



# Clinical applications of lactate testing in patients with sepsis and septic shock

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**Abstract:** Hyperlactatemia is very common in patients with sepsis and septic shock and is closely associated with poor prognosis. The third international consensus definition for sepsis and septic shock recently revised the definition of septic shock. Serum lactate concentration  $>2$  mmol/L was added as a key component in the definition of septic shock. Moreover, the Surviving Sepsis Campaign (SSC) recommended lactate normalization in patients with elevated lactate levels as a marker of tissue hypoperfusion. Therefore, lactate-guided sepsis and septic shock management is preferred rather than central venous oxygen saturation (ScvO<sub>2</sub>) for monitoring patients' tissue hypoperfusion. Hyperlactatemia occurs when glycolytic flux is increased via anaerobic metabolism such as tissue hypoperfusion and  $\beta$ -adrenergic stimulation by endogenous/exogenous catecholamines. Moreover, decreased serum lactate removal due to hepatic and renal dysfunction promotes hyperlactatemia. Thus, lactate-guided treatments should aim to reduce glycolytic flux and enhance lactate removal. To reduce glycolytic flux, tissue oxygen delivery is increased by increasing the cardiac output with sufficient volume resuscitation and improving the hemodynamic state and oxygen contents are increased by treating anemia and providing enough oxygen supply. Moreover, the early reduction of adrenergic vasopressors is important in reducing glycolytic flux. To enhance lactate removal, hepatic and renal function should be preserved by removing toxic materials and correcting the reversible cause of dysfunction. Dichloroacetate and thiamine induce an aerobic pyruvate metabolism in Krebs cycle and may help reduce serum hyperlactatemia. However, the most important treatment is controlling the underlying infection.

**Keywords:** Lactic acid; sepsis; shock

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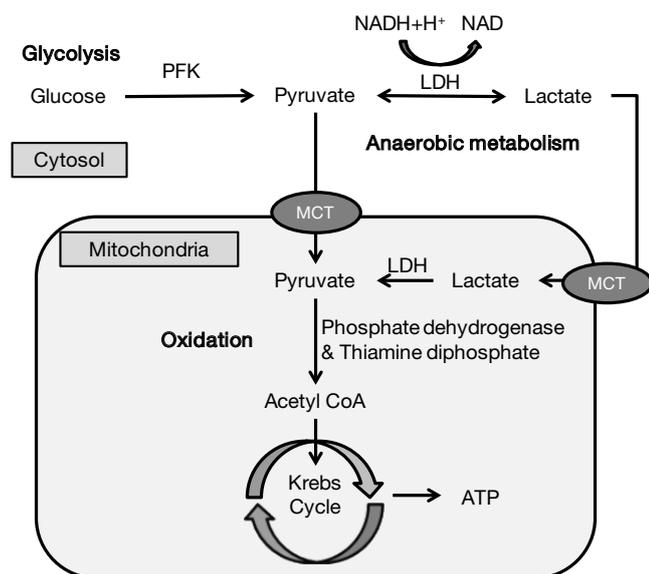
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## Introduction

In 1940s, the entire glycolytic pathway was elucidated. Lactic acid has been known as a product of glycolysis during hypoxia (1). It has been recognized as a metabolite associated with sepsis and with tissue hypoxia for a long time (2). However, a number of studies have suggested that lactate formation during sepsis is due to not only hypoxia but also metabolic processes (3,4). Lactic acidosis results from the accumulation of lactate and protons in the body fluids and is often associated with poor clinical outcomes (5).

Moreover, lactate is a parameter of global tissue hypoperfusion and is essential in identifying patients with "cryptic" shock who require focused early goal-directed therapy (EGDT) (6,7). Most of the lactate produced in shock state is due to inadequate oxygen delivery resulting in tissue hypoxia and causing anaerobic glycolysis. Moreover, a hypermetabolic state, with glycolysis enhanced by catecholamines, contributes to the accumulation of lactate (4). Thus, hyperlactatemia and lactic acidosis are common in patients with septic shock and are associated



