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Etiology and therapeutic approach to elevated lactate

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Abstract

Lactate levels are commonly evaluated in acutely ill patients. Although most commonly used in the context of evaluating shock, lactate can be elevated for many reasons. While tissue hypoperfusion is probably 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 elevation as the clinical and prognostic importance of an elevated lactate varies widely by disease state. Moreover, specific therapy may need to be tailored to the underlying cause of elevation. The current review is based on a comprehensive PubMed search and contains an overview of the pathophysiology of lactate 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 endpoint of resuscitation will be discussed. The review ends with some general recommendations on management of patients with elevated lactate.

Introduction

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 when they observed that a lactate excess of > 4 mmol/L was associated with poor outcomes in patients with undifferentiated shock.[1] Since that time, much has been published on the utilization of lactate in a variety of patient populations. Moreover, causes of elevated lactate apart from tissue hypoperfusion have been recognized and should be considered in the appropriate clinical context.

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

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Conflicts: NONE

For the current review we searched PubMed using the search term *lactate* or *lactic acidosis* in combination 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 utilized as appropriate and articles familiar to the authors were reviewed for broader coverage.

Physiology and Pathophysiology

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 for gluconeogenesis (see Figure 1). Lactate exists in two isomers: L-lactate and D-lactate. Current lactate measurements only include L-lactate (the primary isomer produced in humans) which will be the focus of the current review. D-lactate is produced by bacteria in the human colon when they are exposed 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 and will not be considered further in the current review.[6]

Elevated lactate is not clearly and universally defined but most studies use cut-offs between 2.0 and 2.5 mmol/L[7] whereas “high” lactate has been defined as a lactate level > 4mmol/L in a number of 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 but should be reserved for cases where there is a corresponding acidosis (pH < 7.35).[12] The exact pathophysiology of elevated lactate in various conditions is likely multifactorial, patient-specific, and disease-specific. In general, lactate elevation may be caused by increased production, decreased clearance, or a combination of both. The etiology of elevated lactate is perhaps best studied in shock states. Contributing factors appear to include: hypoperfusion due to macro- and/or microcirculatory dysfunction, mitochondrial dysfunction (including potential lack of key enzymatic co-factors) and the presence of a hypermetabolic state, among others.[13–18] Liver dysfunction may contribute to both increased production and decreased clearance, which becomes even more important in states of hypoperfusion.

Measurement

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

Etiologies of Elevated Lactate

There are a multitude of causes for elevated lactate (see Table 1). Recently, the majority of 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 with sepsis alone. However, any form of shock or tissue hypoperfusion will result in elevated lactate, and a number of causes of elevated lactate exist independent of shock states. The following section will address the various causes of and conditions associated with elevated lactate.

Sepsis and Septic Shock

Septic shock is often associated with macrocirculatory dysfunction causing arterial hypotension, as well as microcirculatory dysfunction, and decreased oxygen and nutrient extraction by peripheral tissues. Lactic acid levels have become a useful marker for tissue hypoperfusion and may also serve as an endpoint 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 with infection, Shapiro *et al*. found that lactate levels could correctly stratify patients according to mortality. Lactate levels of 0–2.4, 2.5–3.9 and ≥4 mmol/L 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 < 2.5 mmol/L or < 4.0 mmol/L (depending on study design) within 24 hours have significantly better outcomes than patients whose elevated lactate persists.[28–32] Serial lactate 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 utilizing the same patient population as Shapiro *et al.*) 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 was 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 profoundly elevated lactate levels in this setting. Investigators found that the elevation was primarily related to increased tissue lactate production and not decreased clearance.[34] In patients with cardiogenic shock requiring extracorporeal membrane oxygenation, lactate has been found to be a useful parameter for predicting mortality.[35] In cardiogenic shock following ST-elevation myocardial infarction, patients with ineffective lactate clearance (<10%) had a lower survival rate.[36] Elevated lactate can also be seen in the setting of pulmonary embolism. Vanni *et al.* showed that elevated lactate (>2 mmol/L) was associated with increased mortality independent of hemodynamic status and right ventricular dysfunction.[37]

