Demystifying Lactate in the Emergency Department

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The role of lactic acid and its conjugate base, lactate, has evolved during the past decade in the care of patients in the emergency department (ED). A recent national sepsis quality measure has led to increased use of serum lactate in the ED, but many causes for hyperlactatemia exist outside of sepsis. We provide a review of the biology of lactate production and metabolism, the many causes of hyperlactatemia, and evidence on its use as a marker in prognosis and resuscitation. Additionally, we review the evolving role of lactate in sepsis care. We provide recommendations to aid lactate interpretation in the ED and highlight areas for future research. [Ann Emerg Med. 2020;75:287-298.]

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INTRODUCTION

Lactate measurement in the emergency department (ED) is a source of both guidance and confusion. Although lactate can be a useful tool when interpreted correctly, improper interpretation can mislead clinicians and result in inappropriate care and unnecessary therapies. Our understanding of lactate has developed considerably since it was first isolated in sour milk by Swedish chemist Carl Wilhelm Scheele in 1780.[1] Since then, lactic acid and its conjugate base, lactate, have become integral parts of the diagnostic, therapeutic, and prognostic management of patients in the ED. However, significant controversy and misinterpretation surround the use of lactate, particularly in light of more recent national sepsis quality measures. We provide a review of the physiologic description of lactate and its application in the ED.

Chemistry

Lactic acid is an organic α-hydroxy acid with the chemical formula $CH_3CH(OH)COOH$. With a pK_a of 3.86, lactic acid readily deprotonates a hydrogen ion to form its conjugate base, the lactate ion. At physiologic pH in human beings, the ratio between the lactate ion and lactic acid is approximately 3,000:1, so the lactate anion is commonly referred to as "lactate."[2] Lactate exists as 2 stereoisomers: L-(+)-lactate and D-(–)-lactate. L-lactate composes nearly the entirety of lactate present in human beings because mammalian cells exclusively contain L-lactate dehydrogenase, the enzyme that converts pyruvate to lactate. In normal physiologic states, D-lactate is produced in nanomolar concentrations in mammalian cells.[3] However, it may accumulate in certain pathologic conditions and cause a metabolic acidosis.[4-7] We will refer to L-lactate as lactate unless otherwise specified.

Physiologic Function of Lactate

In times of both rest and exercise, lactate serves 2 important functions: maintaining blood glucose by acting as a carbon substrate for gluconeogenesis, and acting as an oxidizable agent that can be shuttled from areas of high glycolysis and glycogenolysis activity to areas of high cellular respiration to engage in oxidative phosphorylation.[8] Lactate uptake and use is increased in the heart and brain under times of metabolic stress, including sepsis and shock, with the heart using lactate for up to 60% of its metabolic demand, and the brain up to 25%.[9,10] The myocardium oxidizes lactate as a carbon source for oxidative phosphorylation and is a net consumer of lactate. During states of moderate exercise, myocardial uptake of lactate increases proportionally with the workload.[11,12] Similarly, neurons and astrocytes in the brain will take up lactate and oxidize it as a fuel source to generate energy both at rest and during times of hypoglycemia, exercise, and cardiopulmonary resuscitation.[13]

Lactate Homeostasis

Traditionally, lactate has been viewed as an end product of anaerobic metabolism largely in skeletal muscle, a concept known as the "oxygen debt model" that was pioneered in the 1920s.[14] In the setting of decreased oxygen availability, pyruvate is produced from glucose through glycolysis and then reduced to lactate by L-lactate dehydrogenase. This reaction allows nicotinamide adenine dinucleotide (reduced) to be oxidized to nicotinamide

adenine dinucleotide (oxidized), which serves as a necessary oxidizing agent in the generation of adenosine triphosphate (Figure 1).[15] In this conventional perspective, lactate was considered simply a metabolic waste product generated as a cost for resupplying the cell with nicotinamide adenine dinucleotide (oxidized).

More contemporary understanding recognizes lactate as a key player both in energy use and oxidation/reduction reactions, even under aerobic conditions.[16] Several studies have demonstrated that lactate was produced by glycolysis at rest when skeletal muscle was fully oxygenated and during periods of activity in which the anaerobic threshold had not been reached.[17] The proinflammatory cytokine milieu with increased catecholamine levels, often observed in sepsis or other states of physiologic stress, causes an increased metabolic state. Glucose use is increased, and so is the presence of transporters and enzymes that are associated with glycolysis and lactate metabolism.[9] Increased glycolysis leads to an increased concentration of pyruvate, which exceeds the oxidative capacity of the tricarboxylic acid cycle cycle and is subsequently converted to lactate.

Metabolism

The average lactate turnover rate at a physiologically steady state is approximately 20 mmol/kg per day.[18] The liver metabolizes approximately 70% to 75% of circulating lactate.[19] This typically occurs in periportal hepatocytes,

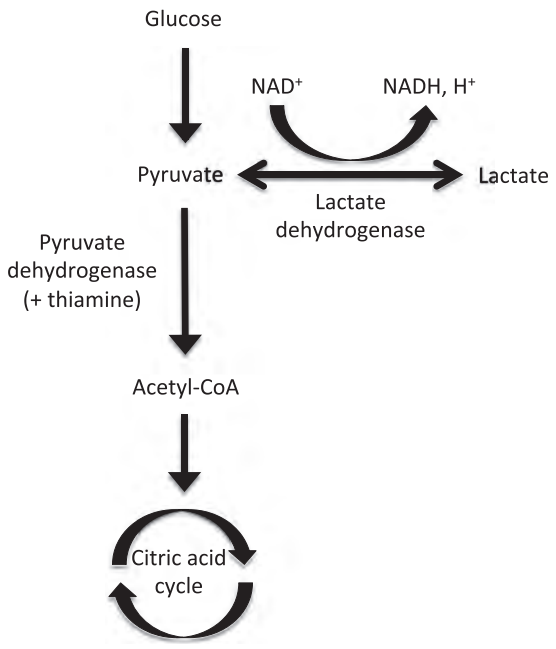

Figure 1. Biochemical pathway of glucose showing creation of lactate.

where lactate is used for either gluconeogenesis or, less so, oxidation.[19] The glucose created through gluconeogenesis is then released back into circulation to be redistributed through the body. Several factors are associated with decreased hepatic clearance, including acidosis, underlying cirrhosis, and hypoperfusion.[20] Renal clearance accounts for approximately 25% to 30% of lactate removal.[21] The majority occurs in the renal cortex, where cells will take up lactate and then either oxidize it for energy or use it for gluconeogenesis to create glucose to be exported back to the renal medulla or systemic circulation. Only an estimated 10% of renal clearance is through actual urinary excretion.

Classification of Lactic Acidosis

A "lactic acidosis" refers specifically to an elevated serum lactate level with a pH less than or equal to 7.35.[22] In contrast, hyperlactatemia has several definitions, but most commonly refers to a serum lactate level greater than or equal to 2 mmol/L, regardless of pH.[23] In 1976, Cohen and Woods[24] categorized lactic acidosis into 2 groups (type A and B) based on the presence or absence of clinical evidence of tissue hypoxia, and provided a useful framework to develop management strategies (Table 1). The cause of lactic acidosis may be multifactorial and might not exclusively fall into either type A or B.

