Etiology and Therapeutic Approach to Elevated Lactate Levels

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Abstract

Lactate levels are commonly evaluated in acutely ill patients. Although most often used in the context of evaluating shock, lactate levels can be elevated for many reasons. While tissue hypoperfusion may be the most common cause of elevation, many other etiologies or contributing factors exist. Clinicians need to be aware of the many potential causes of lactate level elevation as the clinical and prognostic importance of an elevated lactate level varies widely by disease state. Moreover, specific therapy may need to be tailored to the underlying cause of elevation. The present review is based on a comprehensive PubMed search between the dates of January 1, 1960, to April 30, 2013, using the search term *lactate* or *lactic acidosis* combined with known associations, such as *shock, sepsis, cardiac arrest, trauma, seizure, ischemia, diabetic ketoacidosis, thiamine, malignancy, liver, toxins, overdose,* and *medication*. We provide an overview of the pathogenesis of lactate level elevation followed by an in-depth look at the varied etiologies, including medication-related causes. The strengths and weaknesses of lactate as a diagnostic/prognostic tool and its potential use as a clinical end point of resuscitation are discussed. The review ends with some general recommendations on the management of patients with elevated lactate levels.

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Lactate levels in clinical practice are often used as a surrogate for illness severity and to gauge response to therapeutic interventions. The use of lactate as a clinical prognostic tool was first suggested in 1964 by Broder and Weil[1] when they observed that a lactate level of more than 4 mmol/L was associated with poor outcomes in patients with undifferentiated shock. Since then, much has been published on the use of lactate in a variety of patient populations. Moreover, causes of elevated lactate levels apart from tissue hypoperfusion have been recognized and should be considered in the appropriate clinical context.

This review focuses on the use and interpretation of lactate levels across various disease states and clinical scenarios. First, we describe the physiologic features and pathogenesis of lactate production. We then discuss the different etiologies of elevated lactate levels, focusing first on states of tissue hypoxia/hypoperfusion (type A) and then on other causes not related to tissue hypoxia (type B).[2] Last, a clinical checklist for the differential diagnosis and approach to treatment of elevated lactate levels is proposed, and limitations are discussed.

For the present review, we searched PubMed between the dates January 1, 1960, to April 30, 2013, using the search term *lactate* or *lactic acidosis* combined with known associations, such as *shock, sepsis, cardiac arrest, trauma, seizure, ischemia, diabetic ketoacidosis, thiamine, malignancy, liver, toxins, overdose,* and *medication*. No formal inclusion criteria were used, but the primary search was restricted to human studies in English, and preference was given to newer studies. Additional references found in these articles were used as appropriate, and articles familiar to the authors were reviewed for broader coverage.

PHYSIOLOGY AND PATHOGENESIS

Lactate is produced by most tissues in the human body, with the highest level of production found in muscle.[3,4] Under normal conditions, lactate is rapidly cleared by the liver, with a small amount of additional clearance by the kidneys.[3,5] In aerobic conditions, pyruvate is produced via glycolysis and then enters the Krebs cycle, largely bypassing the production of lactate. Under anaerobic conditions, lactate is an end product of glycolysis and feeds into the Cori cycle as a substrate

ARTICLE HIGHLIGHTS

■ Elevated lactate levels can be caused by a variety of conditions, including shock, sepsis, cardiac arrest, trauma, seizure, ischemia, diabetic ketoacidosis, thiamine deficiency, malignancy, liver dysfunction, genetic disorders, toxins, and medications

■ Elevated lactate levels have been associated with increased mortality rates in a variety of diseases, such as sepsis, trauma, and cardiac arrest

■ Decreased lactate clearance has been found to be associated with increased mortality rates in sepsis, post—cardiac arrest, trauma, burns, and other conditions

■ The use of lactate clearance as an end point of resuscitation might prove beneficial, but further research is warranted

■ When approaching the patient with an elevated lactate level, the possibility of a multifactorial etiology must be considered

■ Despite its imperfect sensitivity and specificity, the lactate assay remains a clinically useful test that can alert a clinician to underlying hypoperfusion in need of immediate treatment or an etiology not readily apparent on initial evaluation

for gluconeogenesis (Figure 1). Lactate exists in 2 isomers: L-lactate and D-lactate. Current lactate measurements include only L-lactate (the primary isomer produced in humans), which is the focus of the present review. D-Lactate is produced by bacteria in the human colon on exposure to large amounts of unabsorbed carbohydrates. In the setting of alteration in the intestinal flora and a high carbohydrate load (such as in short bowel syndrome), there will be an excess production of D-lactate, which can cross into the bloodstream and potentially cause neurologic symptoms. The role of D-lactate has been described elsewhere[6] and will not be considered further in the present review.