Hemorrhagic shock is another potential cause of elevated lactate. Akkose *et al*. measured lactate levels in 60 patients presenting to an emergency department and found that lactate levels were significantly elevated in both traumatic and non-traumatic hemorrhagic shock as

compared to controls, with the traumatic group having the highest value. The study was not adequately powered to detect any difference in mortality.[38]

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 rise in lactate. Etiologies of persistently elevated lactate in the post-arrest 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 post-arrest patients, the combination of initial lactate level and the need for vasopressor support in the immediate post-arrest period could stratify patients and accurately predict outcome. Post-arrest patients with an initial lactate <5 mmol/L had a mortality of 39% whereas mortality rose to 92% with an initial lactate > 10mmol/L.[40] Furthermore, the ability to clear lactate in the post-arrest period was a predictor of increased survival in two studies of post-arrest patients.[41,42]

Trauma

Hypoperfusion, most often related to blood loss, is common among patients with traumatic injury.[43] While the presence of vital sign abnormalities may help to identify shock, their absence does not definitively exclude occult hypoperfusion.[44] Lactate 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 non-survivors compared to survivors of trauma.[43,46–51] One study reports a calculated sensitivity of 84% and specificity of 86% for death in patients with torso trauma and a lactate level > 4mmol/L.[50] The degree of elevated lactate and rate of lactate clearance strongly correlates with the risk of multi-organ dysfunction and survival following traumatic injury, and lactate clearance could potentially serve as an endpoint to guide resuscitation.[52–54]

Seizure

Seizures, depending on the type, can result in a profound elevation of lactate. 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 beyond the expected 1–2 hours following a seizure may suggest a different or concomitant underlying etiology and warrants further consideration.[55,56]

Excessive Muscle Activity

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

Elevated lactate 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 is common in acute severe asthma and that lactate increases in the first 6 hours after admission. They found no association with mortality or progression to respiratory failure. Betaagonists used in asthma treatment may also play a role due to excessive adrenergic stimulation (see Table 2) but the exact pathophysiology of elevated lactate 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 but further research is necessary to clarify this relationship.[62]

Elevated lactate due to excessive muscle activity has 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 *et al.* found elevated lactic acid levels to be 96% sensitive and 38% specific for mesenteric ischemia.[64] Furthermore, elevated lactate in the setting of mesenteric ischemia has been associated with increased mortality.[65,66] In cases of abdominal pain where mesenteric ischemia is considered, lactate measurements may be a useful way to guide and expedite further diagnostic workup, since lactate has been shown in animal models to increase within one hour of induced bowel ischemia.[67,68] While lactate levels are typically elevated in mesenteric ischemia, this may not always be the case and larger studies are required to determine the true sensitivity and specificity.[69] Aside from mesenteric ischemia, other acute abdominal diseases such as bacterial peritonitis and acute pancreatitis can cause elevated lactate.[70]

In a study of severely injured trauma patients, lactate levels were significantly higher in patients with acute lower extremity compartment syndrome.[71] Both in Fournier's gangrene and other types of necrotizing soft tissue infections, lactate has been associated with mortality.[72–74]

Burns and Smoke Inhalation

In severe burns, lactate has been found to be a strong predictor of outcome. Jeng *et al.* showed that the initial lactate level was a useful parameter to separate survivors from non-survivors.[75] Another prospective study by Kamolz *et al.* found similar results with a cut-off level for initial lactate of 2 mmol/L. Moreover, they showed that rapid lactate clearance was associated with decreased mortality.[76] Furthermore, since 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 burn patients even though the role of lactate as a resuscitation end-point is questionable.[77]

Smoke inhalation victims are at particular risk of elevated lactate due to potential inhalation of cyanide and/or carbon monoxide (see Table 2).