**Figure 1** Glucose metabolism producing pyruvate and lactate. Glucose is converted to pyruvate in the cytosol as part of glycolysis. In aerobic conditions, pyruvate is transported into the mitochondria through MCT, while phosphate dehydrogenase and thiamine diphosphate are converted into acetyl-CoA to produce ATP via Krebs cycle, which is also called TCA cycle. In anaerobic conditions, Krebs cycle activity is reduced, thus, this allows the LDH to enhance lactate formation in the cytosol. Excess lactate is transported into the mitochondria again through MCTs and is oxidized to pyruvate in the Krebs cycle pathway. MCT, mono-carboxylate transporter; ATP, adenosine triphosphate; LDH, lactate dehydrogenase; TCA, tricarboxylic acid.

with significant morbidity and mortality (2). As a result, the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) has included hyperlactatemia over 2 mmol/L in the revised definition of septic shock (8). Since three independent international multicenter randomized controlled trials (ProCESS, ARISE, and ProMISE) confirmed that EGDT did not confer a mortality benefit compared with usual resuscitation, the Surviving Sepsis Campaign (SSC) focused on implementing the lactate-guided sepsis management bundle (9-12). The campaign guideline suggests guiding resuscitation to normalize lactate in patients with elevated lactate levels (12). A few recent studies showed that an early lactate clearance strategy and a lactate-guided resuscitation reduced mortality in patients with sepsis and septic shock (7,13-15). This study aimed to review the clinical aspect of lactic acidosis in patients with sepsis and septic shock.

## Lactic acid formation and clearance

Lactic acid is normally produced in excess by about 20 mmol/kg/day, which enters the bloodstream (16,17). The tissues that normally produce excess lactic acid include the skin, red cells, brain tissue, muscles, and gastrointestinal tract. During heavy exercise, the skeletal muscles produce most of the excess lactic acid (17). Moreover, the lungs can produce lactate during acute lung injury without tissue hypoxia, and leukocytes generate lactate during phagocytosis or when activated in sepsis (18-20). In pathological conditions in which oxygen delivery is limited, lactate production occurs in other tissues (2).

Lactate is formed from pyruvate in the cytosol as part of glycolysis. Its concentration is in equilibrium with that of pyruvate and is maintained by lactate dehydrogenase (LDH), an enzyme that favors lactate production and normally maintains a constant lactate to pyruvate ratio of approximately 10:1 (21). Therefore, lactate increases when the production of pyruvate exceeds its utilization in the mitochondria. Pyruvate is essentially produced via glycolysis; hence, any increase in glycolysis, regardless of its origin, can increase lactatemia (4). Meanwhile, pyruvate is essentially metabolized to acetyl coenzyme A (acetyl-CoA) by pyruvate dehydrogenase (PDH), which enters the tricarboxylic acid (TCA) cycle under aerobic conditions (2). The TCA cycle also called Krebs cycle. Under anaerobic conditions, the Krebs cycle cannot metabolize pyruvate; thus, pyruvate is shunted toward lactate (Figure 1) (2).

Lactate can be metabolized by the liver and kidneys either by direct oxidation or as a source of glucose (21). Generated lactate can be transformed into oxaloacetate or alanine via the pyruvate pathway or can be utilized directly by periportal hepatocytes (60%) to produce glycogen and glucose (neoglycogenesis and neoglucogenesis; Cori cycle) (4). Furthermore, the kidneys participate in 30% of lactate metabolism, with the cortex classically acting as the metabolizer by neoglucogenesis and the medulla as a producer of lactate (4).

Lactate is not only transformed into glucose via the Cori cycle, it is also removed through oxidation (22). This oxidative compartment which is likely close to the mitochondria is considered responsible for lactate uptake by mono-carboxylate transporter (MCT) into mitochondria and oxidation via pyruvate and the Krebs cycle with adenosine triphosphate (ATP) production (3). This intracellular lactate shuttle balances the lactate level between producing by glycolysis and clearance by oxidation (21) (Figure 1).

## The role of lactic acid

In addition of glucose metabolism, lactate plays a crucial role in various functions of the neurologic system, cancer metabolism, in various functions of the immune system, wound healing, and ischemic injuries (1).

