

Lactic Acidosis Update for Critical Care Clinicians

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Abstract. Lactic acidosis is a broad-anion gap metabolic acidosis caused by lactic acid overproduction or underutilization. The quantitative dimensions of these two mechanisms commonly differ by 1 order of magnitude. Overproduction of lactic acid, also termed type A lactic acidosis, occurs when the body must regenerate ATP without oxygen (tissue hypoxia). Circulatory, pulmonary, or hemoglobin transfer disorders are commonly responsible. Overproduction of lactate also occurs with cyanide poisoning or certain malignancies. Underutilization involves removal of lactic acid by oxidation or conversion to glucose. Liver disease, inhibition of gluconeogenesis, pyruvate dehydrogenase (thiamine) deficiency, and uncoupling of oxidative phosphorylation are the most common causes. The kidneys also contribute to lactate removal. Concerns have been raised regarding the role of metformin in the production of lactic acidosis, on the basis of individual case reports. The risk appears to be considerably less than with phenformin and

involves patients with underlying severe renal and cardiac dysfunction. Drugs used to treat lactic acidosis can aggravate the condition. NaHCO_3 increases lactate production. Treatment of type A lactic acidosis is particularly unsatisfactory. NaHCO_3 is of little value. Carbicarb is a mixture of Na_2CO_3 and NaHCO_3 that buffers similarly to NaHCO_3 but without net generation of CO_2 . The results from animal studies are promising; however, clinical trials are sparse. Dichloroacetate stimulates pyruvate dehydrogenase and improves laboratory values, but unfortunately not survival rates, among patients with lactic acidosis. Hemofiltration has been advocated for the treatment of lactic acidosis, on the basis of anecdotal experiences. However, kinetic studies of lactate removal do not suggest that removal can counteract lactate production in any meaningful way. The ideal treatment is to stop acid production by treating the underlying disorder.

Problems with acid-base balance and electrolyte disturbances have been masterfully presented and explained by Halperin and colleagues (1–3) in a series of entertaining and enlightening books. I heartily encourage readers to profit from these delightful publications, as I have. An additional scholarly source, which should always be within reach of critical care clinicians, is the monograph by Narins *et al.* (4). Briefly, lactic acid or lactate is a metabolic dead-end, because pyruvate, the sole immediate precursor, is also the only route of metabolic transformation. Approximately 1400 mmol of lactic acid are produced daily, which are buffered by 1400 mmol of HCO_3^- to form sodium lactate. The liver is responsible for oxidizing lactate to restore this amount of HCO_3^- . This task is formidable, because the lactate concentrations in plasma remain below 1 mM. The role of the liver in lactate homeostasis is considerable. However, total cessation of lactate clearance by the liver does not invariably lead to lactic acidosis. Extrahepatic tissues may compensate for loss of the normal contribution of the liver. The kidneys also contribute to lactate removal; estimates vary but are approximately 10 to 20% of the total lactate metabolized. The kidneys dispose of lactate in three ways: excretion, gluconeogenesis, and oxidation. Urinary excretion is

a very minor component, because the renal threshold is 6 to 10 mM.

All tissues can produce lactic and pyruvic acid from glucose (Figure 1). Red blood cells produce lactic acid as a byproduct of the regeneration of ATP during anaerobic glycolysis but cannot use lactic acid. All other tissues can use lactic acid to produce acetyl-CoA via pyruvate dehydrogenase (PDH). Lactate dehydrogenase is located in the cytosol and catalyzes the interconversion between lactate and pyruvate. The NADH/NAD⁺ cofactor system exchanges the hydrogen atoms released or consumed. Therefore, the lactate/pyruvate ratio is always proportional to the NADH/NAD⁺ ratio in the cytosol. Under normal conditions, the lactate/pyruvate ratio ranges from approximately 4:1 to 10:1. The lactate concentration in plasma is normally 0.4 to 1.0 mM but can increase to >20 mM. A high concentration of lactate is attributable to a high concentration of pyruvate or a high level of NADH in the cytosol, or both. A high NADH/NAD⁺ ratio occurs as a result of underutilization of NADH with hypoxia or, less commonly, overproduction of NADH with hypoxia and/or oxidation of ethanol in the liver. Pyruvate levels increase if the compound is produced more rapidly or utilized less rapidly. The formation of pyruvate has the greatest effect on pyruvate concentrations. The rate of production can increase 50-fold if either glucose or glycogen is required to generate ATP in the absence of oxygen.