Diabetic Ketoacidosis

While not traditionally appreciated, elevated lactate may occur in diabetic ketoacidosis (DKA), but does not appear to be associated with worse outcomes in contrast to other disease states.[9] Cox *et al.* conducted a retrospective study of 68 DKA patients and found that 40% had a lactate level >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 in DKA may be due not only to hypoperfusion but also to an altered metabolic profile, but further investigation is warranted.[9,78]

Thiamine Deficiency

Thiamine serves as a co-factor for multiple cellular enzymes including pyruvate dehydrogenase and α-ketoglutarate dehydrogenase, components essential to the tricarboxylic acid cycle and aerobic carbohydrate metabolism (see Figure 1). In the absence of thiamine, anaerobic metabolism predominates and lactate production increases.[79] The development of elevated lactate in both serum and cerebrospinal fluid secondary to thiamine deficiency has been well described.[80–83]

Risk factors for thiamine deficiency include states of nutritional deficiency such as alcoholism, chronic liver disease, chronic wasting diseases, hyperemesis gravidarum, anorexia nervosa, and gastric bypass surgery.[84–88] Elevated lactate resulting from thiamine deficiency is an often overlooked but easily treated condition that should be considered in cases of otherwise unexplained elevated lactate.[89–92]

Malignancy

The majority of cancer patients who present with cancer-related elevated lactate 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.[93,94]

Liver Dysfunction

The liver is the organ primarily responsible for lactate clearance, and in the presence of significant liver dysfunction lactate clearance may be impaired.[95,96] Additionally, studies have shown that the acutely injured liver may itself act as a source of lactate.[97–100] Clinicians should be cautioned against attributing a high lactate level to liver disease alone without adequately investigating and/or treating for other, more reversible causes of elevated lactate.[101] Moreover, in shock states, accompanying liver failure likely accentuates lactic acid 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 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.[102]

Pharmacologic Agents and Toxins Associated with Elevated Lactate

A number of medications and toxins associated with elevated lactate are listed in Table 2.[61,103–135] Due 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 proven. 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 but are beyond the scope of the current review, particularly overdoses. Special attention is paid below to metformin and alcohol due 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.[136] Today, metformin is the only biguanide used clinically for the management of diabetes mellitus. Metformin is thought to

increase the risk of elevated lactate, but the correlation remains controversial. The proposed mechanism includes inhibition of gluconeogenesis and mitochondrial impairment.[104]

Recently a major Cochrane meta-analysis concluded that there was no increased risk of the development of elevated lactate for metformin compared to non-metformin treatment, however this may reflect usage in selected study populations and not necessarily those with overdoses or use in renal insufficiency, for example.[137] The estimated rate of confirmed elevated lactate (lactate >5 mmol/L) was reported to be around 5 cases per 100,000 patients based on numbers from the Food and Drug Administration (FDA) from 1996.[103] 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 observed in metformin users may be related to an exacerbation of their chronic disease or another acute insult and is not necessarily related to metformin.[104,139] Pure metformin-associated elevated lactate is often seen with accumulation due to kidney failure, liver failure or overdose. In cases with renal failure, the suggested treatment is hemodialysis, which will correct the metabolic acidosis and remove metformin.[104]

Alcohols

The association between elevated lactate and ethanol remains controversial and studies show varying results. Although ethanol may increase lactate levels in an experimental setting, clinically significant elevated lactate is rare in patients with no other complaints or co-morbidities.[127–129] Ruling out and treating other causes of severely elevated lactate in these patients are therefore important and lactate 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 such as thiamine deficiency, seizures, sepsis, and other toxins. Other alcohols (propylene glycol and methanol) have been implicated in elevated lactate and lactate can be falsely elevated in ethylene glycol poisoning.[140–143]

Approach to the Patient with Elevated Lactate

In broad terms, elevated lactate can be divided into two categories: cases where it is driven by hypoperfusion/hypoxemia, and cases where 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 that remains elevated is often quite important prognostically, and treatment is aimed at improving perfusion to the affected tissues. In shock, this can involve volume resuscitation, vasopressors, or inotropes, depending on the etiology of the shock. In regional ischemia, this 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 stems either 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 between all of the above 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[144–146], but the association varies widely when patients are stratified according to disease (Figure 2). With the same cut-off (lactate > 4 mmol /L), in-hospital mortality approaches zero in uncomplicated DKA but reaches more than 75% in the post-cardiac arrest patient. 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 septic or post-cardiac arrest patient.

The evaluation of elevated lactate must include the consideration of a multifactorial etiology. Many patients are at increased risk of multiple potential causes such as thiamine deficiency or liver dysfunction in septic shock[18], seizures in the setting of alcohol intoxication or drug abuse[147,148] or cyanide/carbon monoxide poisoning in the setting of burns with concurrent smoke inhalation[149].