Aerobic glycolysis in the brain is very important process in gene expression of neonate (23) and is connected to the development of synapses, neuron projections, and learning (24). Specifically, lactic acid which comes from glycolysis in astrocytes is entered to neurons through MCTs. And it plays a signaling function and stimulation of gene expression, which can lead to a long-term memory formation (25). Moreover, chronic stress is associated with sustained elevation of cyclic adenosine monophosphate (cAMP) and cognitive impairment (26). Lactate could potentially modulate the over-activated signaling cascades by reducing cAMP, thus preventing memory loss and enhancing neuronal protection (1).

Cancer cells, especially rapid growing type, are known to use an aerobic glycolysis which called Warburg effect. Lactic acid surrounding the tumor tissues can reach up to 40 mmol/L, and lactic acidosis in cancer patients is correlated with rapid cancer growth, metastasis, and poor survival (1,27). Moreover, lactic acid contributes to the reduced immunity of the tumor-infiltration host inflammatory cells such as macrophages and lymphocytes (28-30).

Lactic acid can modulate inflammation and promote immune tolerance (1). Lactic acid increases cellular production of anti-inflammatory cytokines such as interleukin-10 (1,31). On the other hand, it reduces the activities of pro-inflammatory cytokines such as interleukin-12, macrophages, natural killer cells, and tumor necrosis factors (32,33). Aerobic glycolysis is prominently involved in wound healing. Lactic acid around the healing wounds would reach between 5 and 15 mmol/L (34-36). When acute tissue ischemia occur ischemia-induced lactic acid formation is an important cellular response and which is activated by the plasma membrane sodium proton exchanges (37,38). It increases intracellular sodium, and it leads to calcium overload via calcium-sodium exchange and inducing cell death (1,39). In the setting of sepsis related lactic acidosis, animals which pretreated with sodium-proton exchanger blockers develop less hemodynamic instability and better survival compared with non-treated control groups (40,41).

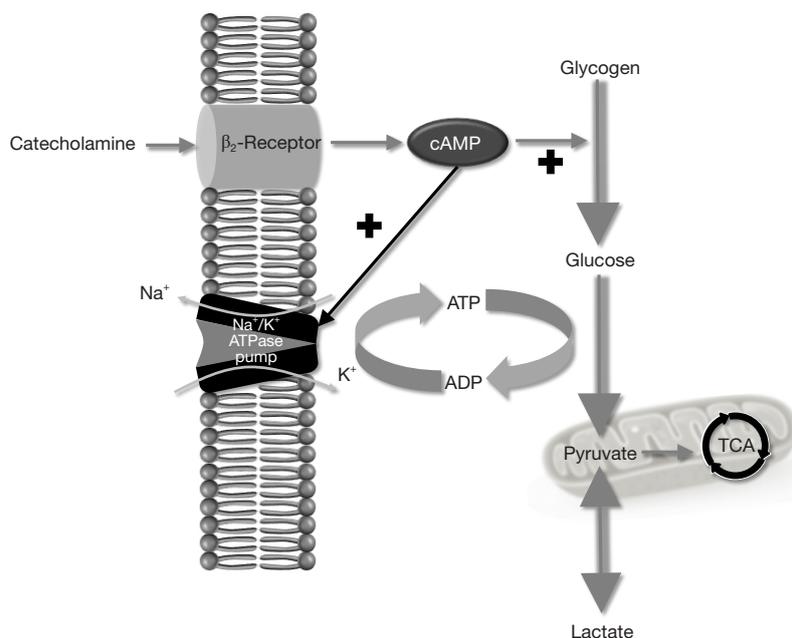
## Hyperlactatemia in sepsis and septic shock

Hyperlactatemia in sepsis and septic shock occurs as a result

of tissue hypoxia, in which the whole body oxygen delivery fails to meet the whole body oxygen requirements (2,42). Therefore, increased blood lactate concentration indicates anaerobic metabolism and tissue hypoxia. It follows from this reasoning that patients with an elevated blood lactate level should be treated by increasing oxygen delivery (21). Although enough oxygen was delivered to the tissues, in the setting of tissue oxygen extraction impairment, anaerobic metabolism generates lactate. Normally, most tissues can extract as much as 70% of the delivered oxygen before anaerobic metabolism. However, in sepsis and septic shock state, this critical oxygen extraction ratio is decreased to 50% or less so that lactic acid formation increases at oxygen deliveries that would normally be sufficient to meet the aerobic oxygen demand (2,43). Microcirculatory dysfunction, which impairs oxygen delivery to the tissues, and mitochondrial dysfunction, which impairs oxygen utility, occur in patients with sepsis so that, even in an adequate oxygenation, anaerobic metabolism occurs and pyruvate is shunted toward lactate production (2,21).

