Causes of lactic acidosis

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INTRODUCTION AND DEFINITION

Lactate levels greater than 2 mmol/L represent hyperlactatemia, whereas lactic acidosis is generally defined as a serum lactate concentration above 4 mmol/L. Lactic acidosis is the most common cause of metabolic acidosis in hospitalized patients. Although the acidosis is usually associated with an elevated anion gap, moderately increased lactate levels can be observed with a normal anion gap (especially if hypoalbuminemia exists and the anion gap is not appropriately corrected). When lactic acidosis exists as an isolated acid-base disturbance, the arterial pH is reduced. However, other coexisting disorders can raise the pH into the normal range or even generate an elevated pH:

- (See "Approach to the adult with metabolic acidosis", section on 'Assessment of the serum anion gap'.)
- (See "Simple and mixed acid-base disorders".)

Lactic acidosis occurs when lactic acid production exceeds lactic acid clearance. The increase in lactate production is usually caused by impaired tissue oxygenation, either from decreased oxygen delivery or a defect in mitochondrial oxygen utilization. (See "Approach to the adult with metabolic acidosis".)

The pathophysiology and causes of lactic acidosis will be reviewed here. The possible role of bicarbonate therapy in such patients is discussed separately. (See "Bicarbonate therapy in lactic acidosis".)

PATHOPHYSIOLOGY

A review of the biochemistry of lactate generation and metabolism is important in understanding the pathogenesis of lactic acidosis [1]. Both overproduction and reduced metabolism of lactate appear to be operative in most patients.

Cellular lactate generation is influenced by the "redox state" of the cell. The redox state in the cellular cytoplasm is reflected by the ratio of oxidized and reduced nicotinamide adenine dinucleotide (ie, NAD^+ [oxidized form] and NADH [reduced form]).

NAD^+ and NADH are involved in many cellular redox reactions, serving, respectively, as an electron acceptor or an electron donor. One of these cellular redox reactions is the equilibrium between pyruvic acid and lactic acid, a reaction catalyzed by the enzyme lactate dehydrogenase (figure 1). Thus, the ratio of pyruvate and lactate is influenced by the ratio of NAD^+ and NADH, such that a reduced redox state (ie, low NAD^+/NADH ratio) is associated with a shift in the ratio from pyruvate to lactate. Many of the factors that reduce the cytoplasmic redox state also accelerate pyruvate generation and simultaneously impair mitochondrial oxidation. These factors combine to increase pyruvate and lactate generation and simultaneously impair mitochondrial pyruvate uptake and oxidation (see 'Mitochondrial dysfunction' below). Inadequate oxygen delivery or utilization and rapid oxidation of certain substrates such as ethanol will have these effects.

Lactate dehydrogenase is stereospecific for the production of the L-isomer of lactate (L-lactate), and, in humans, L-lactate is the dominant isomer that is synthesized and utilized. Although D-lactate is a minor component of mammalian metabolism, it can be a major metabolic product of some bacteria and yeast. (See "D-lactic acidosis".)

Normal individuals produce 15 to 20 mmol/kg of lactic acid per day. Most is derived from glucose metabolism via the glycolytic pathway, although deamination of alanine also generates lactate [2,3]. Balance is maintained by the utilization of an equal amount of lactic acid.

Lactic acid is primarily oxidized to carbon dioxide and water (70 to 80 percent) and used to generate glucose (15 to 20 percent). A small amount of lactate is also converted to alanine. Utilization of lactic acid primarily occurs in the liver, but the kidneys, heart, and other tissues also participate. A large amount of lactic acid is generated from glucose by nonhepatic tissues and from glycogen by muscle. The delivery of this lactic acid to the liver, where it is converted back to glucose, is named the Cori, or lactic acid, cycle.

When lactic acid accumulates in body fluids and its concentration increases, the hydrogen ions are almost completely buffered by extracellular bicarbonate. When lactate is utilized, whether by oxidation to carbon dioxide and water or by conversion to glucose or alanine, a hydrogen ion is also consumed, and a bicarbonate molecule is generated. Thus, in a patient who has accumulated lactic acid, utilization of the lactate will restore the bicarbonate concentration.

Mechanisms of lactate accumulation — Excess lactate can accumulate as a result of increased production and/or diminished utilization [2-5]. In general, three mechanisms, usually occurring together, cause lactate accumulation (table 1) [2,3]:

- Increased pyruvate production.
- Reduced entry of pyruvate into mitochondria, where it is normally oxidized to carbon dioxide and water or converted to glucose precursors.
- A shift of the cellular cytoplasmic redox state such that NADH accumulates and NAD^+ falls. This drives the pyruvate/lactate ratio toward lactate.