The possible causes of lactic acidosis are self-evident. Oxygen deficits (tissue hypoxia) are the most common and often refractory causes, including pulmonary problems (low PO_2), circulatory problems (poor delivery of O_2), and hemoglobin

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1046-6673/1202-0015

Journal of the American Society of Nephrology

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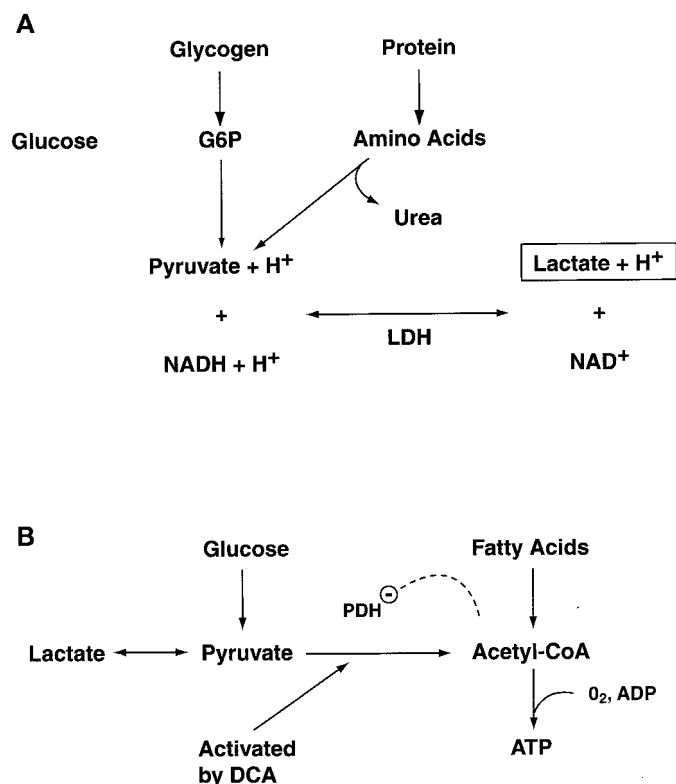


Figure 1. (A) L-Lactic acid synthesis. Lactic acid accumulates if pyruvate or NADH accumulates. G6P, glucose-6-phosphate; LDH, lactate dehydrogenase. (B) Dichloroacetate effects. Dichloroacetate (DCA) activates pyruvate dehydrogenase (PDH), favoring lactate oxidation. Thiamine is a coenzyme for PDH.

problems (low O₂-carrying capacity, for various reasons). Lactic acidosis caused by oxygen deficits is generally termed type A (fast) lactic acidosis. Also possible is compromised lactate metabolism without hypoxia, which is frequently termed type B (slow) lactic acidosis. In the latter case, the causes include high glycolysis rates attributable to low cytosolic ATP levels (violent exercise), uncoupled oxidative phosphorylation, decreased breakdown of lactate because of deficiencies in PDH (thiamine deficiency), high levels of ATP production from fat or low rates of ATP synthesis, and low levels of conversion of lactate to glucose. The latter problem occurs with hepatic destruction or replacement or defects in gluconeogenesis resulting from side effects of drugs or inborn errors of metabolism. Malignant cells produce more lactate than normal cells, even under aerobic conditions. This phenomenon is enhanced if the tumor outstrips the blood supply or if the amount of available thiamine is insufficient. Decreased lactate removal is usually hepatic in origin. Patients with renal failure are at increased risk.