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

Lactate Clearance as an Endpoint of Resuscitation

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

Previous studies have attempted to utilize lactate clearance in a more specific fashion, utilizing a protocol-driven response to persistent elevation.[150,151] Jansen *et al*. studied intensive care unit patients with presumed anaerobic causes of lactate ≥ 3 mEq/L 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; confidence interval 0.43–0.87).[151]

Jones *et al*.[150] performed a randomized trial in patients with severe sepsis or septic shock to determine if impaired lactate clearance could serve as an indicator for use of inotropic support and/or blood transfusion. Specifically, they compared the early goal-directed therapy[152] algorithm of goal central venous pressure 8–12 mm Hg, goal mean arterial pressure ≥ 65 mm Hg, and use of blood and/or dobutamine to achieve a goal of central venous oxygen saturation ($ScvO_2$) ≥ 70% with a modified algorithm replacing $ScvO_2$ with a goal of lactate clearance ≥ 10%. However, only 10% of patients required an intervention at the third step of blood and/or dobutamine for persistent $ScvO_2$ ≤ 70% or lactate clearance ≤ 10% within the first six 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 to $ScvO_2$. Given the non-specific nature of lactate elevation as described throughout this review, the physiologic rationale of providing “blind” usage of dobutamine

without measuring some form of cardiac output to help determine if 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 may be unrecognized ischemic bowel, concomitant fulminant hepatic failure, or inadequate volume resuscitation. Since 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 (one of which could turn out to be decompensated myocardial function requiring dobutamine).

Limitations and Pitfalls of Interpreting Elevated Lactate in Clinical Practice

As reviewed above, the etiologies of lactate elevation are quite varied (Table 1). The clinical significance of elevated lactate also varies widely, as shown in 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 elevation can be present in a given patient making interpretation challenging. Given the wide variety of etiologies of lactate and the varied clinical significance (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 both 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 patients with superior mesenteric artery occlusion, 13/27 patients had a normal lactate.[153] In a study by Dugas *et al*., 45% of patients in vasopressor-dependent septic shock did not mount a lactic acid level > 2.4 mmol/L initially, but their mortality remained high.[154] The reason some patients express lactate more than others in these scenarios is not well understood. Dugas *et al*. found an association between elevated lactate and both liver disease and bacteremia in their study of patients in vasopressor-dependent shock. The association between lactate elevation and liver injury in the Dugas *et al*, study illustrates a potential confounder that may occur in patients with sepsis given the high frequency of concurrent liver involvement.[154]

Conclusion

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

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Abbreviations

DKA	diabetic ketoacidosis
$ScvO_2$	central venous oxygen saturation

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Article Highlights

- Elevated lactate can be caused by a number of conditions including shock, sepsis, cardiac arrest, trauma, seizure, ischemia, diabetic ketoacidosis, thiamine deficiency, malignancy, liver dysfunction, genetic disorders, toxins, and medications
- Elevated lactate has been associated with increased mortality in a number of diseases such as sepsis, trauma and cardiac arrest
- Decreased lactate clearance has been found to be associated with increased mortality in sepsis, post-cardiac arrest, trauma, burns and other conditions
- The use of lactate clearance as an endpoint of resuscitation might prove beneficial but further research is warranted
- When approaching the patient with elevated lactate, the possibility of a multifactorial etiology must be considered
- In spite of 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