The contribution of lactate overproduction to the development of metabolic acidosis seems clear in certain disorders. As an example, plasma lactate levels may transiently increase to 15 to 25 mmol/L after a grand mal seizure or with maximal exercise [6], and the blood pH can fall as low as 6.8 [7,8]. However, the rate of lactate utilization in such patients can also increase rapidly, reaching rates as high as 320 mmol/hour [2]. As a result, blood pH and plasma bicarbonate levels rapidly return to normal after the seizure or exercise has ceased.

A marked increase in lactate production, in part due to catecholamine stimulation of glycolysis, also plays an important role in the lactic acidosis associated with shock, especially septic shock [9,10]. A similar mechanism explains the development of lactic acidosis when high doses of inhaled beta agonists are used to treat severe asthma [11].

The very high potential metabolic capacity for lactate utilization that is apparent in patients following grand mal seizures suggests that there must be a component of decreased lactate utilization in disorders such as shock in which lactic acidosis occurs despite more modest lactate overproduction.

The importance of impaired lactate metabolism is illustrated by the observation that, when lactic acid is infused into normal animals at rates similar to the rate of overproduction that occurs in shock, hepatic utilization of lactate increases, resulting in only a minimal fall in arterial pH [5]. In shock, reduced hepatic perfusion and an associated intracellular acidosis probably combine to substantially diminish hepatic lactate metabolism [4,5,12]. The role of diminished

lactate metabolism in sepsis is supported by the decrease in lactate levels that occurs when dichloroacetate, a stimulator of pyruvate dehydrogenase activity (accelerating pyruvate entry into mitochondria), is administered [13].

CLINICAL CAUSES

The causes of lactic acidosis can generally be divided into those associated with obviously impaired tissue oxygenation (type A) and those in which systemic impairment in oxygenation does not exist or is not readily apparent (type B) (table 1). However, there is frequently overlap between type A and type B lactic acidosis. In sepsis, for example, there is both an increase in lactate production resulting from microcirculatory failure and also a decrease in lactate clearance that is not solely due to diminished oxygen delivery.

Type A lactic acidosis — Most cases of lactic acidosis are due to marked tissue hypoperfusion resulting from hypovolemia, cardiac failure, sepsis, or cardiopulmonary arrest [2,3,14,15]. In some of these patients, concurrent respiratory acidosis contributes to the acidemia [14]. (See "Definition, classification, etiology, and pathophysiology of shock in adults" and "Clinical manifestations and diagnosis of cardiogenic shock in acute myocardial infarction".)

The clinical manifestations of shock include:

- A reduction in systemic blood pressure, the degree of which may be minimized by marked vasoconstriction
- Cool, clammy extremities, with the exception of the flushed, hyperemic skin of early septic shock
- Oligoanuria
- Impaired mental status

The prognosis is generally poor unless tissue perfusion can be rapidly restored. Both the initial serum lactate level and the rate at which lactate levels fall [16] are strong predictors of survival in patients with shock due to sepsis [17,18]. (See "Treatment of severe hypovolemia or hypovolemic shock in adults" and "Prognosis and treatment of cardiogenic shock complicating acute myocardial infarction" and "Evaluation and management of suspected sepsis and septic shock in adults".)

Type B lactic acidosis — Evidence of systemic hypoperfusion is **not** apparent in type B lactic acidosis. The mechanisms that may be involved in type B lactic acidosis include toxin-induced impairment of cellular metabolism and regional areas of ischemia.

Diabetes mellitus — Diabetes mellitus can be associated with lactic acidosis by at least three mechanisms:

- Biguanide therapy in type 2 diabetes with metformin or, in the past, with phenformin can cause type B lactic acidosis. Metformin is most likely to generate lactic acidosis when high levels result from an accidental or intentional acute overdose. (See "Metformin poisoning".)

- Biguanide therapy in patients with reduced kidney function can generate toxic levels since these drugs are almost entirely removed by the kidneys, thereby resulting in lactic acidosis. However, this is uncommon, and patients who develop severe lactic acidosis in the setting of reduced kidney function almost always have additional risk factors. (See "Metformin poisoning", section on 'Risk factors'.)

- A moderate degree of lactic acidosis unrelated to biguanide therapy occurs in some patients with diabetic ketoacidosis [2,19]. It is likely that hypovolemia plays an important role. In addition, hyperlactatemia has been reported in patients with diabetes independent of ketoacidosis [20], possibly due to decreased pyruvate dehydrogenase activity.