Treatment of Lactic Acidosis

Type A Lactic Acidosis

The only effective treatment for type A lactic acidosis is cessation of acid production via the improvement of tissue oxygenation. Appropriate measures include treatment of shock,

restoration of the circulating fluid volume, improvement or augmentation of cardiac function, resection of ischemic areas, and amelioration of sepsis. Sepsis causes a series of circulatory disturbances that lead to tissue hypoxia. This fact should already be well known to readers, and little has changed regarding this issue.

NaHCO₃ and Carbicarb

NaHCO₃ therapy is of little value for type A lactic acidosis. The hydrogen ion loads, which may be produced at 72 mmol/min, make NaHCO₃ therapy of doubtful value. However, such therapy may possibly “buy time.” Carbicarb is a mixture of Na₂CO₃ and NaHCO₃ that buffers similarly to NaHCO₃ but without the net generation of CO₂. The results from clinical trials are sparse. Bersin and Arieff (5) studied ventilated dogs made hypoxic. They found that muscle O₂ consumption increased with carbicarb and decreased with NaHCO₃. Arterial pressure decreased less with carbicarb (−12 versus −46 mmHg, *P* < 0.006), and the cardiac output was stable with carbicarb but decreased with NaHCO₃ (from 143 to 98 ml/kg per min, *P* < 0.004). Stroke volume also improved with carbicarb, without a change in pulmonary capillary wedge pressure, suggesting that carbicarb has beneficial effects on myocardial contractility. Rhee *et al.* (6) administered carbicarb, NaHCO₃, and NaCl, in random order, to dogs with hypoxic lactic acidosis. NaHCO₃ increased PCO₂ and lactate production. Carbicarb increased pH and the cardiac index, without increasing lactate levels. The stroke volume index was also increased, and the heart rate was decreased. However, in another dog study, Blecic *et al.* (7) found that carbicarb was not superior to other regimens in a model of cardiac arrest. I am not aware of any controlled human carbicarb trials.

Dichloroacetate

Dichloroacetate has received much attention for the treatment of lactic acidosis (8). Dichloroacetate exerts multiple effects on pathways of intermediate metabolism. The drug stimulates peripheral glucose utilization and inhibits gluconeogenesis, thus reducing hyperglycemia in animals and human subjects with diabetes mellitus. Dichloroacetate inhibits lipogenesis and cholesterol genesis, thus decreasing circulating lipid and lipoprotein levels in short-term studies of patients with acquired or hereditary disorders of lipoprotein metabolism. By stimulating the activity of PDH, dichloroacetate facilitates oxidation of lactate and decreases morbidity in acquired and congenital forms of lactic acidosis (Figure 1). However, in a randomized controlled trial in patients with lactic acidosis, dichloroacetate was disappointing. Stacpoole *et al.* (9) studied the compound in patients with severe type A lactic acidosis. Those authors observed that dichloroacetate decreased the lactate concentrations in the treated patients but had no beneficial effects on outcomes. The authors concluded that dichloroacetate treatment of patients with severe lactic acidosis results in statistically significant but clinically unimportant changes in arterial blood lactate concentrations and pH and fails to alter either hemodynamics or survival rates.