Elevated lactate levels are not clearly and universally defined, but most studies use cutoff values of 2.0 to 2.5 mmol/L,[7] whereas "high" lactate levels have been defined as greater than 4.0 mmol/L in several studies.[8-11] Furthermore, the "normal value" may vary depending on the assay used. The terms *lactate* and *lactic acid* are often used interchangeably, but lactate (the component measured in blood) is strictly a weak base, whereas lactic acid is the corresponding acid. *Lactic acidosis* is often used clinically to describe elevated lactate levels, but it should be reserved for cases in which there is a corresponding acidosis (pH <7.35).[12] The exact pathogenesis of elevated lactate levels in various conditions is likely multifactorial, patient specific, and disease specific. In general, lactate level elevation may be caused by increased production, decreased clearance, or a combination of both. The etiology of elevated lactate levels is perhaps best studied in shock states. Contributing factors seem to include hypoperfusion due to macrocirculatory or microcirculatory dysfunction, mitochondrial dysfunction (including a potential lack of key enzymatic cofactors), and the presence of a hypermetabolic state, among others.[13-18] Liver dysfunction may contribute to increased production and decreased clearance, which becomes even more important in states of hypoperfusion.

MEASUREMENT

Lactate levels can be rapidly and easily measured in most clinical settings. A recent review by Kruse et al[7] on the measurement of lactate levels concluded that peripheral venous lactate levels are highly correlated with arterial blood lactate levels, thus establishing that either method can be used. Tourniquet use during blood collection and the routine use of ice for transportation do not affect lactic acid levels provided the samples are measured within 15 minutes using a point-of-care device.[19] Generally, samples should be processed within 15 to 30 minutes to avoid falsely elevated levels of lactate and should be kept on ice if processed later.[20,21] Studies have reported that although anion gap and base excess are associated with lactate, they do not necessarily predict elevated lactate levels accurately.[22,23]

ETIOLOGIES OF ELEVATED LACTATE LEVELS

There are a multitude of causes for elevated lactate levels (Table 1). Recently, most of the medical literature on the importance of lactate levels has focused on septic shock, and this literature-based selection bias may lead clinicians to associate elevated lactate levels with sepsis alone. However, any form of shock or tissue hypoperfusion will result in elevated lactate levels, and a variety of causes of elevated lactate levels exist independent of shock states. The following subsections address the various

causes of and conditions associated with elevated lactate levels.

Sepsis and Septic Shock

Septic shock is often associated with macrocirculatory dysfunction (causing arterial hypotension), microcirculatory dysfunction, and decreased oxygen and nutrient extraction by peripheral tissues. Lactate levels have become a useful marker for tissue hypoperfusion and may also serve as an end point for resuscitation in patients with sepsis and septic shock.[24,25]

The prognostic value of isolated lactate measurements and serial measurements has been investigated in various settings.[8,26,27] In a study of 1278 patients being admitted to the hospital with infection, Shapiro et al[10] found that lactate levels could correctly stratify patients according to mortality. Lactate levels of 0 to 2.4, 2.5 to 3.9, and 4.0 mmol/L or higher were associated with mortalities of 4.9% (95% CI, 3.5%-6.3%), 9.0% (95% CI, 5.6%-12.4%), and 28.4% (95% CI, 21%-36%), respectively.[10] Furthermore, evaluation of lactate clearance through serial measurements has been shown to be a useful predictor of morbidity and mortality. Patients who clear an initially elevated lactate level to less than 2.5 mmol/L or less than 4.0 mmol/L (depending on study design) within 24 hours have significantly better outcomes than patients whose elevated lactate levels persist.[28-32] Serial lactate level measurements may be useful in documenting treatment response to various therapeutic interventions (see below).

Lactate may also be useful in identifying an otherwise unrecognized population of critically ill patients with normal blood pressure. Howell et al[8] (largely using the same patient population as Shapiro et al[10]) enrolled patients admitted from the emergency department with clinically suspected infection, and Mikkelsen et al[33] included patients with severe sepsis. Both studies found that elevated lactate levels were associated with mortality independent of shock, a phenomenon called *occult* or *cryptic* shock.

