CHEST

Lactic Acidosis in Sepsis: It's Not All Anaerobic

Implications for Diagnosis and Management

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Increased blood lactate concentration (hyperlactatemia) and lactic acidosis (hyperlactatemia and serum pH < 7.35) are common in patients with severe sepsis or septic shock and are associated with significant morbidity and mortality. In some patients, most of the lactate that is produced in shock states is due to inadequate oxygen delivery resulting in tissue hypoxia and causing anaerobic glycolysis. However, lactate formation during sepsis is not entirely related to tissue hypoxia or reversible by increasing oxygen delivery. In this review, we initially outline the metabolism of lactate and etiology of lactic acidosis; we then address the pathophysiology of lactic acidosis in sepsis. We discuss the clinical implications of serum lactate measurement in diagnosis, monitoring, and prognostication in acute and intensive care settings. Finally, we explore treatment of lactic acidosis and its impact on clinical outcome.

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> "I have yet to see any problem, however complicated, which, when you looked at it in the right way, did not become still more complicated."
>
> –Poul William Anderson

Blood lactate concentration is often measured in patients with severe sepsis and particularly those in septic shock. Lactic acidosis has been traditionally interpreted as a biological marker of tissue hypoxia because of inadequate oxygen delivery and as a predictor of adverse outcome.[1] This view is too simplified and does not take into consideration the many causes on increased lactate accumulation that can occur in the absence of tissue hypoxia or in addition to tissue hypoxia. Lactate is not just metabolic waste arising from anaerobic glycolysis. Rather, it is an important energy "shuttle" whose production is triggered by a variety of metabolites even before the onset of anaerobic metabolism as part of an adaptive response to a hypermetabolic state and, in particular, during sepsis.[2] Here, we review hyperlactatemia and lactic acidosis in sepsis and implications for diagnosis and treatment.

Lactic acid has been recognized as a metabolite associated with sepsis for almost 200 years[3] and with tissue hypoxia for more than 100 years.[4] In 1961, Huckabee first

ABBREVIATIONS: ATP = adenosine triphosphate; NADH = nicotinamide adenine dinucleotide hydride; NAD^+ = oxidized form of nicotinamide adenine dinucleotide; Na^+-K^+-ATPase = sodium-potassium-adenosine triphosphatase; RCT = randomized control trial

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recognized that blood lactate concentration could be increased out of proportion to pyruvate and associated with acidosis (lactic acidosis) or, in contrast, that blood lactate concentration could be increased, accompanied by a proportional increase in pyruvate without acidosis.[5,6] In 1976, Cohen and Woods divided hyperlactatemia into two categories: lactic acidosis associated with clinical evidence of inadequate tissue oxygenation (type A) and hyperlactatemia in which clinical evidence of tissue hypoxia was absent (type B). Type B hyperlactatemia was further subdivided into B_1, in which hyperlactatemia was associated with certain underlying diseases such as liver failure; B_2, in which hyperlactatemia was due to drugs or toxins; and B_3, in which hyperlactatemia was caused by inborn errors of metabolism.[7]

Lactate Production

Under normal conditions, lactate is produced at the remarkably high rate of approximately 1.5 mol per day; thus, lactate is not simply a waste product indicating anaerobic metabolism. Rather, the "lactate shuttle" theory highlights the role of lactate in the distribution of oxidative and gluconeogenic substrates as well as in cell signalling.[8,9] Lactate produced in one location can be used as a preprocessed fuel for mitochondrial respiration by numerous distant tissues or can be used by the liver in gluconeogenesis.[10,11] Normal lactate production arises mainly from skeletal muscle; skin, brain, intestine, and erythrocytes also contribute.[12] The lungs can create lactate during acute lung injury without tissue hypoxia,[13,14] and leukocytes also generate lactate during phagocytosis or when activated in sepsis.[15] In pathological conditions in which oxygen delivery is limited, lactate generation develops in other tissues.

