

# Lactic Acidosis in Sepsis: It's Not All Anaerobic

## Implications for Diagnosis and Management



Bandarn Suetrong, MD; and Keith R. Walley, MD

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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**KEY WORDS:** cardiopulmonary resuscitation; sepsis; septic shock; shock

“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.<sup>1</sup> 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.<sup>2</sup> 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<sup>3</sup> and with tissue hypoxia for more than 100 years.<sup>4</sup> In 1961, Huckabee first

**ABBREVIATIONS:** ATP = adenosine triphosphate; NADH = nicotinamide adenine dinucleotide hydride; NAD<sup>+</sup> = oxidized form of nicotinamide adenine dinucleotide; Na<sup>+</sup>-K<sup>+</sup>-ATPase = sodium-potassium-adenosine triphosphatase; RCT = randomized control trial  
**AFFILIATIONS:** Centre for Heart Lung Innovation, University of British Columbia, Vancouver, BC, Canada.

**CORRESPONDENCE TO:** Keith R. Walley, MD, Centre for Heart Lung Innovation, St. Paul's Hospital, 1081 Burrard Street. Vancouver, BC, Canada V6Z 1Y6; e-mail: [Keith.Walley@hli.ubc.ca](mailto:Keith.Walley@hli.ubc.ca)

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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.<sup>5,6</sup> 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<sub>1</sub>, in which hyperlactatemia was associated with certain underlying diseases such as liver failure; B<sub>2</sub>, in which hyperlactatemia was due to drugs or toxins; and B<sub>3</sub>, in which hyperlactatemia was caused by inborn errors of metabolism.<sup>7</sup>

## 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.<sup>8,9</sup> 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.<sup>10,11</sup> Normal lactate production arises mainly from skeletal muscle; skin, brain, intestine, and erythrocytes also contribute.<sup>12</sup> The lungs can create lactate during acute lung injury without tissue hypoxia,<sup>13,14</sup> and leukocytes also generate lactate during phagocytosis or when activated in sepsis.<sup>15</sup> 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 phosphofruktokinase in the Embden-Meyerhof pathway.<sup>16</sup> 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

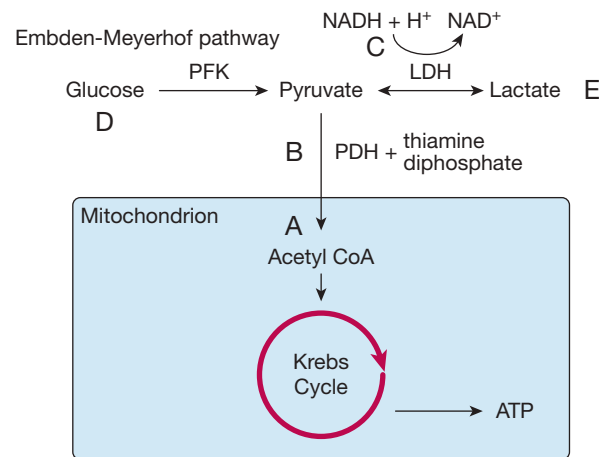


Figure 1 – The pathway from glycolysis to pyruvate to lactate production is illustrated, with key features leading to increased lactate concentrations labeled in red. A, Lactic acidosis from tissue hypoxia. Anaerobic metabolism reduces flux through the Krebs cycle so pyruvate is shunted toward lactate. 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<sup>+</sup>, 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<sup>+</sup> = nicotinamide adenine dinucleotide; PDH = pyruvate dehydrogenase; PFK = phosphofruktokinase.

(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<sup>+</sup>. Conditions which result in a reducing cellular environment (elevated NADH/oxidized form of nicotinamide adenine dinucleotide [NAD<sup>+</sup>]), 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<sup>+</sup> 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 gluconeogenesis (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,  $\beta$ -adrenergic stimulation, and shock.<sup>17,18</sup> The brain also consumes lactate when metabolic requirements are increased.<sup>19</sup> 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<sup>+</sup>, but conversion of pyruvate to lactate consumes the molar equivalent H<sup>+</sup> 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<sup>+</sup> (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<sup>+</sup> 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.<sup>20</sup> In patients with vasopressor-dependent septic shock, Dugas and colleagues<sup>21</sup> 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.<sup>22</sup> 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,<sup>23</sup> 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).<sup>6</sup> 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).<sup>24,25</sup> This sloped relationship was subsequently found to be artifactual,<sup>23</sup> and clinical trials aiming to increase oxygen delivery to meet potential unmet oxygen demand did not improve survival and may have increased mortality.<sup>26</sup> 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.<sup>27-31</sup> 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
Glucose-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

oxygen delivery and death is very short, less than 1 h,<sup>23</sup> 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