Cardiogenic, Obstructive, and Hemorrhagic Shock

The utility of lactate in cardiogenic shock has not been evaluated extensively, but studies in patients with myocardial dysfunction resulting in shock after cardiac surgery found elevated
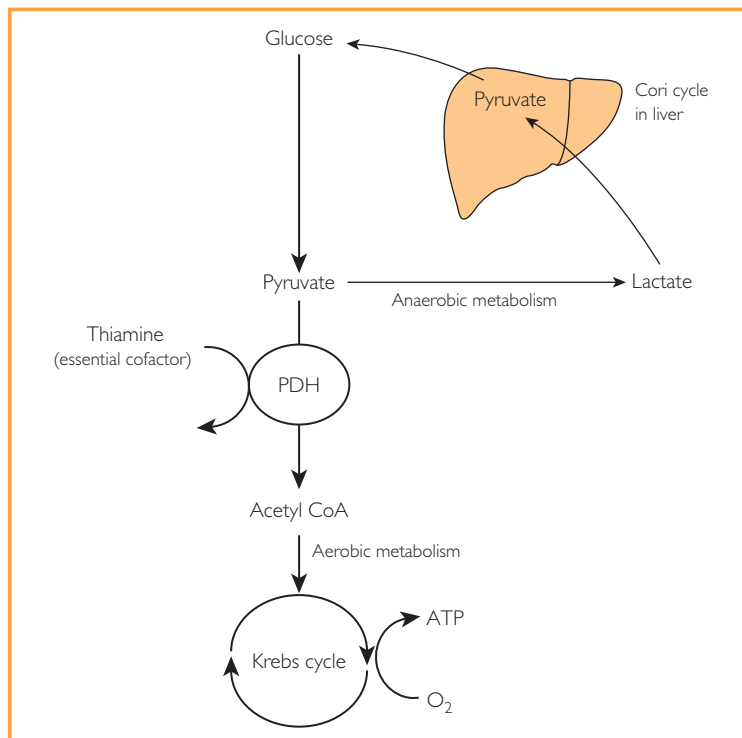

FIGURE 1. Aerobic and anaerobic metabolism. ATP = adenosine triphosphate; CoA = coenzyme A; PDH = pyruvate dehydrogenase.

lactate levels in this setting. Investigators found that the elevation was primarily related to increased tissue lactate production and not to decreased clearance.[34] In patients with cardiogenic shock requiring extracorporeal membrane oxygenation, lactate has been found to be a useful variable for predicting mortality.[35] In cardiogenic shock after ST-elevation myocardial infarction, patients with ineffective lactate clearance (<10%) had a lower survival rate.[36] Elevated lactate levels can also be seen in the setting of pulmonary embolism. Vanni et al[37] found that elevated lactate levels (>2 mmol/L) were associated with increased mortality rates independent of hemodynamic status and right ventricular dysfunction.

Hemorrhagic shock is another potential cause of elevated lactate levels. Akkose et al[38] measured lactate levels in 60 patients presenting to an emergency department and found that lactate levels were significantly elevated in traumatic and nontraumatic hemorrhagic shock compared with controls, with the traumatic group having the highest value. The study was not adequately powered to detect differences in mortality rates.[38]

TABLE 1. Causes of Elevated Lactate Levels

Shock
    Distributive
    Cardiogenic
    Hypovolemic
    Obstructive
Post—cardiac arrest
Regional tissue ischemia
    Mesenteric ischemia
    Limb ischemia
    Burns
    Trauma
    Compartment syndrome
    Necrotizing soft-tissue infections
Diabetic ketoacidosis
Drugs/toxins
    Alcohols
    Cocaine
    Carbon monoxide
    Cyanide
Pharmacological agents
    Linezolid
    Nucleoside reverse transcriptase inhibitors
    Metformin
    Epinephrine
    Propofol
    Acetaminophen
    β_2-Agonists
    Theophylline
Anaerobic muscle activity
    Seizures
    Heavy exercise
    Excessive work of breathing
Thiamine deficiency
Malignancy
Liver failure
Mitochondrial disease

Cardiac Arrest

The role of lactate in the post—cardiac arrest population has also been explored. The ischemia that occurs due to lack of blood flow during arrest, as well as the inflammation resulting from ischemia-reperfusion injury, is the likely cause of the initial increase in lactate levels. Etiologies of persistently elevated lactate levels in the postarrest period may include systemic inflammatory response and ongoing tissue hypoxia, myocardial stunning causing cardiogenic shock, an uncorrected underlying etiology of the original arrest, microcirculatory dysfunction, and mitochondrial injury and dysfunction.[39-41]

In a retrospective cohort of patients after cardiac arrest, the combination of initial lactate level and the need for vasopressor support in the immediate postarrest period could stratify patients and accurately predict outcome. Post-cardiac arrest patients with an initial lactate level less than 5 mmol/L had a mortality of 39%, whereas mortality increased to 92% with an initial lactate level greater than 10 mmol/L.[40] Furthermore, the ability to clear lactate in the postarrest period was a predictor of increased survival in 2 studies of patients after cardiac arrest.[41,42]

Trauma

Hypoperfusion, most often related to blood loss, is common in patients with traumatic injury.[43] Although the presence of vital sign abnormalities may help identify shock, their absence does not definitively exclude occult hypoperfusion.[44] Lactate level elevation may help identify a patient whose initially normal vital signs may mask ongoing tissue hypoperfusion.[45]