Type A lactic acidosis is defined by lactate accumulation in the setting of poor tissue perfusion or oxygenation. Common clinical entities leading to type A lactic acidosis include shock, cardiac arrest, severe hypoxemia, severe anemia, regional tissue hypoperfusion, or excessive muscular contraction. In these scenarios, oxygen demand outstrips the available oxygen supply, either systemically or regionally, leading to lactate accumulation. Type B lactic acidosis refers to lactate elevation in the absence of cellular hypoxia. Common causes of type B lactate accumulation in the ED include medications (eg, albuterol, epinephrine) or underlying disease process states (eg, sepsis, malignancy, end-stage liver disease, diabetic ketoacidosis).

Accumulation of D-lactate leading to an acidosis is rare and more difficult to recognize because measuring it requires a separate analytic test. In short bowel syndrome, decreased digestion of carbohydrates leads to the presence of sugars in the colon. Bacteria then ferment these sugars to create D-lactate and additionally convert L-lactate to D-lactate.[2,4] Diabetic ketoacidosis and propylene glycol administration have also been associated with D-lactate buildup.

LABORATORY EVALUATION

Methods for Lactate Measurement

Standard measurement of lactate typically occurs either through enzymatic spectrophotometry or electrode-based

Table 1. Classification of elevated lactate level as defined by Cohen and Woods.[24]

Type	Cause	Clinical Scenarios
A	Lactate accumulation in the setting of poor tissue perfusion or hypoxia (either regional or global)	
		Global: Shock (cardiogenic, obstructive, distributive, hypovolemic) or profound hypotension, severe anemia, cardiac arrest, trauma, burns, carbon monoxide, cyanide
		Regional: Limb or mesenteric ischemia, localized trauma or burns, compartment syndrome, necrotizing soft tissue infection, microcirculatory dysfunction*
		Exertional: Convulsions or seizure, increased work of breathing, strenuous exercise
B	Lactate accumulation in the absence of clinical evidence of tissue hypoperfusion or hypoxia	
B1	Lactate elevation associated with underlying disease process	Malignancy, sepsis, thiamine deficiency, liver failure, renal insufficiency, pheochromocytoma, diabetic and alcoholic ketoacidosis
B2	Lactate elevation caused by a drug or toxin	Metformin, acetaminophen, β_2-agonists (including albuterol, epinephrine), sympathomimetics, theophylline, nucleoside reverse-transcriptase inhibitors, alcohol, toxic alcohols, propofol, cyanide, carbon monoxide
B3	Lactate elevation caused by congenital errors of metabolism	Pyruvate dehydrogenase deficiency, pyruvate carboxylase deficiency, glucose-6-phosphatase deficiency, congenital mitochondriopathies

*Area of ongoing research.

amperometry. Both methods correlate extremely well when done properly. After blood is drawn, RBC metabolism continues to generate lactate, particularly if significant delays exist before analysis. This undesirable elevation can be diminished by immediately cooling the blood sample or by use of a "gray top" collection tube, which contains sodium fluoride, a preservative that inhibits cellular metabolism.[25] However, a specimen analyzed within 15 minutes from drawing blood will have minimal distortion of lactate, even if no method to prevent additional metabolism is performed.[26] Whole blood and finger-stick samples can be analyzed with electrode-based amperometry at the bedside, providing a point-of-care lactate level, whose values correlate well with standard assays and provide results significantly quicker.[27,28]

Effect of Tourniquet Use on Lactate

There has been concern that tourniquet use may elevate local lactate levels by leading to transient ischemia and subsequent anaerobic metabolism. An older study involving arterial tourniquet application in the operating room to induce ischemia resulted in a linear increase in serum lactate level, up to 206% of baseline values, after 75 minutes of tourniquet application.[29] However, the application of a venous tourniquet does not significantly alter venous lactate levels.[26,30]

Difference Between Arterial and Venous Lactate Results

Arterial and peripheral venous lactate values correlate very well when the results fall within normal limits; however, mild discrepancies arise with hyperlactatemia.[31-36] Central lactate values correlate extremely well with arterial values at all levels.[37] Arterial and central blood samples represent lactate that is systemically circulated, whereas venous samples reflect the local milieu, thus explaining the small discrepancies between these sites. However, drawing arterial blood can be painful, time consuming, and challenging in certain patient populations. It is therefore appropriate, particularly in patients without an arterial line, to start with and trend peripheral venous samples.

Effect of Lactated Ringer's Solution on Serum Lactate

Lactated Ringer's solution is a commonly administered resuscitation fluid that may improve patient-centered outcomes compared with normal saline solution, particularly in septic patients.[38-40] Each liter of lactated Ringer's solution contains 28 to 29 mmol of sodium lactate. In a 70-kg adult, approximately 1,400 mmol (20 mmol/kg) of lactate is metabolized *daily*. To our knowledge, there is no published evidence that a bolus of lactated Ringer's solution significantly increases lactate compared with normal saline solution, although transient

elevations can be observed, particularly if venipuncture occurs in the immediate vicinity of the lactated Ringer's solution infusion site.[41,42] In patients with liver failure or significant hepatic hypoperfusion, there may be an increase in serum lactate level because of an inability of the liver to metabolize the additional lactate burden.[43]

LACTATE IN SEPSIS

Among its many uses as a diagnostic test, lactate level has long been used as a marker of resuscitation, for risk stratification, and as a mortality prediction tool in sepsis. Despite a commonly held belief that elevated lactate levels in sepsis occur as a consequence of anaerobic metabolism from tissue malperfusion, there is mounting evidence that this may not be the primary source of lactate production, particularly in patients without overt shock physiology. Indeed, accelerated aerobic glycolysis from adrenergic stress is now thought to be a significant cause of hyperlactemia in septic patients, with additional contributions from impaired clearance, medication effects, microcirculatory dysfunction, and tissue malperfusion.[44-47] Cytopathic hypoxia and direct mitochondrial impairment have been proposed as another cause, although the exact mechanism remains incompletely understood and further research is required.[48,49]

Anatomic Location of Lactate Generation in Sepsis

The specific anatomic site of lactate generation in septic patients remains controversial. The 2 regions suspected to generate the majority of lactate in sepsis are the lungs and skeletal muscle. The strongest evidence comes from the lungs as generators of lactate in sepsis.[50-53] One hypothesis is that neutrophil β_2-receptor stimulation by endogenous catecholamines causes significant lactate production, which is further substantiated by the large number of these receptors found in the lungs.[54] Muscle tissue has been shown to have significantly higher lactate levels than supplying arteries in septic shock.[46] An additional source of lactate elevation in sepsis is leukocyte glycolysis. Like other tissues, inflammatory cells undergo accelerated aerobic glycolysis during sepsis and have a markedly increased lactate output, similar to that which occurs in the lungs.[54]

Microcirculatory dysfunction has been proposed as a source of lactate in sepsis. Proinflammatory cytokines lead to endothelial and hematologic cell dysfunction, causing heterogeneous areas of low or slow flow at the capillary-venule-arteriole level. This leads to scattered areas of tissue hypoxia despite normal macrocirculatory parameters.[55-57] Using dark-field microscopy to visualize the microcirculation, investigators have linked the density of microscopic vascular dysfunction to illness severity, elevated lactate levels, and worsened outcomes.[56,58,59] Further study is needed to determine the importance of microcirculatory dysfunction in sepsis and potential therapies to correct it.