Lactate arises from the metabolism of glucose (Fig 1). Glycolysis metabolizes glucose to pyruvate, which is catalyzed by phosphofructokinase in the Embden-Meyerhof pathway.[16] Further metabolism of pyruvate follows one of two routes. First, under aerobic conditions, pyruvate enters mitochondria and is converted to acetyl coenzyme A by pyruvate dehydrogenase, which enters the tricarboxylic acid (Krebs) cycle. Note that thiamine diphosphate is a coenzyme required for the catalytic activity of several enzymes involved in two-carbon transfers, including pyruvate dehydrogenase. Once within the Krebs cycle, stepwise metabolism of acetyl coenzyme A occurs in concert with stepwise transport of electrons in high-energy states down to lower energy states with the production of adenosine triphosphate

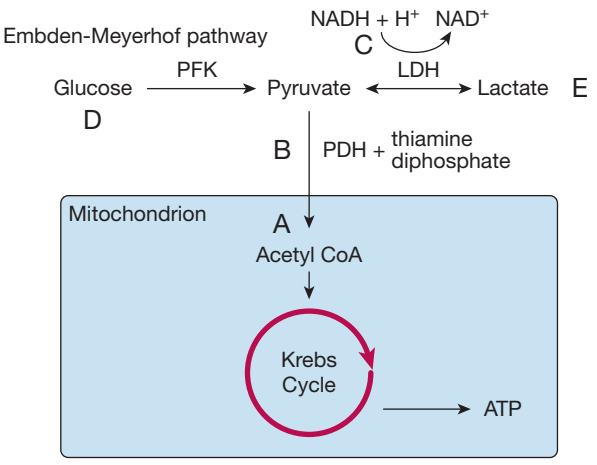

Figure 1 – *The pathway from glycolysis to pyruvate to lactate production is illustrated, with key features leading to increased lactate concentrations labeled in red. A, Lactic acidosis from tissue hypoxia. Anaerobic metabolism reduces flux through the Krebs cycle so pyruvate is shunted toward lactate. B, Hyperlactatemia not directly resulting from tissue hypoxia. Thiamine deficiency reduces flux of pyruvate to the Krebs cycle, increasing lactate production. C, A reducing environment has increased NADH/NAD+, which favors lactate production. D, Increased glycolytic flux through the Embden-Meyerhof pathway results in increased pyruvate availability, potentially beyond the capacity of mitochondrial respiration to metabolize pyruvate, so lactate production increases. E, Decreased lactate clearance also increases lactate concentrations even in the absence of tissue hypoxia. ATP = adenosine triphosphate; CoA = coenzyme A; LDH = lactate dehydrogenase; NADH = nicotinamide adenine dinucleotide hydride; NAD+ = nicotinamide adenine dinucleotide; PDH = pyruvate dehydrogenase; PFK = phosphofructokinase.*

(ATP) molecules. Oxygen provides a very low-energy electron sink at the end of the electron transport chain, allowing generation of 38 ATP molecules for each molecule of metabolized glucose.

The second route for pyruvate is conversion to or from lactate in the cytosol. This reaction is bidirectionally catalyzed by lactate dehydrogenase, resulting in a normal lactate:pyruvate ratio of approximately 10:1. When sufficient oxygen is not available, the Krebs cycle cannot metabolize pyruvate so lactate is generated (Fig 1A). This is tissue hypoxia. However, lactate production independent of tissue hypoxia can also occur. Entry of pyruvate into the Krebs cycle, catalyzed by pyruvate dehydrogenase, can be limited by thiamine deficiency, which results in diversion of pyruvate toward lactate production (Fig 1B). The conversion of pyruvate to lactate requires nicotinamide adenine dinucleotide hydride (NADH) and H^+. Conditions which result in a reducing cellular environment (elevated NADH/oxidized form of nicotinamide adenine dinucleotide [NAD^+]), such as ethanol ingestion and ketoacidosis, promote production of lactate independent of tissue oxygenation (Fig 1C). Importantly, in patients with sepsis, increased glycolytic flux results in increased

pyruvate production and hence lactate production, again with a normal lactate:pyruvate ratio (Fig 1D). For example, an increase in glycolytic flux exceeding the oxidative capacity of mitochondria can occur with severe exercise (eg, work of breathing), during catecholamine administration, and during sepsis. An elevated adenosine diphosphate and inorganic phosphate:ATP ratio and NADH:NAD^+ ratio also promote glycolytic flux.

Lactate Clearance

Lactate is a transportable metabolite that then can be metabolized for energy production by local or distant mitochondria (pyruvate and then the Krebs cycle) or as a substrate for gluconeogeneses (the Cori cycle). Lactate is metabolized primarily by the liver and, to some extent, by the kidneys. Cardiac myocytes use lactate as fuel in some circumstances, such as during exercise, β-adrenergic stimulation, and shock.[17,18] The brain also consumes lactate when metabolic requirements are increased.[19] A decreased rate of lactate clearance is therefore an additional cause of increased lactate concentration that is not directly related to tissue hypoxia (Fig 1E).