Endogenous and exogenous catecholamines are highly associated with lactic acid production in sepsis and septic shock (21). Because aerobic glycolysis is stimulated by high levels of circulating epinephrine. By binding to the  $\beta_2$ -adrenergic receptor on the plasma membrane, epinephrine increases the glycolytic flux both directly and by stimulation of the ubiquitous adenosine triphosphatase sodium/potassium pump ( $\text{Na}^+/\text{K}^+$ -ATPase) and the resultant consumption of ATP (2,4,5,44). Thereby, ATP consumption generates adenosine diphosphate (ADP) via phosphofructokinase stimulation, thus reactivating glycolysis (4). Glycolytic flux can exceed the capacity of PDH to catalyze the conversion of pyruvate into acetyl-CoA. Therefore, pyruvate is inevitably converted to lactate by LDH (*Figure 2*) (2).

Reduced lactate clearance enhanced hyperlactatemia. In sepsis patients whose vital signs were stable, hyperlactatemia might be induced by the dysfunction of hepatic lactate clearance, which is primarily due to PDH inhibition (2,45). In patients with sepsis and low-flow state, chronic liver disease further compromises lactate clearance (5,46). PDH converts pyruvate into acetyl-CoA, allowing pyruvate to enter the mitochondria. PDH activity was decreased in patients with septic muscle and is restored by dichloroacetate, decreasing lactatemia in patients with sepsis (4). However, chronic liver disease alone causes only minimal hyperlactatemia, and kidney failure adds to the impairment in lactate clearance (5).



**Figure 2** Catecholamine-induced glycolytic flux. Circulatory endogenous and exogenous catecholamines bind to  $\beta_2$ -adrenergic receptor in the cell membrane. It increases the production of cyclic AMP (cAMP) and stimulates both direct glycogenolysis, indirectly enhancing glycolysis through ATP sodium/potassium ( $\text{Na}^+/\text{K}^+$ -ATPase) pump activation. This activation requires ATP consumption, and generated ADP reactivates glycolysis, increasing pyruvate and lactate production. ATP, adenosine triphosphatase; ADP, adenosine diphosphatase.

### Role of lactic acid: prognosis marker of sepsis and septic shock

Lactic acidosis results from the accumulation of lactate and protons in the body fluid (5). However, glycolytic flux from glucose to pyruvate generates  $\text{H}^+$ , but conversion of pyruvate to lactate consumes the molar equivalent  $\text{H}^+$  flux; therefore, increased generation of lactate resulting in hyperlactatemia is not, by itself, acidosis, but ATP hydrolysis is the major generator of  $\text{H}^+$  and becomes the source of acidosis (2).

Regardless of the source, increased lactate levels have been associated with worse outcomes (17). Moreover high initial lactate level as well as longer normalization time was associated with increased hazard of mortality (47). Lactic acidosis can cause a reduction of cardiac contractility and vascular hypo-responsiveness to vasopressors through various mechanisms. It is a precipitator of mortality and contributes to a worsening of underlying comorbidities (17). In normotensive patients with sepsis, a lactate concentration more than 4 mmol/L was found to be independently correlated with higher mortality and therefore needs urgent recognition and proper resuscitation (48). However, patients with septic shock with intermediate concentrations

of lactate (2–4 mmol/L) have poorer prognosis than those with normal lactate concentration (49). Moreover, in the severity score, lactate weighted scoring system discriminated mortality significantly than others such as sequential organ failure assessment score (50).

In the Third International Consensus Definitions for Sepsis and Septic Shock, elevated lactate level was included as the third important variable along with hypotension and sustained need for vasopressor therapy to define septic shock (8). The risk adjusted hospital mortality was significantly higher in patients with fluid-resistant hypotension requiring vasopressors and hyperlactatemia compared with those with either hyperlactatemia alone or with fluid resistant hypotension requiring vasopressors but with a lactate level of  $<2$  mmol/L (8).