Anaerobic Metabolism in Sepsis

Although tissue hypoxia and resultant anaerobic metabolism will result in increased lactate production, this relationship has been challenged as the primary cause of hyperlactatemia in sepsis. Certain septic patients develop vasopressor-dependent hypotension, yet never experience an elevated lactate level.[59,60] Another subset of septic patients develops hyperlactatemia with associated high mortality, yet lacks hypotension.[61] Additionally, if anaerobic metabolism from tissue hypoxia were the main source of lactate in sepsis, we would expect to see several things. First, interventions to increase oxygen delivery should consistently decrease lactate levels. However, several studies have failed to support this.[62,63] Furthermore, studies evaluating tissue hypoxia in sepsis and septic shock have found no evidence of cellular hypoxia. In fact, muscle and mucosal pO_2 is often elevated in sepsis.[46,64-66] Tissues with an adequate oxygen supply should not generate lactate, yet the lung is a major source of lactate in sepsis.[50,51]

Lactate in "Occult Hypoperfusion" and "Cryptic Shock"

The terms "occult hypoperfusion" and "cryptic shock" have been used to describe patients with elevated lactate levels and normal blood pressure, and reflect their relatively high mortality rate. Indeed, in the initial early goal-directed therapy trial, one of the inclusion criteria was serum lactate level greater than or equal to 4 mmol/L, regardless of blood pressure.[67] In patients with suspected infection, elevated lactate levels were associated with increased 28-day mortality regardless of blood pressure, and used the term "occult hypoperfusion" to describe this subset of patients, which had previously been used for patients with traumatic injuries and heart failure syndromes.[68-70] Later, Puskarich et al[61] showed that septic patients with cryptic shock, defined as a lactate level greater than or equal to 4 mmol/L without hypotension, and those with "overt" shock, defined as hypotension after a fluid challenge, had similar mortality after protocolized therapy.

LACTATE IN OTHER CONDITIONS

A recent study evaluated patients admitted with a lactate level greater than 4 mmol/L and found 23.2% of cases were from infection, 20% from seizures, and the remaining from causes unrelated to infection.[71]

Trauma, Burns, and Inhalational Injuries

Elevated lactate levels in patients with traumatic injuries are associated with increased mortality.[72-74] Lactate elevation has classically been attributed to global hypoperfusion in the setting of hemorrhagic shock, or regionally, as in the case of arterial vessel injury. However, much as in sepsis, additional mechanisms, such as accelerated glycolysis, cause hyperlactatemia during hemorrhage.[75,76] An elevated initial serum lactate level may occur in patients with occult hypoperfusion and can be used as both a prognostic indictor and a marker of resuscitation.[77,78] A failure to clear lactate in trauma patients has been shown to be a strong independent predictor of mortality, as well as length of stay in the hospital and ICU, and a risk factor for the development of infection, regardless of the initial presenting vital signs.[79]

Lactate serves as a prognostic indicator of infectious complications, organ dysfunction, and mortality, and as a marker of resuscitation in patients with burns and inhalational injuries.[80,81] Lactate levels greater than or equal to 2 mmol/L and the failure to clear an elevated lactate level have been associated with mortality in previous studies and may outperform base excess.[82] It may be reasonable, according to published evidence, to use lactate normalization as a goal in the fluid resuscitation of these patients, although additional evidence is needed before widespread adoption of this approach.[83]

Seizures, Convulsions, and Extreme Exertion

Seizures are known to cause hyperlactemia as a result of local muscle tissue hypoxia and resultant anaerobic metabolism.[84] One study evaluating 157 patients with generalized tonic-clonic seizure showed that 84.7% had elevated lactate levels, with a median of 3.64 mmol/L but with levels as high as 17 mmol/L.[85] Patients with hyperlactemia caused solely by seizures should have rapid clearance within 1 to 2 hours after the seizure resolution.[71,86] There has been no correlation between degree of lactate elevation and outcome.[71] Patients with extreme exertion or agitation, particularly those in physical restraints, develop hyperlactatemia through a similar mechanism. An observational study found that 95% of collapsed Boston Marathon runners had an average lactate level of 3.45 mmol/L.[87]

Thiamine Deficiency

Thiamine is an essential cofactor in the conversion from pyruvate to acetyl coenzyme A. A deficiency in thiamine will therefore result in an inability of pyruvate to enter the tricarboxylic acid cycle and rather undergo anaerobic metabolism, leading to elevated lactate levels (Figure 1). Patients with long-term alcohol use, poor nutritional status, sepsis, or history of gastric bypass surgery are at particular risk for hyperlactatemia as a result of thiamine deficiency.[88] Recent studies have shown that the administration of intravenous thiamine to septic patients is associated with faster lactate clearance and decreased mortality, particularly those with underlying thiamine deficiency or alcohol use disorders.[89-92]

Toxins and Medications

Although lactate elevation in the majority of toxicities is thought to be primarily due to a type B lactic acidosis, the underlying mechanisms for lactate production are often complex and multifactorial. Mechanisms include inhibition of oxidative phosphorylation or mitochondrial damage, β_2-adrenergic stimulation, shock states, increased muscle activity, seizures, renal failure, and hepatic toxicity. Table 2 provides a more comprehensive list of medications and toxins associated with lactate elevation.[93]

Acetaminophen. Lactate elevation has been proposed to be caused by 2 mechanisms in patients with acetaminophen toxicity. Animal models have shown that large acetaminophen ingestions directly inhibit the mitochondrial electron transport chain before any laboratory evidence of hepatotoxicity.[94,95] Later, lactate elevation occurs as a result of increased N-acetyl-p-benzoquinone imine production, the toxic metabolite associated with liver injury. Lactate elevation in acute liver failure portends a poor prognosis.[94]

β_2-Agonists (albuterol, epinephrine). β-Agonists have been shown to result in lactate elevation primarily through accelerated glycolysis, even in fully aerobic conditions.[32] The association between albuterol and lactate elevation was initially limited to case reports; however, recent data suggest it is likely a relatively common phenomenon. A study evaluating 105 children admitted with severe asthma exacerbation reported that 83% had a lactate level greater than 2.2 mmol/L and 45% had lactate levels greater than 5 mmol/L.[96] Lactate elevations associated with albuterol typically resolve quickly after completion of therapy.[97] Epinephrine also causes an elevated lactate level through a similar mechanism.[75,76,98] Previous investigations into the use of epinephrine in septic shock have found that survivors have higher lactate levels in the first hours of resuscitation compared with nonsurvivors.[99]

Carbon monoxide and cyanide. Carbon monoxide reversibly binds to hemoglobin with approximately 200 to 300 times the affinity of oxygen, resulting in decreased arterial oxygen delivery. Furthermore, it binds to cytochrome A, inhibiting oxidative phosphorylation.[100,101] Lactate elevation in pure carbon monoxide poisoning is

Table 2. Toxins associated with hyperlactatemia (adopted from Andersen et al[93]).