- D-lactic acid may accumulate and contribute to the anion gap acidosis of diabetic ketoacidosis. In these patients, the plasma concentration of D-lactic acid often exceeds 2 mmol/L and may reach 8 to 10 mmol/L [21]. The D-lactic acid is derived from methylglyoxal, a metabolite of both acetone and dihydroxyacetone phosphate, which are intermediates that can accumulate in patients with diabetic ketoacidosis. (See 'D-lactic acidosis' below and "D-lactic acidosis", section on 'Pathogenesis'.)

Malignancy — Lactic acidosis occurs rarely in patients with leukemia, lymphoma, and solid malignancies [22-27]. The pathogenesis is not well understood. Anaerobic metabolism due to dense, underperfused clusters of tumor cells and/or metastatic replacement of the hepatic parenchyma has been proposed. However, lactic acidosis can also develop in patients with relatively small tumor burdens [22,24]. Other possible mechanisms include increased rates of lactate production by the neoplastic cells that shift to primarily anaerobic glycolysis (the "Warburg" effect) [28] and thiamine and/or riboflavin deficiency [26]. It is likely that lactate metabolic clearance is also impaired.

Regardless of the mechanism, removal of the tumor (by chemotherapy, irradiation, or surgery) usually corrects the lactic acidosis [22,24-26]. (See "Acute myeloid leukemia: Overview of complications".)

Alcoholism — A mild degree of lactic acidosis can develop in patients with chronic severe alcoholism. Lactate production is usually normal, but lactate utilization may fall as a result of hepatic dysfunction. The oxidation of ethanol generates reduced nicotinamide adenine dinucleotide (NADH) and can thereby reduce the oxidized nicotinamide adenine dinucleotide (NAD^+)/NADH ratio. This ratio change shifts pyruvate toward lactate (see 'Pathophysiology' above). Although the plasma lactate concentration seldom exceeds 3 mmol/L in intoxicated patients, alcohol ingestion can increase the severity of lactic acidosis when other disorders cause overproduction of lactate. (See "Fasting ketosis and alcoholic ketoacidosis", section on 'Alcoholic ketoacidosis'.)

Toxic alcohols — Elevated plasma lactate levels can occur with methanol and ethylene glycol poisoning. The toxic metabolites of these poisons can disrupt normal mitochondrial metabolism. However, pseudolactic acidosis may also occur with ethylene glycol ingestion because the ethylene glycol metabolite glycolate (which is structurally similar to lactate) is measured as lactate in several quantitative lactate assays [29]. (See "Methanol and ethylene glycol poisoning: Pharmacology, clinical manifestations, and diagnosis", section on 'Lactate'.)

HIV infection — Given their increased propensity to serious infection, sepsis-induced lactic acidosis occurs more commonly in patients with acquired immunodeficiency syndrome (AIDS). In addition, lactic acidosis may be caused by antiretroviral medication-induced mitochondrial dysfunction. This form of chronic lactic acidosis can occur in the absence of sepsis or hypoperfusion (type B lactic acidosis). (See "Mitochondrial toxicity of HIV nucleoside reverse transcriptase inhibitors", section on 'Hyperlactatemia and lactic acidosis' and 'Mitochondrial dysfunction' below.)

Beta-adrenergic agonists — Intravenous (IV) epinephrine is associated with a lactic acidosis [30]. The mechanism likely includes both increased glycolysis in skeletal muscle and hypoperfusion of the gastrointestinal tract, which increases lactate production and reduces hepatic lactate uptake. The lactic acidosis reported in some patients with pheochromocytomas may be due to similar mechanisms [31].

Lactic acidosis has been frequently reported in patients with severe bronchospasm who are treated with high-dose, inhaled beta agonists (such as albuterol and salmeterol) [11,32,33]. Although the mechanism is not proven, the lactic acidosis in such patients may be due to adrenergic-induced glycolysis and lipolysis, which increase pyruvate and free fatty acid concentrations, respectively [33]. Free fatty acids can inhibit pyruvate dehydrogenase and thereby impair mitochondrial pyruvate uptake. Pyruvate accumulates and is converted to lactate. Increased lactate production due to marked respiratory effort may also contribute.

Mitochondrial dysfunction — Pyruvate is generated in the cytoplasm and has three metabolic fates: it enters mitochondria via oxidation by pyruvate dehydrogenase to form acetyl-coenzyme A (which is further oxidized by the Krebs cycle, converted to fat, or shunted to form ketoacids); it enters mitochondria via the enzyme pyruvate carboxylase, which generates oxaloacetate (this metabolite either replenishes the Krebs cycle or is converted to glucose); or it remains in the cytoplasm and is converted to lactic acid.