Where Does the Acid Come From?

Note that glycolytic flux from glucose to pyruvate generates H^+, but conversion of pyruvate to lactate consumes the molar equivalent H^+ flux; therefore, increased generation of lactate resulting in hyperlactatemia is not, by itself, acidosis. Where does the acid come from? ATP hydrolysis is the major generator of H^+ (protons = acid). This acid is avidly consumed by the Krebs cycle; therefore, acid builds up during tissue-hypoxic conditions when the Krebs cycle consumption of H^+ is reduced by a decreased Krebs cycle flux. Coincidentally, lactate is also generated when Krebs cycle flux is reduced (Fig 1A), so tissue-hypoxic acidosis appears clinically as "lactic acidosis." But this does not mean that increased lactate production (Fig 1B-D) or decreased lactate consumption (Fig 1E) are due to tissue hypoxia.

Etiologies of Lactic Acidosis

From a clinical perspective, hyperlactatemia develops when lactate production is augmented, lactate utilization and clearance are diminished, or both. Sepsis and shock are common causes of hyperlactatemia.[20] In patients with vasopressor-dependent septic shock, Dugas and colleagues[21] demonstrated that more than half of the patients had elevated lactate concentrations. This finding was confirmed by the recent Surviving Sepsis Campaign Database that illustrated approximately two-thirds of patients with severe sepsis or septic shock had elevated lactate concentrations.[22] A major and vitally important contributor to lactic acidosis is tissue hypoxia. But hyperlactatemia during sepsis is not as straightforward as globally inadequate oxygen delivery, as discussed previously. Observations in dying patients suggest that death rapidly follows the onset of whole-body anaerobic metabolism; typically within an hour,[23] whereas hyperlactatemia in patients with sepsis can persist. Therefore, etiologies other than tissue hypoxia must be considered (although not at the expense of ignoring the possibility of inadequately treated tissue hypoxia!). A list of additional causes of lactic acidosis as described by Cohen and Woods (Table 1) identifies many etiologies that can also be found as additional contributors to lactic acidosis in patients with sepsis. These additional possibilities must be considered and treated where appropriate.

Lactic Acidosis in Sepsis

Inadequate Whole-Body Oxygen Delivery

Lactic acidosis in sepsis and septic shock has traditionally been explained as a result of tissue hypoxia when whole-body oxygen delivery fails to meet whole-body oxygen requirements (Fig 2).[6] Early studies in patients with septic shock, which found a sloped relationship between measurements of whole-body oxygen delivery and consumption, suggested that this was evidence of tissue hypoxia because the slope in an oxygen consumption-delivery relationship was found below the critical oxygen delivery point where anaerobic metabolism occurs (Fig 2).[24,25] This sloped relationship was subsequently found to be artifactual,[23] and clinical trials aiming to increase oxygen delivery to meet potential unmet oxygen demand did not improve survival and may have increased mortality.[26] Yet, early in sepsis, hemodynamic resuscitation reduces lactate concentrations and an increase in the lactate:pyruvate ratio, suggested to be a marker of tissue hypoxia, is observed in patients with septic shock.[27-31] To understand these discordant results in patients with septic shock, it is important to distinguish between the early resuscitation phase and the postresuscitation phase.

Inadequate whole-body oxygen delivery occurs in septic and all other forms of shock, and indeed, defines shock. The timeline between onset of inadequate whole-body

TABLE 1] Causes of Lactic Acidosis (Cohen and Woods' Classification)

Type A (clinical evidence of tissue hypoxia)
Shock (Septic, Hypovolemic, Obstructive, Cardiogenic, "Kombinations", rare Kinds)
Regional hypoperfusion (mesenteric, limb ischemia)
Severe hypoxemia
Severe anemia
Carbon monoxide, cyanide, iron poisoning
Severe muscle activity (exercise, seizures, asthma)
Type B (no clinical evidence of tissue hypoxia)
B1 (association with an underlying disease)
Liver disease
Sepsis
Diabetes mellitus
Malignancy
Pheochromocytoma
Thiamine deficiency
B2 (drugs/toxins)
Biguanides
Epinephrine, terbutaline, other adrenergic agonists
Ethanol, methanol, ethylene glycol, propylene glycol
Propofol
Nitroprusside, inhaled nitric oxide
Fructose
Sorbitol
Salicylates
Acetaminophen
Isoniazid
Linezolid
B3, from inborn errors of metabolism
Gucose-6-phosphatase deficiency (von Gierke's disease)
Fructose-1,6-diphosphatase deficiency
Pyruvate carboxylase deficiency
Pyruvate dehydrogenase deficiency
Oxidative phosphorylation defects
Miscellaneous
D-lactic acidosis
Hypoglycemia