Toxin or Medication	Mechanism of Lactate Elevation	Recommended Therapy or Antidote	Comments
Abrin	Protein inhibitor and causes direct cellular damage, with resultant hepatotoxicity causing poor clearance, seizures	Supportive care	Toxic component of jequirity beans
Acetaminophen	Multiple mechanisms, including direct inhibition of electron transport chain (in the absence of hepatotoxicity), impaired clearance after direct hepatocyte toxicity because of increased NAPQI production	*N*-acetyl cysteine, aggressive supportive care, liver transplantation if indicated	Most common cause of acute liver failure in developed countries
Albuterol	β_2-Receptor activation	N/A	Lactate elevation associated with albuterol resolves after completion of therapy.
Carbon monoxide	Reversibly binds to hemoglobin with approximately 200–300 times the affinity of oxygen, resulting in decreased arterial oxygen content. Binds to cytochrome A, inhibiting oxidative phosphorylation.	Decontamination, hyperbaric oxygen, supportive care	Lactate elevation in pure carbon monoxide poisoning is typically mild, but has been shown to correlate with the severity of toxicity. High lactate levels should raise suspicion for cyanide toxicity.
Cyanide	Impairment of oxidative phosphorylation by inhibiting complex IV in the electron transport train	Decontamination. Antidotes include hydroxycobalamin and sodium thiosulfate with sodium nitrate.	Lactate levels >10 mmol/L are highly concerning for concomitant cyanide poisoning. Animal models have shown that cyanide levels and lactate levels are largely directly correlated.
Ethanol	Increased NADH to NAD^+ ratio	Supportive care	Often increased by a secondary cause, such as sepsis or thiamine deficiency
Metformin	Inhibits gluconeogenesis, thereby decreasing NAD^+ levels. Newer evidence suggests metformin may poison mitochondrial transport chain.	Cessation of metformin; may require dialysis. Supportive care.	
Nucleoside reverse-transcriptase inhibitor	Suspected from poor clearance because of liver injury; animal models have shown impaired mitochondrial function.	Supportive care. Cessation of offending agent.	Examples include didanosine, stavudine, and lamivudine.
Propofol	Exact mechanism is unclear. Several animal studies have suggested a mitochondrial process and include uncoupling of oxidative phosphorylation, oxidation of cytochromes, and inactivation of complex II/III/coenzyme Q.	Removal of propofol, dialysis, supportive care	Characterized by bradycardia, lactic acidosis, hyperkalemia, cardiovascular compromise, hepatic steatosis, rhabdomyolysis, renal injury, and lipemia. Rare except in cases of prolonged high doses of propofol infusion.
Ricin	Protein inhibitor and causes direct cellular damage, with resultant hepatotoxicity causing poor clearance, seizures	Supportive care	Toxic component of castor bean
Sodium azide	When combined with acid, it forms hydrazoic acid, which is highly toxic and causes direct inhibition of oxidative phosphorylation. Seizures.	Supportive care	A white powder used as a reagent in car air bags and laboratory preservatives
Sodium fluoroacetate	Inhibits the Krebs cycle, thus impairing aerobic metabolism. Seizures.	Supportive care	Highly toxic and currently licensed for use only against coyotes in the United States

Sodium nitroprusside	Reacts with oxyhemoglobin to form methemoglobin and releases cyanide ions during this process, thus causing lactate elevation	Immediate cessation of sodium nitroprusside; same therapy as for cyanide toxicity	An arterial and venous vasodilator typically used to rapidly reduce blood pressure in cardiac surgery and hypertensive crises. Toxicity typically occurs in long duration of therapy and in patients with renal insufficiency.
Strychnine	Muscle spasms and convulsions	Supportive care. Recovery is likely if the patient survives longer than 24 h.	A rodenticide but has also been implicated in cocaine and laxatives. Inhibits glycine, which results in CNS hyperexcitability. Causes inhibition of antagonistic muscle groups in the spinal cord, resulting in severe extensor spasms.
Sympathomimetics (methamphetamine, cocaine, etc)	β_2-Receptor activation	Supportive care. Benzodiazepines for agitation.	
Theophylline	Seizures, cardiogenic shock, and catecholamine-induced activation of β_2-adrenergic receptors	Multidose activated charcoal. Supportive measures.	Acute ingestions of >1 g or 15 mg/kg are associated with toxicity in adults or children, respectively.
VPA	Direct damage from metabolites to hepatocytes results in impaired clearance, seizures.	Most cases are self-limited and resolve with removal of VPA. Supportive care.	VPA levels do not correlate with severity of overdose. Lactate levels usually elevated mildly unless a seizure occurs.
Toxic alcohols	Increased NADH to NAD^+ ratio	Supportive care. Toxic alcohols may require fomepizole or dialysis in accordance with time of ingestion and toxicity.	Lactate levels can be falsely elevated in ethylene glycol toxicity. Oftentimes the result of other causes, such as kidney injury, thiamine deficiency, and sepsis.

NAPQI, N-acetyl-p-benzoquinone imine; *NADH*, nicotinamide adenine dinucleotide (reduced); *NAD^+*, nicotinamide adenine dinucleotide (oxidized); *CNS*, central nervous system; *VPA*, valproic acid.

typically mild, but has been shown to correlate with the severity of toxicity.[101-103] Cyanide toxicity is most commonly observed with concomitant carbon monoxide poisoning after smoke inhalation injuries. Cyanide impairs oxidative phosphorylation by inhibiting complex IV in the electron transport train. Animal models have shown that cyanide levels and lactate levels are closely correlated.[104] Lactate levels greater than 10 mmol/L are highly concerning for concomitant cyanide poisoning.[105]

Ethanol. Acute ethanol intoxication causes an elevated lactate level primarily through an increased nicotinamide adenine dinucleotide (reduced) to nicotinamide adenine dinucleotide (oxidized) ratio, which favors the creation of lactate. Underlying comorbidities, such as liver impairment, renal disease, or thiamine deficiency, can also lead to lactate elevation.

Metformin. Metformin increases peripheral glucose uptake, thereby inhibiting gluconeogenesis and decreasing the availability of nicotinamide adenine dinucleotide (oxidized), which is necessary to covert lactate to pyruvate. In acute overdose, profoundly elevated lactate levels have been observed but are not correlated with prognosis.[106] Renal impairment with a glomerular filtration rate less than 60 is thought to increase the risk for development of hyperlactatemia.[107]

PROGNOSTIC VALUE AND LACTATE CLEARANCE

Elevated lactate levels and an inability to clear lactate are associated with a worse prognosis in many conditions, particularly in sepsis, trauma, hemorrhage, shock, and cardiac arrest.[108-111] In a prospective cohort study of ED patients with infection, mortality rates increased with increasing lactate levels, with an initial lactate level greater than or equal to 4 mmol/L associated with a 28% inhospital mortality rate.[112] In a separate study of patients with severe sepsis, this relationship was found to be independent of shock state.[113] Unsurprisingly, increasing lactate concentrations in septic shock are also associated with increasing inhospital mortality, even without signs of overt shock.[69,114] However, despite the emphasis on specific lactate-level cutoffs found in current definitions and Centers for Medicare and Medicaid Services recommendations, mortality and poor prognosis are associated with even mildly elevated lactate values.[115] Thus, lactate may be best thought of as a continuous rather than dichotomous variable in regard to prognostication and risk stratification.