As in sepsis and cardiac arrest, initial lactate levels have been found to be significantly higher in nonsurvivors compared with survivors of trauma.[43,46-51] One study reported calculated sensitivity of 84% and specificity of 86% for death in patients with torso trauma and a lactate level greater than 4 mmol/L.[50] The degree of elevated lactate levels and the rate of lactate clearance strongly correlate with the risk of multiorgan dysfunction and survival after traumatic injury, and lactate clearance could potentially serve as an end point to guide resuscitation.[52-54]

Seizure

Seizures, depending on the type, can result in a profound elevation of lactate levels. Elevated lactate levels in this setting are transient, which is important for the clinician to recognize. Once the seizure has resolved, the production of lactate ceases, and lactate is rapidly cleared. Persistently elevated lactate levels beyond the expected 1 to 2 hours after a seizure may suggest a different or concomitant underlying etiology and warrant further consideration.[55,56]

Excessive Muscle Activity

Lactate levels increase with heavy exercise, mainly due to anaerobic metabolism.[57] Siegel et al[58] found that lactate levels were elevated in 95% of collapsed marathon runners, with levels of 1.1 to 11.2 mmol/L.

Elevated lactate levels in the setting of acute severe asthma may be caused, at least in part, by excessive muscle work.[59] Rabbat et al[60] found that elevated lactate levels are common in acute severe asthma and that lactate levels increase in the first 6 hours after hospital admission. They found no association with mortality or progression to respiratory failure. β-Agonists used in asthma treatment may also play a role owing to excessive adrenergic stimulation, but the exact pathogenesis of elevated lactate levels in asthma warrants further research.[61] Furthermore, excessive muscle work and respiratory muscle fatigue independent of the underlying etiology have been suggested to cause elevated lactate levels, but further research is necessary to clarify this relationship.[62]

Elevated lactate levels due to excessive muscle activity have also been associated with the use of restraints. A delirious or intoxicated patient may struggle against restraints and produce lactate due to muscle activity and tissue hypoxia. Sudden death has been reported in this population, although whether that is a result of acidosis remains unknown. Proper sedation or alternative methods for restraint may be required for patient safety in this scenario.[63]

Regional Ischemia

Early recognition of mesenteric ischemia can be challenging. Lange and Toivola[64] found elevated lactate levels to be 96% sensitive and 38% specific for mesenteric ischemia; however, other investigators report much lower sensitivity.[65] Furthermore, elevated lactate levels in the setting of mesenteric ischemia have been associated with increased mortality rates.[66,67] In cases of abdominal pain in which mesenteric ischemia is considered, lactate level measurements may be a useful way to guide and expedite further diagnostic workup because lactate has been found in animal models to increase within 1 hour of induced bowel ischemia.[68,69] However, as noted, lactate levels are not always elevated in patients with mesenteric ischemia, and larger studies are required to determine the true sensitivity and specificity.[70] Aside from mesenteric ischemia, other acute abdominal diseases, such as bacterial peritonitis and acute pancreatitis, can cause elevated lactate levels.[71]

In a study of severely injured trauma patients, lactate levels were significantly higher in those with acute lower extremity compartment syndrome.[72] In Fournier gangrene and other types of necrotizing soft-tissue infections, lactate has been associated with mortality.[73-75]

Burns and Smoke Inhalation

In severe burns, lactate has been found to be a strong predictor of outcome. Jeng et al[76] found that the initial lactate level was a useful variable to separate survivors from nonsurvivors. Another prospective study by Kamolz et al[77] found similar results with a cutoff level for initial lactate of 2 mmol/L. Moreover, they showed that rapid lactate clearance was associated with decreased mortality rates. Furthermore, because sepsis with multisystem organ failure is a major cause of morbidity and mortality in burns, lactate values should be obtained and taken into consideration when dealing with patients with burns, although the role of lactate as a resuscitation end point is questionable.[78]

Smoke inhalation victims are at particular risk for elevated lactate levels due to potential inhalation of cyanide or carbon monoxide.