A variety of congenital or acquired mitochondrial defects that impair pyruvate utilization may generate lactic acidosis [34]:

- **Inherited disorders** – Many inherited defects in mitochondrial DNA cause a spectrum of disorders that are grouped together as the mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome [35]. Approximately 80 percent of these patients have a single-point mutation in the mitochondrial gene that encodes a specific transfer RNA. (See "Mitochondrial myopathies: Clinical features and diagnosis", section on 'MELAS'.)

- **Thiamine deficiency** – Thiamine is a necessary cofactor for two key enzymes in the tricarboxylic acid cycle: pyruvate dehydrogenase and alpha-ketoglutarate dehydrogenase. Thiamine deficiency can generate lactic acidosis, especially when thiamine deficient patients receive high glucose loads (ie, patients receiving total parenteral nutrition) [36,37]. The acidosis persists despite treatment with sodium bicarbonate but rapidly resolves with intravenous thiamine. Lactate clearance has also been shown to improve after administration of thiamine in critically ill patients [38].

- **Drug-induced mitochondrial dysfunction** – Lactic acidosis can also be generated by drugs that impair mitochondrial protein synthesis and reproduction [34]:

  - Mitochondria are believed to have prokaryotic origins (prokaryotes are unicellular organisms that lack membrane-bound organelles, such as nuclei, mitochondria, etc). This may make mitochondria uniquely susceptible to drugs that target bacterial or viral metabolism. A number of antiretroviral drugs, such as HIV nucleoside reverse transcriptase inhibitors, can impair mitochondrial metabolism and generate lactic acidosis. These syndromes are also often associated with hepatic and muscle lipid deposition. (See "Mitochondrial toxicity of HIV nucleoside reverse transcriptase inhibitors", section on 'Hyperlactatemia and lactic acidosis'.)

  - The infusion of high doses of the hypnotic sedative propofol has also been reported to cause lactic acidosis in both children and adults [39]. The mechanism has not been clearly elucidated. This form of lactic acidosis is often associated with rhabdomyolysis,

hyperlipidemia, electrocardiogram abnormalities that mimic the Brugada syndrome, arrhythmias, heart failure, acute kidney injury, and hepatomegaly. (See "Sedative-analgesia in ventilated adults: Medication properties, dose regimens, and adverse effects", section on 'Adverse effects'.)

- Linezolid is an oxazolidinone antibiotic that targets bacterial protein synthesis by inhibiting a subunit of bacterial ribosomes. It can also affect human mitochondrial ribosomes and protein synthesis, which sometimes leads to the development of lactic acidosis. Although linezolid-induced lactic acidosis was first reported after prolonged courses of antibiotic treatment, other cases have developed soon after initiation of the drug [40,41]. One case report described lactic acidosis developing in a patient with MELAS syndrome who was receiving linezolid. Although not a listed contraindication, extra caution seems appropriate when prescribing linezolid to patients with inherited mitochondrial disorders [41].

D-lactic acidosis — D-lactic acidosis is a rare form of lactic acidosis that can occur in patients with short bowel syndrome or other forms of gastrointestinal malabsorption. In these patients, abnormally large amounts of glucose and starch are metabolized (fermented) by intestinal bacteria to multiple organic acids, including D-lactic acid. Because humans metabolize D-lactic acid very slowly, systemic absorption of the D-optical isomer of lactic acid from the bowel can lead to high plasma D-lactate levels and metabolic acidosis. High D-lactate levels also generate a wide spectrum of neurologic abnormalities, including weakness, cerebellar dysfunction, and confusion [42].

Other causes of D-lactic acidosis include rapid and high-dose intravenous infusion of propylene glycol (a solvent for some intravenous medications) and diabetic ketoacidosis. In these settings, D-lactic acid is a metabolic product of other accumulating metabolites: lactaldehyde with propylene glycol and methylglyoxal in diabetic ketoacidosis. D-lactate levels are **not** measured by most laboratories when a "lactate" level is ordered. Quantitation of D-lactate levels requires a special analytic test. (See "D-lactic acidosis".)

DIAGNOSIS

The normal plasma lactate concentration is 0.5 to 1.5 mmol/L. Lactic acidosis is generally defined as a plasma lactate concentration greater than 4 mmol/L, even in the absence of overt acidemia.

The recognition of lactic acidosis has increased dramatically over the past several years as a result of the wide acceptance of early goal-directed therapy of sepsis and septic shock [43]. The screening and triage processes for patients with suspected sepsis include a blood lactate level. (See "Evaluation and management of suspected sepsis and septic shock in adults", section on 'Monitor response'.)