A decrease in lactate concentrations during resuscitation is associated with improved mortality.[116-118]

Although there is no clear target percentage decrease or time frame to decrease lactate level, achieving a "normal" lactate level quickly appears to be a reasonable goal; there is no consensus at this point.[117,118] Although earlier studies evaluated protocoled lactate measurements in the care of septic patients and showed noninferiority to targeting central venous oxygen saturation levels, a similar benefit in mortality was associated with simply measuring more than one lactate level in the ED.[116,119] Some authors have suggested that measuring lactate itself has mortality benefits, but it is more likely that early measurement of lactate is a marker of timely and appropriate care.[117] More recently, a large randomized controlled trial showed that a resuscitation strategy targeting peripheral perfusion compared with lactate normalization did not reduce all-cause 28-day mortality.[120]

HOW TO USE LACTATE IN THE ED

The diagnostic utility of lactate in the ED is diverse: it functions as a marker of resuscitation, identifies patients with occult hypoperfusion, and provides prognostic information. Figure 2 provides a framework to guide appropriate interpretation and use of lactate level. Assuming an appropriately collected and analyzed lactate sample, the first decision point is to determine whether there is concern for shock or hypoperfusion. Any patient with hyperlactatemia and evidence of circulatory shock and general hypoperfusion clearly benefits from resuscitation to restore adequate tissue perfusion. Patients with evidence of regional hypoperfusion (eg, limb or mesenteric ischemia) require emergency intervention to restore perfusion to the affected region, and an elevated lactate level may help guide providers to an accurate and timely diagnosis. In patients who lack overt shock or hypoperfusion, an elevated lactate level should be interpreted in the context of the patient's medical history, medication list, or any exposures. As we described earlier, hyperlactatemia can also occur from overproduction, impaired clearance, or a combination of both in the absence of tissue malperfusion. Common medications administered in the ED (eg, albuterol) and brief episodes of extreme exertion can result in hyperlactatemia that typically clears quickly without any intervention. Septic patients may have an elevated lactate level from accelerated glycolysis caused by adrenergic stress and may benefit from resuscitation, particularly if there is legitimate concern for occult shock. Patients with renal failure and cirrhosis will have higher lactate levels than counterparts without these conditions. Oncology patients, particularly those with hematologic malignancy, often have

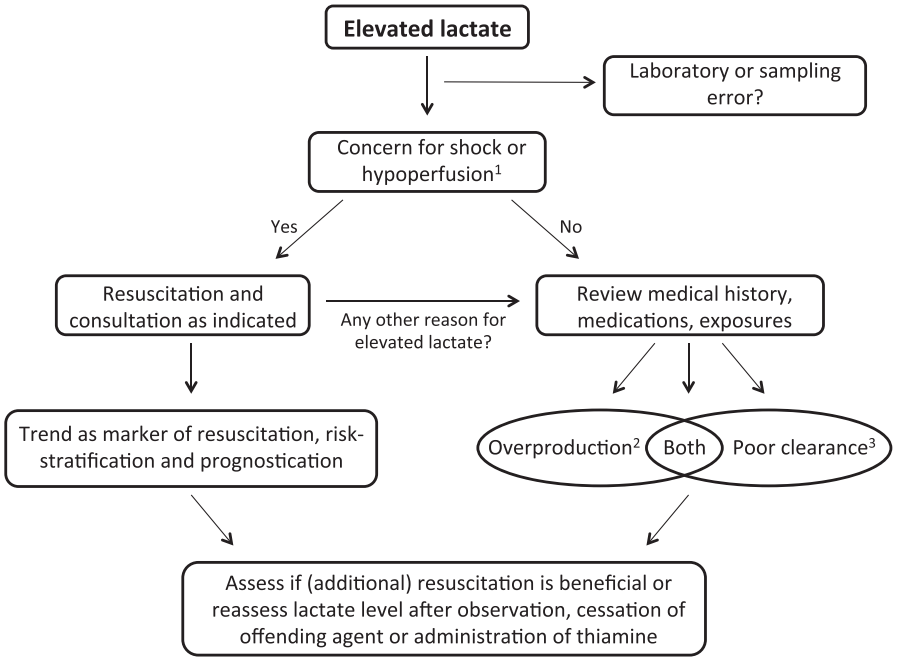

Figure 2. Framework to guide appropriate interpretation and use of lactate level.

elevated lactate levels from tumor turnover, rather than infection or hypoperfusion.

Any test showing an elevated lactate level should be repeated. Lactate clearance is associated with improved outcomes and successful resuscitation, and risk stratifies patients with cardiac arrest, shock, or hypoperfusion. A failure to clear lactate should cause providers to pause and then reevaluate the elevated lactate level to determine whether additional resuscitation or therapies are needed. In certain instances, such as in patients beginning to receive epinephrine, an increase in lactate level is associated with increased survival. Patients at risk for thiamine deficiency may require the administration of thiamine to help clear lactate. In patients who are anticipated to rapidly clear lactate without any intervention, a failure to do so should prompt a reanalysis of the current presentation to ensure no other processes are present.

Lactate levels may also provide false reassurance because not all patients with hypoperfusion will generate elevated lactate levels. For instance, certain patients with superior mesenteric artery occlusion will have normal lactate levels.[121] Likewise, not all patients with vasopressor-dependent hypotension will have hyperlactatemia, yet they have a high mortality rate.[59,60]

CONCLUSION

Lactate measurement is an important tool for clinicians in the ED. Significant advances have occurred in our understanding of the physiology and interpretation of lactate level, and it is now clear that lactate participates in many different physiologic processes. An oversimplified interpretation may mislead providers, but the savvy provider may recognize that lactate level may be the result of overproduction, impaired elimination, or both, which may guide him or her toward appropriate interventions. With a more nuanced understanding of lactate level interpretation, this important diagnostic and prognostic tool becomes even more beneficial.

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REFERENCES

1. Gladden LB. 200th Anniversary of lactate research in muscle. *Exerc Sport Sci Rev*. 2008;36:109-115.
2. Ewaschuk JB, Naylor JM, Zello GA. D-lactate in human and ruminant metabolism. *J Nutr*. 2005;135:1619-1625.
3. Thornalley PJ. The glyoxalase system: new developments towards functional characterization of a metabolic pathway fundamental to biological life. *Biochem J*. 1990;269:1-11.
4. Hove H, Mortensen PB. Colonic lactate metabolism and D-lactic acidosis. *Dig Dis Sci*. 1995;40:320-330.
5. Lu J, Zello GA, Randell E, et al. Closing the anion gap: contribution of D-lactate to diabetic ketoacidosis. *Clin Chim Acta*. 2011;412:286-291.
6. Christopher MM, Eckfeldt JH, Eaton JW. Propylene glycol ingestion causes D-lactic acidosis. *Lab Invest*. 1990;62:114-118.
7. Jorens PG, Demey HE, Schepens PJ, et al. Unusual D-lactic acid acidosis from propylene glycol metabolism in overdose. *J Toxicol Clin Toxicol*. 2004;42:163-169.
8. Brooks GA. Lactate production under fully aerobic conditions: the lactate shuttle during rest and exercise. *Fed Proc*. 1986;45:2924-2929.
9. Garcia-Alvarez M, Marik P, Bellomo R. Sepsis-associated hyperlactatemia. *Crit Care*. 2014;18:503.
10. Dhainaut JF, Huyghebaert MF, Monsallier JF, et al. Coronary hemodynamics and myocardial metabolism of lactate, free fatty acids, glucose, and ketones in patients with septic shock. *Circulation*. 1987;75:533-541.
11. Gertz EW, Wisneski JA, Stanley WC, et al. Myocardial substrate utilization during exercise in humans. Dual carbon-labeled carbohydrate isotope experiments. *J Clin Invest*. 1988;82:2017-2025.
12. Bergman BC, Tsvetkova T, Lowes B, et al. Myocardial glucose and lactate metabolism during rest and atrial pacing in humans. *J Physiol*. 2009;587(pt 9):2087-2099.
13. van Hall G, Stromstad M, Rasmussen P, et al. Blood lactate is an important energy source for the human brain. *J Cereb Blood Flow Metab*. 2009;29:1121-1129.
14. Hill AV, Lupton H. Muscular exercise, lactic acid, and the supply and utilization of oxygen. *QJM*. 1923;16:135-171.
15. Adeva-Andany M, Lopez-Ojen M, Funcasta-Calderon R, et al. Comprehensive review on lactate metabolism in human health. *Mitochondrion*. 2014;17:76-100.
16. Brooks GA. Cell-cell and intracellular lactate shuttles. *J Physiol*. 2009;587(pt 23):5591-5600.