Diabetic Ketoacidosis

Although not traditionally appreciated, elevated lactate levels may occur in diabetic ketoacidosis (DKA), but they do not seem to be associated with worse outcomes, in contrast to other disease states.[9] Cox et al[9] conducted a retrospective study of 68 patients with DKA and found that 40% had a lactate level greater than 4 mmol/L. In this cohort, there was no correlation between lactate and intensive care unit length of stay or mortality. A positive correlation of lactate with glucose and a negative correlation between lactate and thiamine levels raises the possibility that elevated lactate levels in DKA may be due not only to hypoperfusion but also to an altered metabolic profile, but further investigation is warranted.[9,79]

Thiamine Deficiency

Thiamine serves as a cofactor for multiple cellular enzymes, including pyruvate dehydrogenase and α-ketoglutarate dehydrogenase, components essential to the tricarboxylic acid cycle and aerobic carbohydrate metabolism (Figure 1). In the absence of thiamine, anaerobic metabolism predominates, and lactate production increases.[80] The development of elevated lactate levels in serum and cerebrospinal fluid secondary to thiamine deficiency has been well described.[81-84]

Risk factors for thiamine deficiency include states of nutritional deficiency, such as alcoholism, chronic wasting diseases, hyperemesis gravidarum, anorexia nervosa, and gastric bypass surgery.[85-89] An elevated lactate level resulting from thiamine deficiency is an often overlooked but easily treated condition that should be considered in cases of otherwise unexplained elevated lactate levels.[90-93]

Malignancy
Most patients with cancer who present with cancer-related elevated lactate levels are adults with rapidly progressive leukemia or lymphoma, often with liver involvement. The pathogenesis is poorly understood but is likely related to tumor overexpression of certain glycolytic enzymes, mitochondrial dysfunction, impaired hepatic clearance, and, perhaps, malnutrition, leading to thiamine deficiency.[94,95]

Liver Dysfunction
The liver is the organ primarily responsible for lactate clearance, and in the presence of severe liver dysfunction, lactate clearance may be impaired.[96,97] Additionally, studies have shown that the acutely injured liver may itself act as a source of lactate.[98-101] Clinicians should be cautioned against attributing a high lactate level to liver disease alone without adequately investigating or treating for other causes of elevated lactate levels.[102] Moreover, in shock states, accompanying liver failure likely accentuates lactic acid level elevation secondary to poor clearance but is not the proximate cause of the initially increased production.

Inborn Errors of Metabolism
In rare cases, especially in the pediatric population, elevated lactate levels can be caused by inborn errors of metabolism. The genetic disorders involved can cause dysfunction in a variety of metabolic steps, including gluconeogenesis, pyruvate dehydrogenase, the tricarboxylic acid cycle, and the respiratory chain.[103]

PHARMACOLOGIC AGENTS AND TOXINS ASSOCIATED WITH ELEVATED LACTATE LEVELS
A variety of medications and toxins associated with elevated lactate levels are listed in Table 2.[61,104-131] Owing to the rarity of most of these clinical scenarios, there is a lack of research on treatment options, and some of the associations are highly suspected but not fully proved. Treatment choice should be based on the specific clinical scenario, and current recommendations as noted in Table 2 are often based on case reports and expert opinion. Moreover, many medications and toxins not listed in Table 2 might cause elevated lactate levels but are beyond the scope of the present review, particularly overdoses. Special attention is given in the following subsections to metformin and alcohols owing to the high prevalence of exposure to these agents.

Metformin (Biguanide)
One of the first biguanides, phenformin, was withdrawn from the US market in 1976 because of the common occurrence of elevated lactate levels.[132] Today, metformin is the only biguanide used clinically for the management of diabetes mellitus. Metformin is thought to increase the risk of elevated lactate levels, but the correlation remains controversial. The proposed mechanism includes inhibition of gluconeogenesis and mitochondrial impairment.[105]

Recently, a major Cochrane meta-analysis concluded that there was no increased risk of elevated lactate levels for metformin compared with nonmetformin treatment; however, this may reflect use in selected study populations and not necessarily those with overdoses or use in renal insufficiency, for example.[133] The estimated rate of confirmed elevated lactate levels (lactate level >5 mmol/L) was reported to be approximately 5 cases per 100,000 patients based on numbers from the Food and Drug Administration from 1996.[104] Patients with diabetes who develop this complication are often ill and have numerous comorbid issues, such as renal insufficiency and congestive heart failure. The elevated lactate levels observed in metformin users may be related to an exacerbation of their chronic disease or another acute insult and are not necessarily related to metformin use.[105,134] Pure metformin-associated elevated lactate levels are often seen with accumulation due to kidney failure, liver failure, or overdose. In patients with renal failure, the suggested treatment is hemodialysis, which will correct the metabolic acidosis and remove metformin.[105]

TABLE 2. Common Drugs and Toxins Associated With Elevated Lactate Levels[a]