### Role of lactic acid: lactate-guided septic shock management

Since the time Rivers *et al.* first proposed EGDT, central venous oxygen saturation ( $\text{ScvO}_2$ ) has been widely used as a surrogate marker of the balance between oxygen delivery and consumption (6,51). Moreover, lactate is a useful biomarker of tissue hypoxia and anaerobic metabolism,

reflecting disease severity and lactate clearance, and can be used as a therapeutic target instead of ScvO<sub>2</sub> (51,52). However, current clinical trials have shown that EGDT targeting ScvO<sub>2</sub> fails to improve outcomes compared with usual therapy or lactate-based protocols (9-11,51).

Recent SSC guideline recommended guiding resuscitation to normalize lactate in patients with elevated lactate levels, a marker of tissue hypoperfusion (12). Since 2013, they recommended bundle therapy for sepsis and septic shock; it consisted of four components that should be performed within 3 hours and three components that should be performed within 6 hours. The 3-hour bundle recommended the measurement of lactate levels, while the 6-hour bundle recommended the re-measurement of lactate if the initial lactate level was elevated (53).

The Sepsis-3 task force recommended that the monitoring of lactate should not be used as a guide to evaluate patient's therapeutic response or should not be used as an indicator of illness severity. They recognized that serum lactate measurements are commonly, but not universally, available, especially in developing countries (8). However, there were five randomized controlled trials with 647 patients, which have evaluated the lactate-guided resuscitation of patients who had septic shock (7,13,14,52,54). Results showed that mortality was reduced in patients who received lactate-guided resuscitation compared with those who received resuscitation without lactate monitoring [risk ratio, 0.67; 95% confidence interval (CI), 0.53–0.84] (12). Two other meta-analyses of 647 patients demonstrated a moderate evidence of decreasing mortality in lactate guiding resuscitation strategy, compared with either usual critical care or with ScvO<sub>2</sub> guiding strategy (15,55).

### Lactate versus lactate clearance in patients with sepsis and septic shock

Repeated measurements of blood lactate levels after quantitative resuscitation can serve as a surrogate marker of patient's response to therapy and may be more predictive of mortality than the initial lactate value. While the current surviving sepsis guidelines recommended the re-measurement of lactate levels within 6 hours if the initial lactate levels were elevated, no study has yet examined which time point is the most significant prognostic value of lactate from the recognition of shock at the emergency department in patients with septic shock. Nguyen *et al.* re-measured the lactate levels of patients 6 hours after the initial lactate level check and found that an optimal cutoff lactate clearance

<10% had a sensitivity of 44.7% and specificity of 84.4% for predicting in-hospital mortality (56). Several studies also reported about lactate kinetics and clearance. These studies showed that lactate clearance greater than 10%, based on the initial measurement obtained during the first 2 to 6 hours of resuscitation, predicted survival in patients with septic shock (56-58). Moreover, it was demonstrated that for every 10% increase in lactate clearance, there was a corresponding 11% decrease in in-hospital mortality (56). In general, <10% of lactate clearance 6 hours from initial resuscitation was an independent predictor of in-hospital mortality (57,59). There was a systemic review and meta-analysis about lactate clearance and mortality in critically ill patients. They show that lactate clearance is strongly associated with all-cause mortality and rapid clearance is a strong predictor of survivor (60). However, there is not enough evidence to suggest a specific cutoff value of lactate clearance for resuscitation target goal, because among the recent studies there was a significant heterogeneity such as different time point and severity. Thus, we recommend to the clinicians to follow the current guidelines implementing a guided resuscitation to normalize lactate levels in patients with septic shock, although it supported with weak recommendations and low-quality evidence.

Marty *et al.* measured the lactate levels at time 0 (T<sub>0</sub>), T<sub>6</sub>, T<sub>12</sub>, and T<sub>24</sub> and showed that the best predictor of death was the T<sub>24</sub> clearance (61). Similarly, Herwanto *et al.* investigated the role of 6-, 12-, and 24-h lactate clearance in patients with sepsis and septic shock and showed only the 24-h lactate clearance measurement to be associated with mortality (62). Chertoff *et al.* reported that there was a delay in lactate clearance measurement 24–48 hours after initial resuscitation and that the median clearance of 31.6% was significantly associated with mortality (63). Although some changes in lactate kinetics were clearly significant within 6 to 24 hours after resuscitation, it is currently not possible to define the best time interval between lactate measurements (64).