17. Brooks G. Lactate: glycolytic product and oxidative substrate during sustained exercise in mammals—the "lactate shuttle." In: Gilles R, ed. *Comparative Physiology and Biochemistry: Current Topics and Trends, Vol A, Respiration-Metabolism-Circulation*. Berlin, Germany: Springer; 1985:208-218.
18. Ahlborg G, Wahren J, Felig P. Splanchnic and peripheral glucose and lactate metabolism during and after prolonged arm exercise. *J Clin Invest*. 1986;77:690-699.
19. Poole RC, Halestrap AP. Transport of lactate and other monocarboxylates across mammalian plasma membranes. *Am J Physiol*. 1993;264(4 pt 1):C761-C782.
20. Iles RA, Cohen RD, Rist AH, et al. The mechanism of inhibition by acidosis of gluconeogenesis from lactate in rat liver. *Biochem J*. 1977;164:185-191.
21. Leal-Pinto E, Park HC, King F, et al. Metabolism of lactate by the intact functioning kidney of the dog. *Am J Physiol*. 1973;224:1463-1467.
22. Luft D, Deichsel G, Schmulling RM, et al. Definition of clinically relevant lactic acidosis in patients with internal diseases. *Am J Clin Pathol*. 1983;80:484-489.
23. Khosravani H, Shahpori R, Stelfox HT, et al. Occurrence and adverse effect on outcome of hyperlactatemia in the critically ill. *Crit Care*. 2009;13:R90.
24. Cohen RD, Woods HF. *Clinical and Biochemical Aspects of Lactic Acidosis*. Oxford, England: Blackwell Scientific Publications; 1976.
25. Seymour CW, Carlbom D, Cooke CR, et al. Temperature and time stability of whole blood lactate: implications for feasibility of pre-hospital measurement. *BMC Res Notes*. 2011;4:169.
26. Jones AE, Leonard MM, Hernandez-Nino J, et al. Determination of the effect of in vitro time, temperature, and tourniquet use on whole blood venous point-of-care lactate concentrations. *Acad Emerg Med*. 2007;14:587-591.
27. Shapiro NI, Fisher C, Donnino M, et al. The feasibility and accuracy of point-of-care lactate measurement in emergency department patients with suspected infection. *J Emerg Med*. 2010;39:89-94.
28. Baig MA, Shahzad H, Hussain E, et al. Validating a point of care lactate meter in adult patients with sepsis presenting to the emergency department of a tertiary care hospital of a low- to middle-income country. *World J Emerg Med*. 2017;8:184-189.
29. Korth U, Merkel G, Fernandez FF, et al. Tourniquet-induced changes of energy metabolism in human skeletal muscle monitored by microdialysis. *Anesthesiology*. 2000;93:1407-1412.
30. Balakrishnan V, Wilson J, Taggart B, et al. Impact of phlebotomy tourniquet use on blood lactate levels in acutely ill patients. *CJEM*. 2016;18:358-362.
31. Ding X, Gao J, Xie C, et al. Prevalence and clinical correlation of dysphagia in Parkinson disease: a study on Chinese patients. *Eur J Clin Nutr*. 2018;72:82-86.
32. Younger JG, Falk JL, Rothrock SG. Relationship between arterial and peripheral venous lactate levels. *Acad Emerg Med*. 1996;3:730-734.
33. Theerawit P, Na Petvicham C. Correlation between arterial lactate and venous lactate in patients with sepsis and septic shock. *Crit Care*. 2014;18(suppl 1):P177.
34. Nascente AP, Assuncao M, Guedes CJ, et al. Comparison of lactate values obtained from different sites and their clinical significance in patients with severe sepsis. *Sao Paulo Med J*. 2011;129:11-16.
35. Bloom B, Pott J, Freund Y, et al. The agreement between abnormal venous lactate and arterial lactate in the ED: a retrospective chart review. *Am J Emerg Med*. 2014;32:596-600.
36. Theerawit P, Na Petvicharn C, Tangsujaritvijit V, et al. The correlation between arterial lactate and venous lactate in patients with sepsis and septic shock. *J Intensive Care Med*. 2018;33:116-120.
37. Middleton P, Kelly AM, Brown J, et al. Agreement between arterial and central venous values for pH, bicarbonate, base excess, and lactate. *Emerg Med J*. 2006;23:622-624.
38. Self WH, Semler MW, Wanderer JP, et al. Balanced crystalloids versus saline in noncritically ill adults. *N Engl J Med*. 2018;378:819-828.
39. Semler MW, Self WH, Wanderer JP, et al. Balanced crystalloids versus saline in critically ill adults. *N Engl J Med*. 2018;378:829-839.
40. Winters ME, Sherwin R, Vilke GM, et al. What is the preferred resuscitation fluid for patients with severe sepsis and septic shock? *J Emerg Med*. 2017;53:928-939.
41. Zitek T, Skaggs ZD, Rahbar A, et al. Does intravenous lactated Ringer's solution raise serum lactate? *J Emerg Med*. 2018;55:313-318.
42. Didwania A, Miller J, Kassel D, et al. Effect of intravenous lactated Ringer's solution infusion on the circulating lactate concentration: part 3. Results of a prospective, randomized, double-blind, placebo-controlled trial. *Crit Care Med*. 1997;25:1851-1854.
43. Shin WJ, Kim YK, Bang JY, et al. Lactate and liver function tests after living donor right hepatectomy: a comparison of solutions with and without lactate. *Acta Anaesthesiol Scand*. 2011;55:558-564.
44. Marik PE, Bellomo R. Stress hyperglycemia: an essential survival response! *Crit Care*. 2013;17:305.
45. Gibot S. On the origins of lactate during sepsis. *Crit Care*. 2012;16:151.
46. Levy B, Gibot S, Franck P, et al. Relation between muscle Na^+K^+ ATPase activity and raised lactate concentrations in septic shock: a prospective study. *Lancet*. 2005;365:871-875.
47. Gore DC, Jahoor F, Hibbert JM, et al. Lactic acidosis during sepsis is related to increased pyruvate production, not deficits in tissue oxygen availability. *Ann Surg*. 1996;224:97-102.
48. Adrie C, Batchelet M, Vayssier-Taussat M, et al. Mitochondrial membrane potential and apoptosis peripheral blood monocytes in severe human sepsis. *Am J Respir Crit Care Med*. 2001;164:389-395.
49. Boczkowski J, Lisdero CL, Lanone S, et al. Endogenous peroxynitrite mediates mitochondrial dysfunction in rat diaphragm during endotoxemia. *FASEB J*. 1999;13:1637-1646.
50. Opdam H, Bellomo R. Oxygen consumption and lactate release by the lung after cardiopulmonary bypass and during septic shock. *Crit Care Resusc*. 2000;2:181-187.
51. Iscra F, Gullo A, Biolo G. Bench-to-bedside review: lactate and the lung. *Crit Care*. 2002;6:327-329.
52. Brown SD, Clark C, Gutierrez G. Pulmonary lactate release in patients with sepsis and the adult respiratory distress syndrome. *J Crit Care*. 1996;11:2-8.
53. Douzinas EE, Tsidemiadou PD, Pitaridis MT, et al. The regional production of cytokines and lactate in sepsis-related multiple organ failure. *Am J Respir Crit Care Med*. 1997;155:53-59.
54. Haji-Michael PG, Ladriere L, Sener A, et al. Leukocyte glycolysis and lactate output in animal sepsis and ex vivo human blood. *Metabolism*. 1999;48:779-785.
55. Ince C. The microcirculation is the motor of sepsis. *Crit Care*. 2005;9(suppl 4):S13-S19.
56. Trzeciak S, Cinel I, Phillip Dellinger R, et al. Resuscitating the microcirculation in sepsis: the central role of nitric oxide, emerging concepts for novel therapies, and challenges for clinical trials. *Acad Emerg Med*. 2008;15:399-413.
57. Puskarich MA, Shapiro NI, Massey MJ, et al. Lactate clearance in septic shock is not a surrogate for improved microcirculatory flow. *Acad Emerg Med*. 2016;23:690-693.
58. Hernandez G, Boerma EC, Dubin A, et al. Severe abnormalities in microvascular perfused vessel density are associated to organ dysfunctions and mortality and can be predicted by hyperlactatemia and norepinephrine requirements in septic shock patients. *J Crit Care*. 2013;28; 538.e9-14.
59. Hernandez G, Bruhn A, Castro R, et al. Persistent sepsis-induced hypotension without hyperlactatemia: a distinct clinical and physiological profile within the spectrum of septic shock. *Crit Care Res Pract*. 2012;2012:536852.