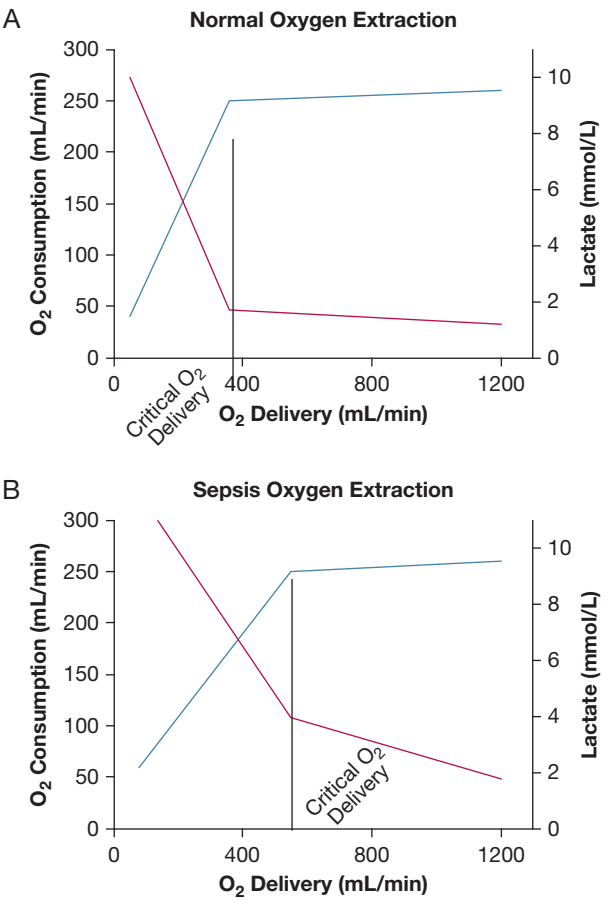

Figure 2 – *A, Normal oxygen (O_2) extraction. When oxygen delivery (cardiac output multiplied by oxygen carrying capacity of the blood) decreases from normal high levels (approximately 1,000 mL/min), there is no significant change in oxygen consumption (basal metabolism) (blue line) until oxygen delivery falls below a critical value (critical O_2 delivery). Below this critical value, tissue hypoxia ensues with generation of lactic acid (red line). Normally, this critical oxygen delivery point occurs at a very low value (approximately 4 mL O_2/kg/min) when oxygen extraction ratio of the tissues is about 70% (O_2 consumption divided by O_2 delivery). B, Sepsis oxygen extraction. Sepsis impairs tissue oxygen extraction so the onset of anaerobic metabolism occurs at an increased critical oxygen delivery and at a decreased critical oxygen extraction ratio. Even before the onset of true tissue hypoxia, lactate concentrations can rise above the normal range because of nonanaerobic factors such as increased glycolysis from sepsis and catecholamine administration.*

oxygen delivery and death is very short, less than 1 h,[23] which emphasizes the importance of early and adequate hemodynamic resuscitation, optimally driven by a resuscitation protocol. A variety of related resuscitation protocols that achieve reasonable physiologic targets for volume administration, blood pressure support using infused vasoconstrictors, and oxygen delivery related to oxygen demand have been highly effective in decreasing mortality of septic shock from 40% to 60% to approximately 20% reported in recent randomized controlled trials (RCTs).[32,33] Thus, anaerobic metabolism is a key element of lactic acidosis found during the early resuscitation phase of septic shock. Early institution of antibiotic therapy and early hemodynamic resuscitation combined have been transformative therapies in increasing survival of patients with sepsis and septic shock.