Drug/toxin	Risk factors	Proposed mechanism	Suggested treatment in addition to cessation of the offending agent
Metformin[104,105b]	Congestive heart failure, kidney failure, liver failure, or overdose	Inhibition of gluconeogenesis and mitochondrial impairment, inhibition of lactate elimination	Consider hemodialysis
Acetaminophen[131]	Overdose	Impairment of the mitochondrial electron transport chain; later hepatotoxicity and systemic effects	Enteral activated charcoal and N-acetylcysteine
NRTI[106-108]	Female sex	Direct mitochondrial toxicity	No specific treatment
Linezolid[109-111]	Possibly prolonged use in elderly patients	Direct mitochondrial toxicity	No specific treatment
β_2-Agonists[61,112,113]	Not applicable	β_2-Adrenergic stimulation causing increased glycogenolysis, glycolysis, and lipolysis; free fatty acids released by lipolysis may inhibit PDH	Depending on the clinical situation, the β_2-agonist may/should be continued
Propofol[114-117]	Prolonged high-dose use (propofol infusion syndrome[c])	Impairment of the mitochondrial electron transport chain and fatty acid oxidation	Supportive treatment and potentially hemodialysis should be considered
Epinephrine[118,119]	Not applicable	Likely due to β_2-adrenergic stimulation (see β_2-agonists)	Depending on the clinical situation, epinephrine may be continued
Theophylline[120,121]	Overdose, although reported in standard doses	Increased levels of catecholamines (see β_2-agonists)	Enteral activated charcoal; hemodialysis in severe cases
Alcohols (ethanol, methanol, propylene glycol)[122-124bd]	Clinical relevance controversial and may be confounded by comorbidities (thiamine deficiency, seizures, sepsis, and other toxins)	Increased NADH levels due to ethanol metabolism may inhibit PDH and the use of lactate; contributions from underlying comorbidities or possibly ketoacidosis may play a role	Identification and treatment of underlying disorders, including administration of thiamine
Cocaine[125,126]	Not applicable	β_2-Adrenergic stimulation (see β_2-agonists); vasoconstriction causing ischemia	Supportive care and benzodiazepine
Carbon monoxide[127,128]	Not applicable	Decreased oxygen-carrying capacity of the blood	High-flow/hyperbaric oxygen; consider co-exposure to cyanide
Cyanide[129,130]	Not applicable	Noncompetitive inhibition of cytochrome c oxidase causing mitochondrial dysfunction and inability to use oxygen	Hydroxocobalamin or other cyanide antidote kit (sodium nitrite, amyl nitrite, sodium thiosulfate); consider co-exposure to carbon monoxide

[a]NADH = nicotinamide adenine dinucleotide; NRTI = nucleoside reverse transcriptase inhibitor, PDH = pyruvate dehydrogenase.
[b]See the text for more details.
[c]The propofol infusion syndrome is characterized by cardiac failure, rhabdomyolysis, metabolic acidosis, and renal failure.
[d]Ethylene glycol may cause falsely elevated lactate levels.

Alcohols

The association between elevated lactate levels and ethanol remains controversial, and studies show varying results. Although ethanol may increase lactate levels in an experimental setting, clinically significant elevated lactate levels are rare in patients with no other concerns or comorbidities.[122-124] Ruling out and treating other causes of severely elevated lactate levels in these patients are, therefore, important, and lactate level elevation should not solely be attributed to the potential effects of ethanol. Ethanol-intoxicated patients might be at increased risk for other causes of elevated lactate levels, such as thiamine deficiency, seizures, sepsis, and other toxins. Other alcohols (propylene glycol and methanol) have been implicated in elevated lactate levels, and lactate levels can be falsely elevated in ethylene glycol poisoning.[135-138]

APPROACH TO THE PATIENT WITH AN ELEVATED LACTATE LEVEL

In broad terms, elevated lactate levels can be divided into 2 categories: cases in which it is driven by hypoperfusion/hypoxemia and cases

in which it is not. The hypoperfusion-driven cases include all forms of shock, the post—cardiac arrest state, and regional ischemia. In all of these clinical scenarios, lactate levels that remain elevated are often important prognostically, and treatment is aimed at improving perfusion to the affected tissues. In shock, treatment can involve volume resuscitation, vasopressors, or inotropes, depending on the etiology of the shock. In regional ischemia, treatment can involve surgery to restore circulation or remove damaged tissue.

The second general category includes cases not driven by hypoperfusion. This group includes drug effects, seizures, malignancy, and thiamine deficiency. In these cases, the elevated lactate levels stem from dysfunction of cellular metabolism or overproduction from increases in metabolism or muscle work. The treatments are, therefore, quite different from those used for hypoperfusion, focusing on stopping or reversing offending agents (possibly requiring dialysis in cases such as metformin or salicylate toxicity), remedying the deficit in metabolism (as in correction of DKA or thiamine replacement), or targeting the underlying organ dysfunction.