60. Wacharasint P, Nakada TA, Boyd JH, et al. Normal-range blood lactate concentration in septic shock is prognostic and predictive. *Shock*. 2012;38:4-10.
61. Puskarich MA, Trzeciak S, Shapiro NI, et al. Outcomes of patients undergoing early sepsis resuscitation for cryptic shock compared with overt shock. *Resuscitation*. 2011;82:1289-1293.
62. Hayes MA, Timmins AC, Yau EH, et al. Elevation of systemic oxygen delivery in the treatment of critically ill patients. *N Engl J Med*. 1994;330:1717-1722.
63. Marik PE, Sibbald WJ. Effect of stored-blood transfusion on oxygen delivery in patients with sepsis. *JAMA*. 1993;269:3024-3029.
64. Boekstegers P, Weidenhofer S, Kapsner T, et al. Skeletal muscle partial pressure of oxygen in patients with sepsis. *Crit Care Med*. 1994;22:640-650.
65. Rosser DM, Stidwill RP, Jacobson D, et al. Oxygen tension in the bladder epithelium rises in both high and low cardiac output endotoxemic sepsis. *J Appl Physiol (1985)*. 1995;79:1878-1882.
66. Sair M, Etherington PJ, Peter Winlove C, et al. Tissue oxygenation and perfusion in patients with systemic sepsis. *Crit Care Med*. 2001;29:1343-1349.
67. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. 2001;345:1368-1377.
68. Ander DS, Jaggi M, Rivers E, et al. Undetected cardiogenic shock in patients with congestive heart failure presenting to the emergency department. *Am J Cardiol*. 1998;82:888-891.
69. Howell MD, Donnino M, Clardy P, et al. Occult hypoperfusion and mortality in patients with suspected infection. *Intensive Care Med*. 2007;33:1892-1899.
70. Meregalli A, Oliveira RP, Friedman G. Occult hypoperfusion is associated with increased mortality in hemodynamically stable, high-risk, surgical patients. *Crit Care*. 2004;8:R60-R65.
71. Contenti J, Occelli C, Lemoel F, et al. Blood lactate measurement within the emergency department: a two-year retrospective analysis. *Am J Emerg Med*. 2018;37:401-406.
72. Manikis P, Jankowski S, Zhang H, et al. Correlation of serial blood lactate levels to organ failure and mortality after trauma. *Am J Emerg Med*. 1995;13:619-622.
73. Abramson D, Scalea TM, Hitchcock R, et al. Lactate clearance and survival following injury. *J Trauma*. 1993;35:584-588; discussion 8-9.
74. Kaplan LJ, Kellum JA. Initial pH, base deficit, lactate, anion gap, strong ion difference, and strong ion gap predict outcome from major vascular injury. *Crit Care Med*. 2004;32:1120-1124.
75. Luchette FA, Robinson BR, Friend LA, et al. Adrenergic antagonists reduce lactic acidosis in response to hemorrhagic shock. *J Trauma*. 1999;46:873-880.
76. McCarter FD, Nierman SR, James JH, et al. Role of skeletal muscle Na^+-K^+ ATPase activity in increased lactate production in sub-acute sepsis. *Life Sci*. 2002;70:1875-1888.
77. Blow O, Magliore L, Claridge JA, et al. The golden hour and the silver day: detection and correction of occult hypoperfusion within 24 hours improves outcome from major trauma. *J Trauma*. 1999;47:964-969.
78. Crowl AC, Young JS, Kahler DM, et al. Occult hypoperfusion is associated with increased morbidity in patients undergoing early femur fracture fixation. *J Trauma*. 2000;48:260-267.
79. Claridge JA, Crabtree TD, Pelletier SJ, et al. Persistent occult hypoperfusion is associated with a significant increase in infection rate and mortality in major trauma patients. *J Trauma*. 2000;48:8-14; discussion 14-15.
80. Andel D, Kamolz LP, Roka J, et al. Base deficit and lactate: early predictors of morbidity and mortality in patients with burns. *Burns*. 2007;33:973-978.
81. Mokline A, Abdenneji A, Rahmani I, et al. Lactate: prognostic biomarker in severely burned patients. *Ann Burns Fire Disasters*. 2017;30:35-38.
82. Jeng JC, Jablonski K, Bridgeman A, et al. Serum lactate, not base deficit, rapidly predicts survival after major burns. *Burns*. 2002;28:161-166.
83. Sanchez M, Garcia-de-Lorenzo A, Herrero E, et al. A protocol for resuscitation of severe burn patients guided by transpulmonary thermodilution and lactate levels: a 3-year prospective cohort study. *Crit Care*. 2013;17:R176.
84. Winocour PH, Waise A, Young G, et al. Severe, self-limiting lactic acidosis and rhabdomyolysis accompanying convulsions. *Postgrad Med J*. 1989;65:321-322.
85. Doğan EA, Ünal A, Erdoğan Ç. Clinical utility of serum lactate levels for differential diagnosis of generalized tonic-clonic seizures from psychogenic nonepileptic seizures and syncope. *Epilepsy Behav*. 2017;75:13-17.
86. van Rooij FJ, Admiraal-van de Pas Y. [Lactic acidosis in the postictal state]. *Ned Tijdschr Geneeskd*. 2015;159:A9068.
87. Siegel AJ, Januzzi J, Sluss P, et al. Cardiac biomarkers, electrolytes, and other analytes in collapsed marathon runners: implications for the evaluation of runners following competition. *Am J Clin Pathol*. 2008;129:948-951.
88. Mallat J, Lemyze M, Thevenin D. Do not forget to give thiamine to your septic shock patient! *J Thorac Dis*. 2016;8:1062-1066.
89. Donnino MW, Andersen LW, Chase M, et al. Randomized, double-blind, placebo-controlled trial of thiamine as a metabolic resuscitator in septic shock: a pilot study. *Crit Care Med*. 2016;44:360-367.
90. Holmberg MJ, Moskowitz A, Patel PV, et al. Thiamine in septic shock patients with alcohol use disorders: an observational pilot study. *J Crit Care*. 2018;43:61-64.
91. Marik PE, Khangoora V, Rivera R, et al. Hydrocortisone, vitamin C, and thiamine for the treatment of severe sepsis and septic shock: a retrospective before-after study. *Chest*. 2017;151:1229-1238.
92. Woolum JA, Abner EL, Kelly A, et al. Effect of thiamine administration on lactate clearance and mortality in patients with septic shock. *Crit Care Med*. 2018;46:1747-1752.
93. Andersen LW, Mackenhauer J, Roberts JC, et al. Etiology and therapeutic approach to elevated lactate levels. *Mayo Clin Proc*. 2013;88:1127-1140.
94. Shah AD, Wood DM, Dargan PI. Understanding lactic acidosis in paracetamol (acetaminophen) poisoning. *Br J Clin Pharmacol*. 2011;71:20-28.
95. Bajt ML, Knight TR, Lemasters JJ, et al. Acetaminophen-induced oxidant stress and cell injury in cultured mouse hepatocytes: protection by N-acetyl cysteine. *Toxicol Sci*. 2004;80:343-349.
96. Meert KL, McCaulley L, Sarnaik AP. Mechanism of lactic acidosis in children with acute severe asthma. *Pediatr Crit Care Med*. 2012;13:28-31.
97. Koul PB, Minarik M, Totapally BR. Lactic acidosis in children with acute exacerbation of severe asthma. *Eur J Emerg Med*. 2007;14:56-58.
98. McCarter FD, James JH, Luchette FA, et al. Adrenergic blockade reduces skeletal muscle glycolysis and Na(+), K(+)-ATPase activity during hemorrhage. *J Surg Res*. 2001;99:235-244.
99. Wutrich Y, Barraud D, Conrad M, et al. Early increase in arterial lactate concentration under epinephrine infusion is associated with a better prognosis during shock. *Shock*. 2010;34:4-9.
100. Varon J, Marik PE, Fromm RE, et al. Carbon monoxide poisoning: a review for clinicians. *J Emerg Med*. 1999;17:87-93.
101. Thom SR, Keim LW. Carbon monoxide poisoning: a review epidemiology, pathophysiology, clinical findings, and treatment options including hyperbaric oxygen therapy. *J Toxicol Clin Toxicol*. 1989;27:141-156.
102. Benaissa ML, Mégarbane B, Borron SW, et al. Is elevated plasma lactate a useful marker in the evaluation of pure carbon monoxide poisoning? *Intensive Care Med*. 2003;29:1372-1375.