Furthermore, the interesting issue is whether lactate or lactate clearance is more useful in guiding septic shock management. Lokhandwala *et al.* presented that sensitivity and specificity were significantly different when comparing subsequent lactate levels less than the recommended level *vs.* <10% lactate reduction in the non-vasopressor therapy hyperlactatemia group; however, unlike the complete cohort, no statistical difference was found when comparing a <20% lactate reduction to either of the previous metrics (65). *Table 1* shows a comprehensive summary of the reports

**Table 1** The evidence between the lactate or lactate clearance and its outcomes in patients with sepsis and septic shock

Determine	Population	Type of study	Outcome	Major finding	Interpretation	Year	Ref.
6-hour LC	111 patients in the ED/USA	Single center/prospective Cohort	In-hospital, 30-day, and 60-day mortality	≥10% of LC is associated with decrease in in-hospital, 30-day, and 60-day mortality ( $P \leq 0.001$ , $0.004$ , $0.007$ )	LC is the treatment goal in patients with sepsis	2004	(56)
6-hour LC	166 patients in the ED/USA	Multicenter/prospective Cohort	In-hospital mortality	Mortality of patients with LC $\leq 10\%$ was higher than that of patients with LC $\geq 10\%$ (60% vs. 19%, $P < 0.001$ )	LC is an end point of early sepsis resuscitation	2009	(57)
LC of each 2 hours for 8 hours	348 patients in the ICU/Netherlands	Multicenter/RCT	In-hospital mortality	Patients with LC $\leq 20\%$ or more, measured every 2 hours, on guided treatment had a decreased mortality (HR, 0.61; 95% CI, 0.43–0.87).	Lactate-guided therapy was significantly reduced hospital mortality	2010	(7)
Any LC within 6 hours	187 patients in the ED/USA	Multicenter/prospective, post hoc analysis	In-hospital mortality	Lactate normalization was the strongest predictor of survival (OR, 5.2; 95% CI, 1.7–15.8) followed by LC $\geq 50\%$ (OR, 4.0; 95% CI, 1.6–10.0). However, LC $\geq 10\%$ was not a predictor of survival (OR, 1.6; 95% CI, 0.6–4.4).	Early lactate normalization was the strongest predictor of survival	2013	(66)
6-, 12-, and 24-hour LC and lactate	94 patients in the ICU/France	Single center/prospective Cohort	28-day mortality	LC was higher in the survivor group than that in the non-survivor group for 6 hours (13% vs. –13%, $P = 0.021$ ) and 24 hours (42% vs. –17%, $P < 0.001$ ). A 24-hour LC was an independent predictor of survival (OR, 0.35; 95% CI, 0.01–0.76).	During the first 24 hours in the ICU, LC was associated with a 28-day mortality	2013	(61)
LC during ED stay	243 patients in the ED/USA	Single center/retrospective Cohort	28-day mortality	The lack of serial lactate monitoring was associated with mortality (OR, 2.09; 95% CI, 1.12–3.89). Mortality rates in patients with LC $\leq 0\%$ , 0–20%, 20–40%, and $>40\%$ were 52.6%, 36.4%, 29.6% and 6.3%, respectively ( $P < 0.001$ ) LC	Serial lactate is a necessary biomarker, which should be monitored in ED to achieve high ICU mortality especially when there is no marked LC within 12 hours	2015	(64)
12-hour LC and lactate	400 patients in the ICU/Germany	Single center/retrospective Cohort	ICU mortality	In ICU patients with severe hyperlactatemia ( $\geq 10$ mmol/L), a mortality cutoff of 12-hour LC was 32.8% and mortality in ICU patients with LC $< 32.8\%$ was 96.6%	Sever hyperlactatemia is associated with extremely high ICU mortality	2015	(67)
24–48 hours LC	229 patients in ICU/USA	Single center/retrospective Cohort	30-day mortality	Patients with a median LC of 31.6% and an LC of $\geq 31.6\%$ had a reduced risk of mortality (OR, 0.39; 95% CI, 0.20–0.76)	LC may be a useful noninvasive measurement for guiding in the treatment of patients with late-sepsis	2016	(63)
6-hour LC	90 patients in the ED/Iran	Single center/cross sectional	Mortality	LC of the alive subgroup was 10.9% and that of the other subgroup was 6.88% ( $P < 0.001$ )	Patients with lower LC had a high risk of mortality	2016	(59)
Within 6-hour LC and lactate	202 patients in the ED/USA	Single center/retrospective cohort	In-hospital mortality	Lactate $\geq 4$ mmol/L and LC $< 20\%$ were associated with increased in-hospital mortality (OR: 3.18, 95% CI: 1.24–8.16 and OR: 3.11 and 95% CI: 1.39–6.96, respectively), whereas an LC $< 10\%$ has no significant association	Within the 6 hours management, high lactate and low LC were associated with mortality	2016	(65)