Initial aggressive resuscitation aims to address tissue hypoxia as a contributor to lactic acidosis. Following initial resuscitation, other causes of hyperlactatemia

must be considered. Inadequate whole-body oxygen delivery is often not the full explanation for ongoing hyperlactatemia. For example, high serum lactate concentration occurred even when whole-body oxygen delivery was three times higher than the critical oxygen delivery point.[23] In these resuscitated, critically ill patients, increases in oxygen delivery did not cause an increase in oxygen consumption and there is no consistent relationship between oxygen delivery and mixed venous oxygenation or lactic acidosis in patients with sepsis.[34] Furthermore, many patients with sepsis or septic shock have normal lactate:pyruvate ratios while they had lactic acidosis.[27,30,31] Lactic acidosis can develop without tissue hypoxia in various tissues, such as muscle, intestinal mucosa, heart, lung, and brain.[35-38] Interestingly, esmolol administration in patients with septic shock reduced oxygen delivery but also reduced plasma lactate concentrations.[39] Thus, other causes of hyperlactatemia must be considered beyond inadequate whole-body oxygen delivery (Table 1).

Impaired Tissue Oxygen Extraction and the Microcirculation

Sepsis results in an impaired ability of the tissues to extract oxygen. Normally, most tissues can extract as much as 70% of the delivered oxygen before anaerobic metabolism and lactate generation ensue (Fig 2A).[40] During sepsis, this critical oxygen extraction ratio is reduced to 50% or less so that lactic acid formation increases at oxygen deliveries that would normally be sufficient to meet aerobic oxygen demand (Fig 2B).[41] Endothelial inflammatory processes result in microcirculatory dysfunction so that regional and microregional oxygen delivery is not matched with demand.[42] The resultant heterogeneous regions of tissue hypoxia generate lactate.[43,44] In addition, mitochondrial dysfunction occurs during sepsis so that, even in tissues with adequate oxygenation, anaerobic metabolism occurs and pyruvate is shunted toward lactate production. Thus, even when whole-body and organ oxygen delivery is adequate, anaerobic metabolism can occur. A corollary is that increasing whole-body oxygen delivery (increasing cardiac output or increasing hemoglobin to increase oxygen carrying capacity) will not correct impaired tissue oxygen extraction.

Increased Glycolytic Flux and Sodium-Potassium-Adenosine Triphosphatase Activity Through β2 Stimulation

In patients with sepsis, the resting metabolic rate is increased,[45] leading to increased metabolism of glucose. Glycolytic flux can exceed that capacity of pyruvate dehydrogenase to catalyze conversion of pyruvate into acetyl coenzyme A. Therefore, pyruvate is inevitably converted to lactate by lactate dehydrogenase. In septic shock animal models and in septic humans, increased endogenous epinephrine and norepinephrine concentrations are observed and are associated with hyperlactatemia. Sodium-potassium-adenosine triphosphatase (Na^+-K^+-ATPase) activity is increased and is associated with increased glycolytic flux through β2 stimulation.[46-48] These results are supported by the observation that lactate production is reduced by β2 antagonists such as esmolol and by Na^+-K^+-ATPase inhibitors (ouabain) in septic shock or when glycolysis is induced by epinephrine.[49-51]

Diminished Lactate Clearance

In hemodynamically stable patients with sepsis, hyperlactatemia might be the result of impaired lactate clearance rather than overproduction.[52] Although impaired hepatic lactate clearance does not occur in all patients with sepsis,[53,54] this becomes an important issue in patients with significant preexisting or new hepatic dysfunction. Persistent and sometimes marked elevations in lactate concentrations from hepatic dysfunction may inappropriately trigger further resuscitation efforts, including detrimental fluid administration or further administration of catecholamines, which may compound the problem.

Clinical Implications in Diagnosis, Prognostication, and Treatment

How and When Lactate Should Be Measured

Although an increased anion gap can be considered a screening tool for the diagnosis of lactic acidosis,[55] a normal anion gap does not exclude the possibility of lactic acidosis, which can present with a normal anion gap up to 50% of the time.[56] Even in the setting of lactic acidosis, other causes of an increased anion gap should be considered.[57] Therefore, measurement of blood lactate concentration is necessary. In most circumstances, venous blood lactate concentrations are modestly higher than arterial blood lactate, but the correlation between them is as high as $r = 0.94$ (95% CI, 0.91-0.96).[58] Thus, either venous or arterial blood can be assayed. Samples should be measured within 15 min or should be placed on ice if the processing time is longer to prevent artifactually elevated concentrations of lactate derived from erythrocytes and leukocytes.[59]