SUMMARY

- **Pathogenesis**
  - Lactic acidosis is the most common cause of metabolic acidosis in hospitalized patients. Impaired tissue oxygenation, leading to increased anaerobic metabolism, is usually responsible for the rise in lactate production. (See 'Introduction and definition' above.)
  - A plasma lactate concentration that exceeds 4 mmol/L generally defines lactic acidosis, even among patients without systemic acidemia. (See 'Diagnosis' above.)
  - The accumulation of lactate is usually due to enhanced pyruvate production; reduced pyruvate conversion to carbon dioxide and water or to glucose; and an altered redox state within the cell, which shifts the pyruvate/lactate ratio toward lactate. (See 'Pathophysiology' above.)
- **Causes**
  - Type A lactic acidosis is associated with impaired tissue oxygenation due to tissue hypoperfusion in shock (caused by hypovolemia, cardiac failure, or sepsis) or as a result of a cardiopulmonary arrest. Accelerated generation of pyruvate from glucose may also play an important role in some forms of type A lactic acidosis, especially in septic shock. In some patients, concurrent respiratory acidosis contributes to the acidemia. (See 'Type A lactic acidosis' above.)
  - Type B lactic acidosis occurs in patients without overt systemic hypoperfusion. Causes of type B lactic acidosis include toxin-induced impairment of cellular metabolism, regional areas of tissue ischemia, high levels of metformin, malignancy-associated lactic acidosis, alcoholism, and drug-induced mitochondrial dysfunction, often in HIV-infected patients. (See 'Type B lactic acidosis' above.)
  - D-lactic acidosis is an unusual form of metabolic acidosis that occurs in patients with short bowel syndrome or other forms of malabsorption. It may also develop in patients receiving rapid and high-dose infusions of propylene glycol (a solvent for some

intravenous [IV] medications) or in patients with diabetic ketoacidosis. (See 'D-lactic acidosis' above and "D-lactic acidosis".)

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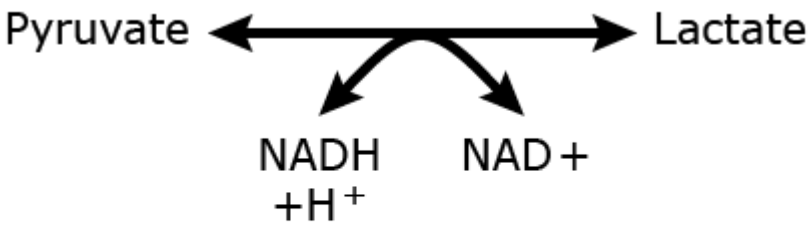
Topic 2370 Version 19.0

GRAPHICS

Metabolism of pyruvate to lactate



NOTE: The enzyme, L-lactate dehydrogenase, catalyzes this reaction

Graphic 91092 Version 2.0

Etiology of lactic acidosis

Increased lactate production
Increased pyruvate production
Enzymatic defects in glycogenolysis or gluconeogenesis (as with type 1 glycogen storage disease)
Respiratory alkalosis, including salicylate intoxication
Pheochromocytoma
Beta-agonists
Sepsis
Impaired pyruvate utilization
Decreased activity of pyruvate dehydrogenase or pyruvate carboxylase
• Congenital
• Possibly a role in diabetes mellitus, Reye syndrome
Altered redox state favoring pyruvate conversion to lactate
Enhanced metabolic rate
• Grand mal seizure
• Severe exercise
• Hypothermic shivering
• Severe asthma
Decreased oxygen delivery
• Shock
• Cardiac arrest
• Acute pulmonary edema
• Carbon monoxide poisoning
• Severe hypoxemia (PO_2 <25 to 30 mmHg)
• Pheochromocytoma
Reduced oxygen utilization
• Cyanide intoxication (decreased oxidative metabolism), which may result from cyanide poisoning or, during a fire, from smoke inhalation of vapors derived from the thermal decomposition of nitrogen-containing materials such as wool, silk, and polyurethane
• Drug-induced mitochondrial dysfunction due to zidovudine or stavudine
• Sepsis

D-lactic acidosis
Primary decrease in lactate utilization
Hypoperfusion and marked acidemia
Alcoholism
Liver disease
Mechanism uncertain
Malignancy
Diabetes mellitus, including metformin in the absence of tissue hypoxia
Acquired immunodeficiency syndrome
Hypoglycemia
Idiopathic

Although this table has been divided into either increased production or decreased utilization of lactate, there is considerable overlap among listed causes.

Graphic 78983 Version 7.0