LC, lactate clearance; Lac, lactate; BP, blood pressure; ED, emergency department; ICU, intensive care unit; RCT, randomized controlled trial; HR, hazard ratio; CI, confidence interval.

regarding the roles of lactate as a prognostic indicator of sepsis and septic shock (7,56,57,59,61,63-67).

After the release of Sepsis-3, our knowledge on the prognostic value of lactate kinetics in patients with septic shock (12) remained insufficient as data on the prognostic value of lactate levels and clearance in patients with septic shock is limited. Thus, further research is needed to determine the prognostic value of lactate or lactate kinetics in patients with septic shock, as defined by Sepsis-3.

### Sepsis and septic shock management enhancing lactate clearance

The important management of lactic acidosis is to treat the underlying cause. Thus, sepsis should be treated immediately by early administration of appropriate antibiotics and infection source control (2).

To reduce lactate production, the macro-circulatory oxygen delivery should improve first. The oxygen delivery depends on the patient's cardiac output, hemoglobin, and oxygen saturation. Adequate volume resuscitation using inotropes, red blood cell transfusion, and provision of adequate oxygen supply are essential (2). The use of catecholamine should be limited as stimulation of  $\beta$ -adrenergic receptors increases glycolytic flux (44). In patients with septic shock, reduction of the norepinephrine dose by adding a low-dose vasopressin improved survival by 10% in patients initially receiving  $<15$   $\mu\text{g}/\text{min}$  norepinephrine in the vasopressin and septic shock trial (68). To reduce lactate production caused by overstimulation of the respiratory muscles, a mechanical ventilator support is required and sometimes neuromuscular blocker may help too (2).

To increase lactate removal, hepatic function should be preserved and monitored. Evidence of decreased hepatic function should be sought, and reversible contributors to hepatic dysfunction should be treated (2). In addition, potential hepatotoxins or renal toxins should be avoided. Continuous renal replacement therapy can be performed in critically ill patients with severe lactic acidosis and acute kidney injury (69). Sodium bicarbonate administration should be avoided, because it increases carbon dioxide production and decreases serum ionized calcium, which may decrease ventricular and vascular contractility (2).

Inducing a pyruvate metabolism in Krebs cycle decreases serum lactate levels. Thiamine administration may enhance aerobic metabolism by converting pyruvate to acetyl-CoA (70). Moreover, dichloroacetate lowers

lactate concentrations and improves acidemia when oxygen is available by enhancing the activity of PDH. However, it does not improve the hemodynamic parameters or survival (71).

### Conclusions

In patients with sepsis and septic shock, hyperlactatemia is promoted by glycolytic flux via anaerobic metabolism with tissue hypoxia,  $\beta$ -adrenergic receptor stimulation by endo/exogenous catecholamine, and decreased clearance due to hepatic and renal dysfunction. It reduces cardiac contractility and vascular hypo-responsiveness to vasopressors; however, it is closely associated with poor prognosis. Therefore, during sepsis and septic shock management, lactate levels should be re-measured and normalized. To normalize the lactate levels, we have to reduce glycolytic flux, enhance lactate removal, and induce pyruvate metabolism in the Krebs cycle. However, the most important treatment is to control the underlying infection.

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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