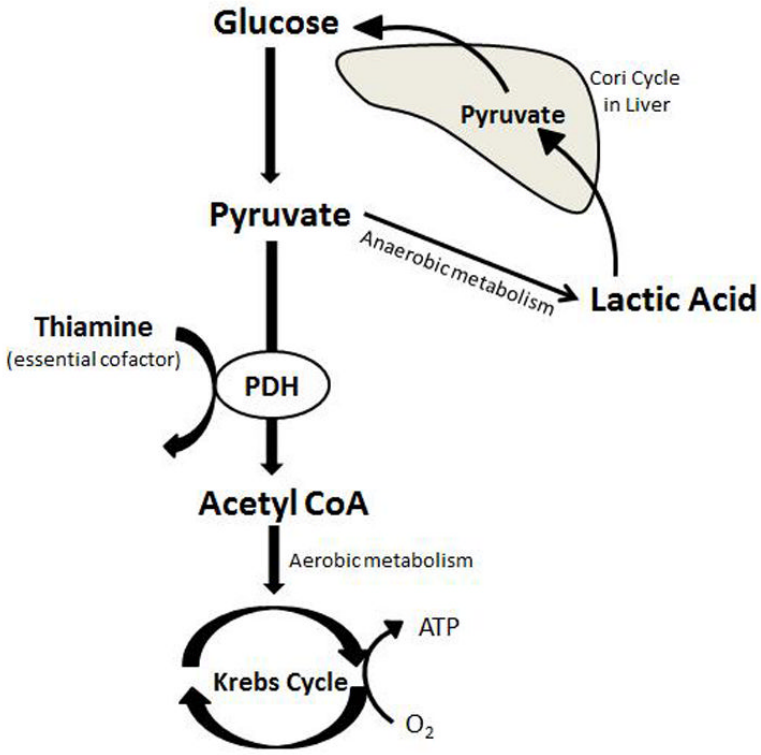

Figure 1.
Aerobic and anaerobic metabolism[a].
[a]ATP = Adenosine triphosphate; CoA = Coenzyme A; PDH = Pyruvate dehydrogenase

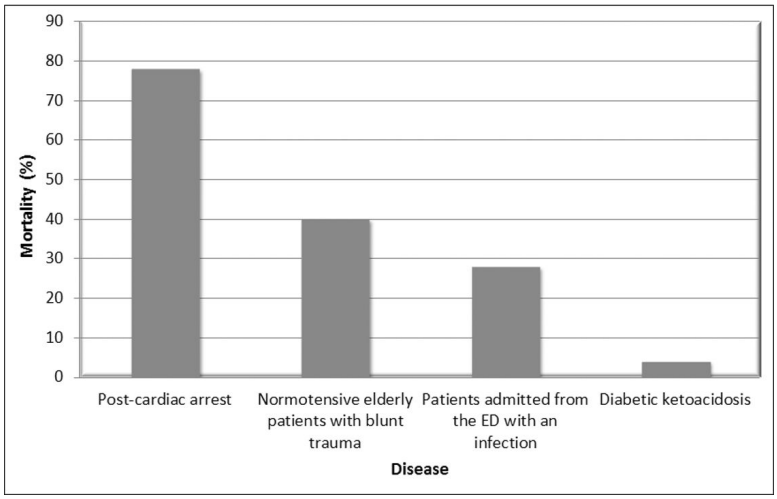

Figure 2.

Elevated lactate (>4 mmol/L) in different diseases and its association with in-hospital mortality[9–11,40a,b].

[a]ED = Emergency Department

[b]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.

Table 1

Causes of elevated lactate

Shock	**Pharmacological agents***
Distributive	Linezolid
Cardiogenic	Nucleoside reverse transcriptase inhibitors
Hypovolemic	Metformin
Obstructive	Epinephrine
Post-cardiac arrest	Propofol
Regional tissue ischemia	Acetaminophen
Mesenteric ischemia	$Beta_2$ agonists
Limb ischemia	Theophylline
Burns	
Trauma	**Anaerobic muscle activity**
Compartment syndrome	Seizures
Necrotizing soft tissue infections	Heavy exercise
Diabetic ketoacidosis	Excessive work of breathing
Drugs/toxins	**Thiamine deficiency**
Alcohols	**Malignancy**
Cocaine	**Liver failure**
Carbon monoxide	**Mitochondrial disease**
Cyanide	

Table 2

Common drugs and toxins associated with elevated lactate[a]