Differentiating among all these causes can be difficult during a patient's initial presentation. The clinical importance, however, is clear. Lactate in the undifferentiated patient has been associated with mortality,[139-141] but the association varies widely when patients are stratified according to disease (Figure 2). With the same cutoff value (lactate level >4 mmol/L), in-hospital mortality approaches zero in uncomplicated DKA but reaches more than 75% in the post—cardiac arrest population. This highlights the importance of using lactate levels in the appropriate clinical context. Thus, lactate elevation is likely irrelevant for prognosis of an asthma exacerbation or DKA but more concerning for a patient with sepsis or after cardiac arrest.

The evaluation of elevated lactate levels must include the consideration of a multifactorial etiology. Many patients are at increased risk for multiple potential causes, such as thiamine deficiency and liver dysfunction in septic shock,[18] seizures in the setting of alcohol intoxication or drug abuse,[142,143] and cyanide/carbon monoxide poisoning in the setting of burns with concurrent smoke inhalation.[144]

Given the complexities mentioned previously, a systematic approach to the patient with an elevated lactate level may be helpful for clinicians evaluating and treating such a patient. Although individual clinical judgment is crucial, a "checklist" tool may help avoid missed opportunities for diagnostic investigations and therapeutic interventions (Table 3).

LACTATE CLEARANCE AS AN END POINT OF RESUSCITATION

As described previously, effective lactate clearance has been associated with decreased mortality in a variety of settings and conditions. Conversely, failure to clear lactate portends a worse outcome. In patients with presumed tissue hypoperfusion (eg, septic shock), failure to clear lactate should prompt reassessment of the resuscitation effort. As discussed throughout this article, lactate level elevation may derive from any of a variety of sources. Persistent lactate level elevation may indicate an unrecognized ischemic bowel, an uncontrolled source of infection, inadequate flow (either from inadequate intravascular volume or inadequate cardiac contractility), concomitant pharmacologic insult (eg, associated metformin-induced mitochondrial injury in a septic patient with renal failure), unrecognized thiamine deficiency, irreversible mitochondrial injury, or other problems. Continual reassessment for unrecognized causes is, therefore, warranted in cases of
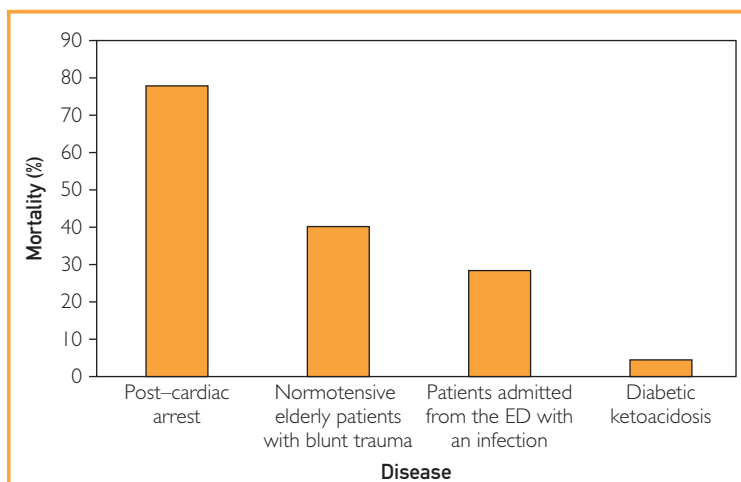

FIGURE 2. Elevated lactate levels (>4 mmol/L) in different diseases and its association with in-hospital mortality.[9-11,40] The mortality in post—cardiac arrest shown here is calculated based on data from Cocchi et al[40] and not specified in the original article. ED = emergency department.

TABLE 3. Clinical Checklist: Evaluation of Elevated Lactate Levels

Evaluate for tissue hypoperfusion and restore adequate perfusion
    Shock (distributive, cardiogenic, hypovolemic, and obstructive), post—cardiac arrest syndrome
    Tissue hypoperfusion should be initially assumed/considered until proved otherwise
    Treatment is variable based on shock etiology

Evaluate for local tissue ischemia and treat accordingly
    Mesenteric ischemia, limb ischemia, burns, trauma, compartment syndrome, necrotizing soft-tissue infections
    Consider early surgical consultation as appropriate

Stop/reverse potential offending agents
    Pharmacological agents: linezolid, nucleoside reverse transcriptase inhibitors, metformin, valproate, theophylline,
        epinephrine, propofol, isoniazid, and salicylates
    Drugs and toxins: cocaine, alcohols, carbon monoxide, and cyanide poisoning
    Consider a toxicology consultation or poison control involvement
    Cessation of exposure and removal of agent (ie, dialysis) when appropriate (Table 2)

Consider thiamine deficiency and treat if suspected
    Patient with malnutrition of any cause, often (but not exclusively) alcoholics
    Intravenous thiamine should be given

Consider current or recent anaerobic muscle activity as etiology
    Heavy exercise, seizures, excessive work of breathing
    Consider other etiologies, especially if rapid clearance is not seen when the inciting problem is treated (ie, should
        rapidly clear after cessation of seizure activity)

Consider other metabolic derangements
    Diabetic ketoacidosis
    Mitochondrial disease
    Liver dysfunction

persistent elevation, because treatment may have to be tailored accordingly.

