor stimulation by high circulating epinephrine levels. ATP consumption increases the glycolytic flux by disinhibiting the PFK reaction. β_2-Adrenoceptor engagement by epinephrine also stimulates glycolysis directly. Oxidative phosphorylation and thus lactate utilization is increased in this setting but falls short of the level of glycolysis resulting in hyperlactatemia. This type of stimulated glycolysis has been dubbed aerobic glycolysis to indicate that it does not depend on tissue hypoxia. Evidence suggests that the glycolytic pathway linked to the sarcolemmal Na$^+$/K$^+$-ATPase activity is functionally compartmentalized from that directed to oxidative metabolism (not shown). Liver dysfunction or decreased kidney function can also reduce lactate clearance and contribute to hyperlactatemia generated by both main mechanisms. Abbreviations: acetyl CoA, acetyl coenzyme A; ADP, adenosine diphosphate; cAMP, cyclic adenosine monophosphate; PC, pyruvate carboxylase; PDH, pyruvate dehydrogenase; TCA, tricarboxylic acid. Reproduced and modified from Kraut and Madias[3] with permission of the Massachusetts Medical Society.

Theoretically, any one of these mechanisms could predominate in a given patient, compelling a variable approach to treatment. If only tissue hypoxia was present, measures to preserve tissue oxygen delivery might be emphasized. If microvascular dysfunction was present, rescuing the microcirculation with dobutamine, acetylcholine, nitroglycerin, or novel agents could improve the hyperlactatemia independent of systemic hemodynamics.[50] By contrast, if aerobic glycolysis was dominant, blocking the release or the effects of epinephrine could be beneficial. Adrenoceptor blockade can lessen hyperlactatemia[51,52] even if

it decreases oxygen delivery.[53] If both mechanisms were operative, targeting each might maximize benefit.

At present, tools to identify the mechanisms of net lactic acid production are not in clinical use, although some are under study. For example, handheld devices permitting direct visualization of the microcirculation are undergoing clinical study.[54] Further research to promote a mechanism-specific approach could improve clinical outcomes by using measures targeted to operative mechanisms while avoiding therapies that are futile or even harmful.

Identifying the pathways of cellular dysfunction could reveal specific targets for treatment. When present, hypoxia impairs vital cellular processes and causes cell death. Delivering adequate oxygen will improve cell function along with stemming net lactic acid production.

The reduction in intracellular pH during lactic acidosis can produce cell injury by activating the sodium/hydrogen exchanger 1 (NHE1), an exchanger ubiquitously present in the cell membrane.[55] Administration of selective inhibitors of NHE1 to experimental animals with lactic acidosis due to severe volume depletion, sepsis, or trauma improved cardiac function, reduced inflammation, ameliorated lactic acidosis, and decreased mortality.[56]

The injurious cellular effects of NHE1 activation in these models are presumed to emanate from the resulting sodium influx that cannot be countered by the suppressed Na^+/K^+-ATPase activity consequent to hypoxia-induced ATP depletion. If generation of lactic acidosis is largely driven by aerobic glycolysis, the prevailing β_2-stimulation of Na^+/K^+-ATPase activity might prevent sodium overload, thereby eliminating the indication for NHE1 inhibition. Although limited work in experimental sepsis suggests benefit,[57,58] additional research is needed to test the utility of NHE1 inhibition in nonhypoxic models of lactic acidosis. Certainly, the beneficial effect of NHE1 inhibition might be multifactorial. Given the encouraging results with NHE1 inhibition, further studies in experimental models of acute lactic acidosis are warranted. If these prove successful, studies in humans would be indicated.

The importance of advancing our understanding of the cellular dysfunction accompanying lactic acidosis is highlighted by the disappointing results of the dichloroacetate trial.[59] Although dichloroacetate, a stimulator of pyruvate dehydrogenase, resulted in significant moderation of hyperlactatemia, it failed to alter either hemodynamics or survival of patients with acute lactic acidosis.[59]

The role of lactate itself on cellular function remains controversial. Studies of isolated frog heart demonstrated a correlation between an increase in ambient lactate concentration and impaired cardiac function.[60] However, infusion of large amounts of sodium lactate, which increased blood lactate levels up to 15 mEq/L, did not depress cardiac output in patients following heart transplantation.[61] Further studies are necessary to examine the potential merits of lactate removal.