Use of blood lactate as a triage tool in the acute care setting is effective, particularly in patients with normal hemodynamic parameters.[60] The latest International Guidelines for Management of Severe Sepsis and Septic Shock (Surviving Sepsis Campaign) recommends measuring blood lactate within 3 h of presentation. Hyperlactatemia > 4 mmol/L is used as one criterion to diagnose severe sepsis.[61] In hemodynamically stable patients with febrile neutropenia, hyperlactatemia is associated with development of septic shock within 48 h.[62]

Lactate and Prognostication

Whether hyperlactatemia arises from true tissue hypoxia or from increased glycolysis as an adaptive response to sepsis, hyperlactatemia in severe sepsis is correlated with an increased mortality rate. Sepsis-induced hypotension without hyperlactatemia has a much better outcome than septic shock with lactic acidosis.[63,64]

Many studies show that initial or persistent hyperlactatemia is associated with adverse outcome, but no clear cut point is evident. In normotensive patients with sepsis, lactate concentration more than 4 mmol/L was found to be independently correlated with higher mortality and therefore needs urgent recognition and proper resucitation.[22] However, in patients with septic shock, intermediate concentrations of lactate (2-4 mmol/L)[65] or even within the high end of the normal range (1.4-2.3 mmol/L)[66] still indicated poorer prognosis than patients with low normal lactate concentrations.

Lactate as a Marker of Response to Treatment

Generally, a decrease of elevated lactate concentrations correlates with better outcome and might reflect successful management. Jansen and colleagues[67] performed a multicenter RCT using lactate-guided therapy compared with control and found a significant reduction of hospital mortality when adjusting for predefined risk. More recently, a study targeting normalization of lactate concentrations during emergency department resuscitation was associated with lower mortality, ICU length of stay, Sequential Organ Failure Assessment scores, and more ventilator and vasopressor free days compared with the no serial lactate measurement group.[68] But lactate alone is not sufficient to judge success or failure of treatment. For example, an increase in blood lactate following infusion of adrenaline in septic shock was associated with better survival.[69] In this case, adrenaline treatment was effective in increasing oxygen delivery; the rise in lactate concentration was secondary to increased glycolysis induced by the catecholamine.

Lactate and Central Venous Oxygen Saturation in Septic Shock

Rivers et al[70] initiated the term "early goal-directed therapy" in severe sepsis and septic shock and found reduced mortality when using protocol-directed therapy. After adequate volume resuscitation and blood pressure support, central venous saturation was used as a target of treatment to determine whether oxygen delivery was adequate. Lactate clearance is an alternative target during septic shock resuscitation because it also reflects adequacy of oxygen delivery and is correlated with outcome.[71,72] Jones and colleagues[73] conducted a RCT using lactate clearance vs central venous oxygen saturation as goals of treatment and found no difference in mortality between the two groups. Interestingly, a decrease in lactate concentration of more than 10% while central venous saturation was still below 70% was associated with better outcome (8% mortality) compared with central venous saturation above 70% without adequate lactate clearance (41% mortality).[74] Nevertheless, both lactate and central venous saturations have limitations in assessment of adequacy of oxygen delivery. When looked at separately as protocol-driving biomarkers with specific thresholds, they do not alter outcome.[32,33] Accordingly, they should generally be used together and in conjunction with other tools such as echocardiography[75,76] or venoarterial carbon dioxide difference[77-79] to better understand the cause, severity, and consequences of shock. We often forget that bedside evidence of good organ function (eg, clear mentation, good urine output) is more valuable than a biomarker measurement alone and should always be used in conjunction with biomarker measurements such as lactate.

Treatment of Lactic Acidosis in Sepsis

The correct treatment of lactic acidosis is to treat the underlying cause. It is therefore essential to rapidly treat sepsis; in particular, early appropriate antibiotic administration and infection source control. Equally important is simultaneous correction of inadequate whole-body oxygen delivery in patients in shock, optimally driven by a resuscitation protocol. It is also essential to consider regional production of lactate at the time of initial resuscitation, particularly when initial resuscitation does not substantially or completely correct lactic acidosis. Bowel ischemia/infarction, limb ischemia from arterial insufficiency or compartment syndrome,

and other tissue sources must be considered, identified, and treated. Following the initial resuscitation, it is necessary to identify additional contributors to ongoing hyperlactatemia to identify and treat these underlying additional causes.