Previous studies have attempted to use lactate clearance in a more specific manner using a protocol-driven response to persistent elevation.[145,146] Jansen et al[146] studied intensive care unit patients with presumed anaerobic causes of lactate levels of 3 mmol/L or greater and randomized them to either standard therapy or standard therapy and a complex treatment algorithm guided (in part) by lactate clearance. Patients in the lactate clearance group had shorter time in the intensive care unit and were weaned faster from mechanical ventilation and inotropes. There was no difference in actual lactate clearance between the groups and no difference in mortality before adjusting for risk factors. When adjusting for predefined risk factors, there was a significant decrease in hospital mortality (hazard ratio, 0.61; 95% CI, 0.43-0.87).[146]

Jones et al[145] performed a randomized trial in patients with severe sepsis or septic shock to determine whether impaired lactate clearance could serve as an indicator for use of inotropic support or blood transfusion. Specifically, they compared the early goal-directed therapy[147] algorithm of goal central venous pressure of 8 to 12 mm Hg, goal mean arterial pressure of at least 65 mm Hg, and use of blood or dobutamine to achieve goal central venous oxygen saturation ($ScvO_2$) of at least 70% with a modified algorithm replacing $ScvO_2$ with a goal lactate clearance of at least 10%. However, only 10% of patients required an intervention at the third step of blood or dobutamine for persistent $ScvO_2$ of 70% or less or lactate clearance of 10% or less within the first 6 hours. Given that only 10% of patients required an intervention at this last step, the study was underpowered to assess this specific use of lactate clearance compared with $ScvO_2$. Given the nonspecific nature of lactate level elevation, as described throughout this review, the physiologic rationale of providing "blind" use of dobutamine without measuring some form of cardiac output to help determine whether contractility is the likely cause remains unclear. For example, this algorithm could lead to the inappropriate provision of dobutamine to a patient with high/normal cardiac output when the cause of persistent lactate level elevation may be unrecognized ischemic bowel, concomitant fulminant hepatic failure, or inadequate volume resuscitation. Because the study was underpowered to detect

change and the physiologic rationale remains unclear, we do not necessarily recommend dobutamine in this scenario but rather a careful reassessment of the patient to attempt to identify and subsequently treat the reason for persistently elevated lactate levels (one of which could turn out to be decompensated myocardial function requiring dobutamine).

LIMITATIONS AND PITFALLS OF INTERPRETING ELEVATED LACTATE LEVELS IN CLINICAL PRACTICE

As reviewed herein, the etiologies of lactate level elevation are varied (Table 1). The clinical importance of elevated lactate levels also varies widely (Figure 2). This difference highlights the importance of considering all potential etiologies in the initial evaluation and using the test result in context with the overall clinical picture. In addition, multiple reasons for lactate level elevation can be present in a given patient, making interpretation challenging. Given the variety of etiologies of lactate elevation and the varied clinical importance (depending on etiology), lactate is not necessarily specific for either diagnosis or prognosis unless thoughtfully coupled with the overall clinical picture.

In addition to being a nonspecific test, lactate may not be as sensitive a test as is commonly thought. In mesenteric ischemia and sepsis, a normal lactate level is often interpreted as reassuring, but studies suggest that this may be a false reassurance. For example, in a study of superior mesenteric artery occlusion, 13 of 27 patients had a normal lactate level.[65] In a study by Dugas et al,[148] 45% of patients with vasopressor-dependent septic shock did not have a lactic acid level greater than 2.4 mmol/L initially, but their mortality rate remained high. The reason some patients express lactate more than others in these scenarios is not well understood. Dugas et al[148] found an association between elevated lactate levels and liver disease and bacteremia in their study of patients with vasopressor-dependent shock. The association between lactate level elevation and liver injury in the study by Dugas et al[148] illustrates a potential confounder that may occur in patients with sepsis given the high frequency of concurrent liver involvement.

CONCLUSION

Elevated lactate levels are encountered in a multitude of clinical presentations and disease states. Patients with elevated lactate levels may be at risk for considerable morbidity and mortality and require a prompt, thoughtful, and systematic approach to diagnosis and treatment. Despite the limitations and complexities discussed, a lactate level is an easily measured laboratory variable that can provide useful bedside information for the clinician when incorporated into the appropriate clinical context.

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