Hemofiltration

Hemofiltration and “continuous renal replacement therapies” have been advocated as treatments for lactic acidosis. Schetz (10) mentioned lactic acidosis as an indication for such treatment and, indeed, critical care physicians in Europe are insistent on such therapies for patients with lactic acidosis. However, controlled studies are lacking. Hilton *et al.* (11) recently presented their observational experience. They claimed that they corrected lactic acidosis without inducing either extracellular volume expansion or hypernatremia. For 89 of 200 patients (45%) with lactic acidosis, the lactic acidosis resolved during treatment with bicarbonate-based hemofiltration. Fifty-seven patients (29%) survived. Significant differences at presentation for the group of patients who survived, compared with those who died, were observed in age, mean arterial pressure, and Acute Physiology and Chronic Health Evaluation II scores. Neither the severity of the presenting acidosis nor the arterial blood lactate concentrations appeared to predict outcomes in that series. Patients who developed acute renal failure and lactic acidosis after cardiac surgery exhibited a low survival rate. The authors suggested that the combination of acute renal failure and lactic acidosis that cannot be safely treated with hemofiltration using lactate-based replacement fluids can be managed with bicarbonate-based hemofiltration. Mariano *et al.* (12) reported success in using continuous renal replacement therapy for the management of phenformin-induced lactic acidosis. However, there is ample reason for skepticism regarding these anecdotal reports. Levraut *et al.* (13) investigated the effects of continual renal replacement therapy on lactate clearance. They studied 10 critically ill patients with acute renal failure and stable blood lactate concentrations, in a two-stage investigation. They measured lactate concentrations in samples of serum and ultrafiltrate from patients receiving continuous venovenous hemofiltration with dialysis, to calculate lactate clearance by the hemofilter. In addition, they conducted an evaluation of total plasma lactate clearance by infusing sodium lactate (1 mmol/kg body wt) in 15 min. They found that, at the end of the lactate infusion, the median blood lactate concentration increased despite renal replacement therapy. The median total plasma lactate clearance was 1379 ml/min (range, 754 to 1881 ml/min), and the median filter lactate clearance was 24 ml/min (range, 7 to 36 ml/min). Therefore, filter lactate clearance accounted for <3% of total lactate clearance. The authors concluded that continuous venovenous hemofiltration with dialysis cannot meet lactate overproduction. The data suggest that a randomized controlled trial of this treatment for lactic acidosis, as was performed for dichloroacetate, is probably not worth the effort.

Type B Lactic Acidosis

Type B lactic acidosis does not have the same treatment urgency as type A lactic acidosis, because the condition is not associated with a primary problem in generating ATP. Therefore, the rate at which hydrogen ions accumulate is much lower. An important cause of type B lactic acidosis involves ethanol intoxication. Ethanol metabolism generates NADH and

leads to the conversion of pyruvate to lactate (Figure 2). Ethanol metabolism must be ongoing for this type of lactic acidosis to occur, and the condition is mild even without treatment. However, the situation may be different in cases of thiamine deficiency. Thiamine (vitamin B1) is a cofactor for PDH. When thiamine is absent, glucose cannot be oxidized anaerobically. The major danger is not lactic acidosis but, rather, the central nervous system injury that is caused when glycolysis is accelerated to supply ATP that can no longer be supplied by the oxidation of ketoacids. This condition (Wernicke-Korsakoff syndrome) can be ameliorated or avoided by supplying thiamine.

Drug-induced lactic acidosis can be caused by oxidative phosphorylation uncouplers or drugs that interfere with gluconeogenesis. Although the lactic acidosis may be severe, the chances for survival are good. The measures required are neutralization of the excess hydrogen ions with NaHCO_3 , slowing of hydrogen ion production with insulin (in the case of metformin-induced lactic acidosis), acceleration of lactate metabolism (perhaps with dichloroacetate), and elimination of the offending drug by renal excretion or other means.

The Biguanide Dilemma

Type 2 diabetes mellitus is increasing dramatically in incidence, and the glycemic treatment is unsatisfactory. Insulin, sulfonylureas, and thiazolidinediones all have various dangerous side effects, and all three lead to additional weight gain in generally already obese patients. The biguanides have appeal because they at least do not engender further weight gain. However, many well documented cases of lactic acidosis in diabetic patients using the biguanide phenformin were reported (14). The association caused phenformin to be removed from the market in the United States in 1978. Metformin is a far less dangerous biguanide and has been widely used in Europe. Putative risk factors for lactic acidosis with biguanide treatment are as follows: age of >60 yr; decreased cardiac, hepatic, or renal function; diabetic ketoacidosis; surgery; respiratory failure; ethanol intoxication; and fasting. Biguanides may inhibit oxidative metabolism and thus increase the concentration