Initial resuscitation aims to correct deficits in whole-body oxygen delivery and the macrocirculation. Macrocirculatory parameters targeted by resuscitation protocols include central venous pressure, mean arterial pressure, cardiac output, and oxygen carrying capacity of the blood. However, effective resuscitation also requires that microcirculation be addressed. Adequate microcirculatory volume to recruit inadequately perfused capillary beds likely requires a more careful assessment of intravascular volume resuscitation. Visualization of central veins and even microscopic examination of the sublingual microcirculation[80] may be helpful. Where marked heterogeneity of the microcirculation is evident by clinical examination of skin mottling or by advanced microscopic techniques, early and unconfirmed reports suggest that agents that improve heterogeneous microcirculatory flow may be helpful (nitric oxide donors,[81] protein C[82]). Because these microcirculatory abnormalities arise as part of the systemic inflammatory response of sepsis, reduction of this inflammatory response by early and adequate treatment of infection (antibiotics and source control) is centrally important.

Limiting the use of adrenergic agonists is important in reducing hyperlactatemia and improving outcome. Beta-adrenergic stimulation, in particular, contributes substantially to increased lactate production in shock states by increasing glycolytic flux.[48] For example, administration of epinephrine in septic shock is associated with as much as a doubling of lactate concentration compared with norepinephrine.[83,84] Choosing a vasopressor with less beta-adrenergic activity may also be helpful by reducing the incidence of arrhythmias.[85] In patients with septic shock, reduction of the norepinephrine dose by adding low-dose vasopressin improved survival by 10% in patients initially receiving less than 15 μg/min norepinephrine in the Vasopressin and Septic Shock Trial.[86] Administration of thiamine may increase aerobic metabolism[87] by ensuring that pyruvate arising from glycolytic flux can progress to oxidative metabolism through the Krebs cycle.

Reduction in unnecessary skeletal muscle work can reduce lactate production. For example, increased work of breathing from asthma and other causes of respiratory distress can contribute substantially to an elevated plasma lactate concentration; this elevated lactate level is a biomarker of potential respiratory failure. Treating the cause of respiratory failure and providing mechanical support of ventilation can reduce muscle work and lactate concentrations. Note that using high-dose inhaled and infused catecholamines in asthma patients is another major contributor to hyperlactatemia.

Attention to hepatic function and potential hepatotoxins are relevant to lactate clearance. Evidence of decreased hepatic function should be sought and reversible contributors to hepatic dysfunction should be treated. For example, hepatic congestion related to heart failure, impaired hepatic circulation, excessive feeding leading to steatosis, and hepatotoxins should be excluded or treated. Significant hepatotoxins and other therapeutics that result in hyperlactatemia should be avoided when possible.

Some specific modalities that aim to lower lactate concentration or improve acidemia have been examined. These approaches do not appear to improve clinical outcomes.

Sodium Bicarbonate: In a RCT comparing equi-osmolar sodium bicarbonate to sodium chloride in patients with lactic acidosis, there were no hemodynamic differences between bicarbonate administration and control.[88] Bicarbonate administration results in increased carbon dioxide production and decreased serum ionized calcium, which may contribute to decreased ventricular and vascular contractility. The latest International Guidelines for Management of Severe Sepsis and Septic Shock recommends against use of bicarbonate therapy for the purpose of improving hemodynamics or reducing vasopressor requirements in patients with hypoperfusion-induced lactic acidemia with pH $\geq$7.15 (grade 2B).[61]

Renal Replacement Therapy: Bicarbonate-based hemodialysis can lower lactate concentrations and normalize pH while avoiding intracellular acidosis and a reduction of ionized calcium. Continuous renal replacement therapy can be performed in critically ill patients with severe lactic acidosis and acute kidney injury.[89] However, no adequately powered RCT with clinical outcome endpoints has yet evaluated renal replacement therapy in this setting.

Dichloroacetate: Dichloroacetate enhances the activity of pyruvate dehydrogenase and lowers lactate concentrations when oxygen is available. A large RCT of dichloroacetate in lactic acidosis illustrated that

dichloroacetate reduces arterial lactate concentrations and improves acidemia, but does not result in improvement of hemodynamic parameters or survival.[90]

Conclusion

Lactic acidosis is common in patients with severe sepsis or septic shock and strongly correlates with illness severity and prognosis. However, it does not exclusively represent tissue hypoxia. It may indicate an adaptive response to metabolic processes of severe infection and response to therapies. Physicians should understand the complexity of lactate metabolism and the limitations of lactate measurements in patient management. Use of lactate clearance as a target of septic shock treatment is promising, but will never be a stand-alone biomarker; it should always be combined with additional clinical information.

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