103. Doğan N, Savrun A, Levent S, et al. Can initial lactate levels predict the severity of unintentional carbon monoxide poisoning? *Hum Exp Toxicol*. 2015;34:324-329.
104. Hottinger DG, Beebe DS, Kozhimannil T, et al. Sodium nitroprusside in 2014: a clinical concepts review. *J Anaesthesiol Clin Pharmacol*. 2014;30:462-471.
105. Baud FJ, Barriot P, Toffis V, et al. Elevated blood cyanide concentrations in victims of smoke inhalation. *N Engl J Med*. 1991;325:1761-1766.
106. Suchard JR, Grotsky TA. Fatal metformin overdose presenting with progressive hyperglycemia. *West J Emerg Med*. 2008;9:160-164.
107. Almirall J, Bricullé M, Gonzalez-Clemente JM. Metformin-associated lactic acidosis in type 2 diabetes mellitus: incidence and presentation in common clinical practice. *Nephrol Dial Transplant*. 2008;23:2436-2438.
108. Donnino MW, Miller J, Goyal N, et al. Effective lactate clearance is associated with improved outcome in post-cardiac arrest patients. *Resuscitation*. 2007;75:229-234.
109. Regnier MA, Raux M, Le Manach Y, et al. Prognostic significance of blood lactate and lactate clearance in trauma patients. *Anesthesiology*. 2012;117:1276-1288.
110. Weil MH, Afifi AA. Experimental and clinical studies on lactate and pyruvate as indicators of the severity of acute circulatory failure (shock). *Circulation*. 1970;41:989-1001.
111. Wardi G, Wali AR, Villar J, et al. Unexpected intensive care transfer of admitted patients with severe sepsis. *J Intensive Care*. 2017;5:43.
112. Shapiro NI, Howell MD, Talmor D, et al. Serum lactate as a predictor of mortality in emergency department patients with infection. *Ann Emerg Med*. 2005;45:524-528.
113. Mikkelsen ME, Miltiades AN, Gaieski DF, et al. Serum lactate is associated with mortality in severe sepsis independent of organ failure and shock. *Crit Care Med*. 2009;37:1670-1677.
114. Nichol AD, Egi M, Pettila V, et al. Relative hyperlactatemia and hospital mortality in critically ill patients: a retrospective multi-centre study. *Crit Care*. 2010;14:R25.
115. Puskarich MA, Illich BM, Jones AE. Prognosis of emergency department patients with suspected infection and intermediate lactate levels: a systematic review. *J Crit Care*. 2014;29:334-339.
116. Dettmer M, Holthaus CV, Fuller BM. The impact of serial lactate monitoring on emergency department resuscitation interventions and clinical outcomes in severe sepsis and septic shock: an observational cohort study. *Shock*. 2015;43:55-61.
117. Jansen TC, van Bommel J, Schoonderbeek FJ, et al. Early lactate-guided therapy in intensive care unit patients: a multicenter, open-label, randomized controlled trial. *Am J Respir Crit Care Med*. 2010;182:752-761.
118. Nguyen HB, Rivers EP, Knoblich BP, et al. Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. *Crit Care Med*. 2004;32:1637-1642.
119. Jones AE, Shapiro NI, Trzeciak S, et al. Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. *JAMA*. 2010;303:739-746.
120. Hernández G, Ospina-Tascón GA, Damiani LP, et al. Effect of a resuscitation strategy targeting peripheral perfusion status vs serum lactate levels on 28-day mortality among patients with septic shock. *JAMA*. 2019;321:654-664.
121. Acosta S, Block T, Bjornsson S, et al. Diagnostic pitfalls at admission in patients with acute superior mesenteric artery occlusion. *J Emerg Med*. 2012;42:635-641.