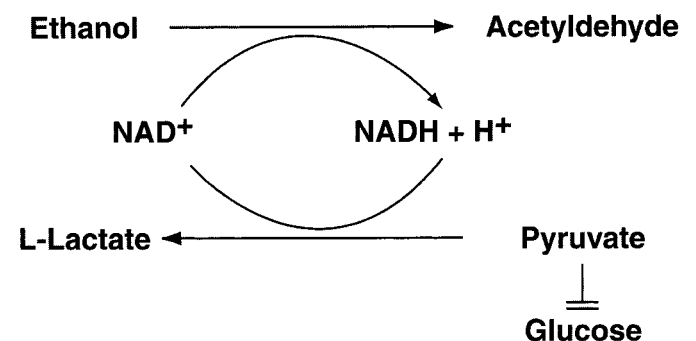


Figure 2. Ethanol-induced L-lactic acidosis. The metabolism of ethanol increases the NADH/NAD^+ ratio, which favors the conversion of pyruvate to lactate rather than to glucose (figures adapted from references 1 and 3).

of NADH, reduce gluconeogenesis, and suppress the gastrointestinal absorption of glucose.

Stang *et al.* (15) determined the incidence of lactic acidosis in a geographically defined population of metformin users. The study included 11,797 Saskatchewan residents who received one or more metformin prescriptions, resulting in 22,296 person-yr of exposure. There were 10 subjects with hospital discharges with a diagnosis of acidosis. However, primary record review revealed only two cases with laboratory findings of elevated blood lactate levels, for an incidence of 9 cases/100,000 person-yr of metformin exposure. In both cases, factors other than metformin could have contributed to the lactic acidosis. No additional cases were found in a review of death registrations in their study. The authors concluded that the rate of lactic acidosis among metformin users in a population with complete ascertainment of hospitalizations and deaths was similar to previously published rates calculated on the basis of passive reporting of cases. The rate of metformin-induced lactic acidosis was well below the lactic acidosis rate of 40 to 64 cases/100,000 patient-yr for patients prescribed phenformin.

The reports of metformin-induced lactic acidosis are necessarily anecdotal. For instance, Reeker *et al.* (16) described a typical patient. A 62-yr-old woman had been found unconscious in her bed. She was resuscitated several times in the ambulance on the way to the hospital. Her rectal temperature was 28°C. She was a diabetic being treated with metformin and glimepiride and had decreased renal function (serum creatinine concentration, 1.5 mg/dl). The patient also had heart failure attributable to heart disease. She exhibited marked lactic acidosis (lactate concentration, 45 mM; pH 6.6). Continuous venovenous hemodialysis with bicarbonate-buffered solutions was performed. The authors concluded that metformin was responsible and suggested that the drug should be prescribed only if the contraindications (in particular, renal failure) are carefully monitored. They also indicated that severe lactic acidosis should be treated early with continuous venovenous hemodialysis with bicarbonate-buffered substitution fluids. The authors may be correct in their assumptions, because “clinical success is always unassailable.” However, multiple factors interacted in the case of this critically ill woman, and doubt remains regarding the pathogenesis and the value of the treatments.

Holstein *et al.* (17) indicated that physicians largely ignore the dangers of metformin. They performed a cross-sectional analysis of 308 consecutive patients with type 2 diabetes mellitus (mean age, 66 yr) who had been previously treated with metformin on an outpatient basis and were admitted to a German general hospital between January 1995 and May 1998, because of acute disease or for optimization of their diabetes mellitus management. All patients underwent a basic investigation, including documentation of the medical history, a physical examination, an electrocardiogram, and an extensive laboratory profile. At the time of admission to the hospital, 73% of the patients were found to have contraindications, risk factors, or intercurrent illnesses necessitating discontinuation of metformin administration; 51% of these patients had several of these conditions. As major contraindications to metformin,

renal impairment was present in 19% of all cases, heart failure in 25%, respiratory insufficiency in 6.5%, and hepatic impairment in 1.3%. Additional risk factors included advanced heart disease in 51% of cases, atrial fibrillation in 9.8%, chronic alcohol abuse in 3.3%, advanced peripheral vascular disease in 2%, and pregnancy in 0.7%. As intercurrent illnesses, cerebral ischemia occurred in 9.8% of cases with metformin treatment, and malignancies were diagnosed in 6.5%. The patients with relative or absolute contraindications to metformin were older and had been previously treated with more cardiovascular medications. Most interestingly, despite the considerable risk for lactic acidosis of many patients, no cases of lactic acidosis were observed.