Effective treatment of lactic acidosis mandates appropriate monitoring of patients. Hemodynamic status, hemoglobin level, and arterial oxygen saturation should be assessed. There is ongoing controversy about the use of protocol-based targets or central venous catheterization, particularly in patients with sepsis.[15,62] Sustained hyperlactatemia has adverse prognostic value and thus blood lactate levels should be monitored. Measurement of either arterial or venous lactate is acceptable because the values are essentially interchangeable.[63] Some experts have advocated determination of lactate clearance using serial blood lactate determinations to judge the effectiveness of treatment.[64] The goal of lactate-guided therapy is normalization of blood lactate level. The value of this approach remains unproven.

Assessment of the acid-base milieu of tissues is important to guide therapy. Usually this is accomplished by measuring arterial blood gases, but venous

Box 1. Teaching Points

- The development of acute lactic acidosis in patients with sepsis or low-flow states is associated with a marked increase in mortality.
- Aggressive resuscitation and elimination or control of the triggering conditions are the mainstay of therapy.
- A decrease in interstitial and intracellular pH can contribute to cellular dysfunction. Administration of base as sodium bicarbonate does not reduce mortality or improve cardiovascular function, even when blood pH is increased.
- Failure of HCO_3^- to improve outcomes is attributed to generation of excess CO_2 and decrease in ionized Ca^{2+}. Hyperventilation to lessen CO_2 accumulation and administration of Ca^{2+} to stabilize blood Ca^{2+} might allow the positive effects of HCO_3^- therapy to be expressed.
- Alternatively, administration of bases that do not generate CO_2 or even consume it, such as THAM or Carbicarb, could improve cellular function.
- Disparate mechanisms can lead to excessive lactic acid generation, including tissue hypoxia and epinephrine-dependent stimulation of Na^+/K^+-ATPase. Measures targeting these mechanisms could improve the treatment of lactic acidosis.
- Activation of NHE1 with a resultant increase in cellular sodium and calcium is deleterious in animal studies, and administration of selective inhibitors of NHE1 improves cardiovascular function and reduces mortality.
- Further examination of the factors involved in producing cellular injury in acute lactic acidosis is indicated to facilitate the development of targeted therapy.
- Lactate-guided therapy might improve clinical outcomes, and the potential benefits of this approach need to be examined further.

Abbreviations: Na^+/K^+-ATPase, adenosine triphosphatase sodium/potassium pump; NHE1, sodium/hydrogen exchanger 1; THAM, tris-hydroxymethyl aminomethane.

blood gases are increasingly used. In individuals without severe hypoperfusion, either approach is acceptable.[65] However, under conditions of severe tissue hypoperfusion, there is marked disparity between the pH and P$_{CO_2}$ of arterial blood and those of venous blood (and the tissues).[23] Nonetheless, the clinical value of monitoring central venous blood gases in such patients remains unproven. Of course, monitoring of arterial blood gases is required in the critically ill for assessing pulmonary gas exchange. Other measures of tissue acid-base milieu, such as gastric tonometry and sublingual capnometry, are also under investigation. The role of these measures in monitoring patients with lactic acidosis remains undefined.

In summary, acute lactic acidosis carries an ominous prognosis. Rapid diagnosis and initiation of therapy is essential to reducing mortality. Newer strategies, such as probing the underlying mechanisms and applying targeted therapy, as well as administration of selective inhibitors of NHE1, could be beneficial and warrant further study. Lactate-guided therapy with the goal of normalizing blood lactate levels (to <2 mEq/L) has shown some benefit and remains under investigation.[66]

Given the critical importance of this disorder in affecting clinical outcome, randomized controlled studies of various treatment regimens would be useful in establishing an evidence-based approach to treatment. Essential teaching points are summarized in Box 1.

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