Drug/toxin	Risk factors	Proposed mechanism	Suggested treatment in addition to cessation of the offending agent
Metformin[b] [103–104]	Congestive heart failure, kidney failure, liver failure or overdose	Inhibition of gluconeogenesis and mitochondrial impairment, inhibition of lactate elimination	Consider hemodialysis
Acetaminophen[155]	Overdose	Impairment of the mitochondrial electron transport chain. Later hepatotoxicity and systemic effects.	Enteral activated charcoal and N-acetylcysteine.
NRTI[105–107]	Female gender	Direct mitochondrial toxicity	No specific treatment
Linezolid[108–110]	Possibly prolonged use in elderly patients	Direct mitochondrial toxicity	No specific treatment
$Beta_2$-agonists [61, 111, 112]	Not applicable	$Beta_2$-adrenergic stimulation causing increased glycogenolysis, glycolysis and lipolysis. Free fatty acids released by lipolysis may inhibit PDH.	Depending on the clinical situation the $beta_2$-agonist may/should be continued
Propofol[117–120]	Prolonged high-dose use (Propofol Infusion Syndrome[d])	Impairment of the mitochondrial electron transport chain and fatty acid oxidation	Supportive treatment and potentially hemodialysis should be considered
Epinephrine[121, 122]	Not applicable	Likely due to $beta_2$-adrenergic stimulation (see $beta_2$-agonists)	Depending on the clinical situation epinephrine may be continued.
Theophylline [123, 124]	Overdose, though reported in standard doses	Increased levels of catecholamines (see $beta_2$-agonists)	Enteral activated charcoal. Hemodialysis in severe cases.
Alcohols (ethanol, methanol, propylene glycol)[b,c] [127–129]	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 utilization of lactate. Contributions from underlying comorbidities or possibly ketoacidosis may play a role	Identification and treatment of underlying disorders including administration of thiamine.
Cocaine [130–131]	Not applicable	$Beta_2$-adrenergic stimulation (see $beta_2$-agonists). Vasoconstriction causing ischemia.	Supportive care and benzodiazepine
Carbon monoxide [132–133]	Not applicable	Decreased oxygen-carrying capacity of the blood.	High-flow/hyperbaric oxygen. Consider co-exposure to cyanide
Cyanide[134–135]	Not applicable	Noncompetitive inhibition of cytochrome c oxidase causing mitochondrial dysfunction and inability to utilize oxygen	Hydroxocobalamin or other cyanide antidote kit (Sodium nitrite, amyl nitrite, sodium thiosulfate). Consider co-exposure to carbon monoxide.

[a] NRTI = Nucleoside reverse transcriptase inhibitor, PDH = Pyruvate dehydrogenase, NADH = Reduced nicotinamide adenine dinucleotide

[b] See text for more details

[c] Ethylene glycol may cause falsely elevated lactate levels

[d] The Propofol Infusion Syndrome is characterized by cardiac failure, rhabdomyolysis, metabolic acidosis and renal failure.

Table 3

Clinical checklist: Evaluation of elevated lactate

- ➢ **Evaluate for tissue hypoperfusion and restore adequate perfusion:**
  - o Shock (distributive, cardiogenic, hypovolemic and obstructive), post-cardiac arrest syndrome
  - o Tissue hypoperfusion should be initially assumed/considered until proven otherwise
  - o Treatment is variable based on shock etiology
- ➢ **Evaluate for local tissue ischemia and treat accordingly:**
  - o Mesenteric ischemia, limb ischemia, burns, trauma, compartment syndrome, necrotizing soft tissue infections
  - o Consider early surgical consultation as appropriate
- ➢ **Stop/reverse potential offending agents:**
  - o Pharmacological agents: linezolid, nucleoside reverse transcriptase inhibitors, metformin, valproate, theophylline, epinephrine, propofol, isoniazid and salicylates
  - o Drugs and toxins: cocaine, alcohols, carbon monoxide and cyanide poisoning
  - o Consider Toxicology consult or Poison Control involvement
  - o Cessation of exposure and removal of agent (i.e. dialysis) when appropriate (see Table 2)
- ➢ **Consider thiamine deficiency and treat if suspected:**
  - o Patient with malnutrition of any cause often (but not exclusively) alcoholics
  - o Intravenous thiamine 100–500 mg should be considered
- ➢ **Consider current or recent anaerobic muscle activity as etiology:**
  - o Heavy exercise, seizures, excessive work of breathing
  - o Consider other etiologies especially if rapid clearance not seen when inciting problem treated (i.e., should rapidly clear after cessation of seizure activity)
- ➢ **Consider other metabolic derangements:**
  - o Diabetic ketoacidosis
  - o Mitochondrial disease
  - o Liver dysfunction