It is not my intention to minimize the potential of metformin to cause lactic acidosis. However, patients with type 2 diabetes mellitus who develop this complication are ill and have numerous concomitant problems, and the literature is difficult to interpret. Prudent physicians should monitor renal function, withhold the drug from patients with renal and/or hepatic insufficiency, and consider severe cardiac failure with poor hepatic and renal perfusion a relative contraindication. Metformin has been used for >40 yr as an effective glucose-lowering agent in type 2 diabetes mellitus. The life-threatening risks associated with metformin are rare and could mostly be avoided by strict adherence to the prescribing guidelines. Given the four decades of clinical experience with metformin, the antihyperglycemic efficacy of the drug, and its benefits in the metabolic syndrome, metformin offers a favorable risk/benefit profile, compared with the chronic morbidity and premature death observed among patients with type 2 diabetes mellitus.

Miscellaneous Issues

How good are we in making the diagnosis of acid-base disturbances in critically ill patients? Arterial blood gases are considered the key to diagnosing acid-base disturbances. Weil *et al.* (18) showed that differences in acid-base status between mixed venous blood and arterial blood exist in critically ill patients undergoing resuscitation. Their study was subsequently supported by animal data showing that mixed venous blood gases were superior to arterial blood gases for the assessment of acid-base status (19). The problem of CO₂ accumulation in the tissues may be exacerbated by the administration of NaHCO₃ to treat lactic acidosis (20). No data have been presented to show that disparities between mixed venous and arterial Pco₂ and pH occur in lactic acidosis attributable to septic shock or other causes. CO₂ elimination cannot be accomplished without increasing pulmonary blood flow. Studies comparing mixed venous and arterial blood gas values in various forms of lactic acidosis and the inclusion of such measurements in studies of lactic acidosis are warranted. An example of such an investigation is the report by Levy *et al.* (21), who found that hemodynamically unstable patients with sepsis requiring catecholamine therapy exhibited lactic acidosis with an elevated lactate/pyruvate ratio and decreased arterial ketone body levels, suggesting decreases in the cytoplasmic and mitochondrial redox states. The duration of lactic

acidosis was associated with the development of multiple organ failure and death in their patients. Mixed venous acid-base assessments permitted elucidation of the findings.

D-Lactic Acidosis

A favorite for board examination questions, this unique form of lactic acidosis can occur in patients with jejunoileal bypasses, small bowel resections, or other forms of short-bowel syndrome (22). Bacteria are responsible for metabolizing glucose and carbohydrate to D-lactic acid, which is then systemically absorbed. Lactate dehydrogenase can effectively metabolize only L-lactate; D-lactate is only slowly metabolized by human subjects. Clues to the condition are a short bowel or other causes of malabsorption, acidosis with a broad anion gap that cannot be explained, and neurologic symptoms. The anion gap is commonly smaller than expected on the basis of the HCO_3^- decrease, because D-lactate is not very well absorbed by renal tubules. The increased anion gap may be the result of D-lactate or some as yet unknown absorbed toxin. A discrepancy between the calculated urine osmolality and the measured urine osmolality (urine osmolal gap) is expected. Treatment consists of fluid resuscitation, restriction of simple sugars, NaHCO_3 administration as necessary, and the judicious use of antibiotics (such as metronidazole). The latter requires some caution, because antibiotics can precipitate the syndrome by permitting overgrowth of lactobacilli (23).

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