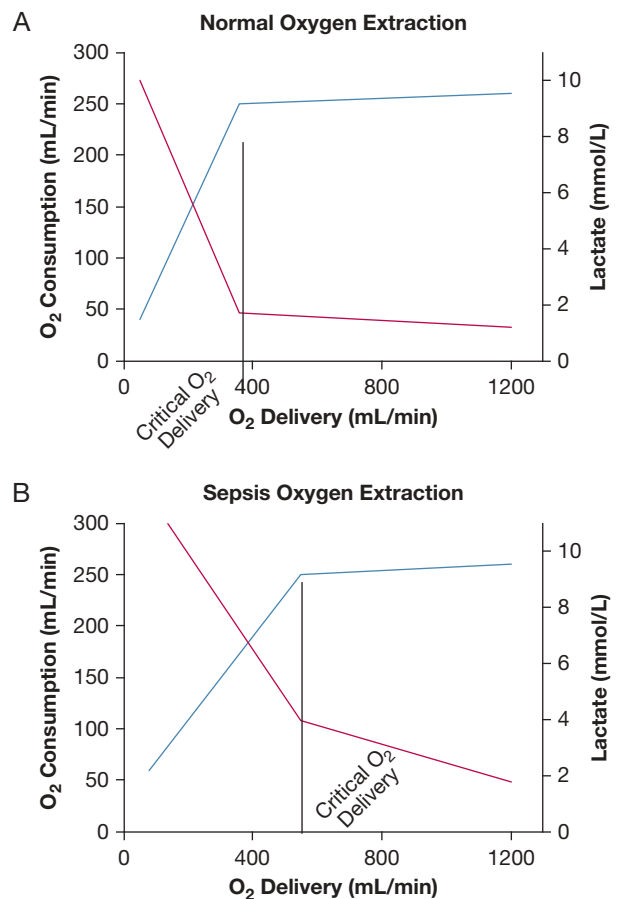


Figure 2 – A, Normal oxygen ( $O_2$ ) extraction. When oxygen delivery (cardiac output multiplied by oxygen carrying capacity of the blood) decreases from normal high levels (approximately 1,000 mL/min), there is no significant change in oxygen consumption (basal metabolism) (blue line) until oxygen 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.

decreasing mortality of septic shock from 40% to 60% to approximately 20% reported in recent randomized controlled trials (RCTs).<sup>32,33</sup> 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.<sup>23</sup> 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.<sup>34</sup> Furthermore, many patients with sepsis or septic shock have normal lactate:pyruvate ratios while they had lactic acidosis.<sup>27,30,31</sup> Lactic acidosis can develop without tissue hypoxia in various tissues, such as muscle, intestinal mucosa, heart, lung, and brain.<sup>35-38</sup> Interestingly, esmolol administration in patients with septic shock reduced oxygen delivery but also reduced plasma lactate concentrations.<sup>39</sup> 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).<sup>40</sup> 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).<sup>41</sup> Endothelial inflammatory processes result in microcirculatory dysfunction so that regional and microregional oxygen delivery is not matched with demand.<sup>42</sup> The resultant heterogeneous regions of tissue hypoxia generate lactate.<sup>43,44</sup> 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 $\beta$ 2 Stimulation*

In patients with sepsis, the resting metabolic rate is increased,<sup>45</sup> 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 ( $\text{Na}^+\text{-K}^+\text{-ATPase}$ ) activity is increased and is associated with increased glycolytic flux through  $\beta$ 2 stimulation.<sup>46-48</sup> These results are supported by the observation that lactate production is reduced by  $\beta$ 2 antagonists such as esmolol and by  $\text{Na}^+\text{-K}^+\text{-ATPase}$  inhibitors (ouabain) in septic shock or when glycolysis is induced by epinephrine.<sup>49-51</sup>

#### *Diminished Lactate Clearance*

In hemodynamically stable patients with sepsis, hyperlactatemia might be the result of impaired lactate clearance rather than overproduction.<sup>52</sup> Although impaired hepatic lactate clearance does not occur in all patients with sepsis,<sup>53,54</sup> 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,<sup>55</sup> 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.<sup>56</sup> Even in the setting of lactic acidosis, other causes of an increased anion gap should be considered.<sup>57</sup> 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).<sup>58</sup> 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.<sup>59</sup>



Use of blood lactate as a triage tool in the acute care setting is effective, particularly in patients with normal hemodynamic parameters.<sup>60</sup> 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.<sup>61</sup> In hemodynamically stable patients with febrile neutropenia, hyperlactatemia is associated with development of septic shock within 48 h.<sup>62</sup>

### *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.<sup>63,64</sup>

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 resuscitation.<sup>22</sup> However, in patients with septic shock, intermediate concentrations of lactate (2-4 mmol/L)<sup>65</sup> or even within the high end of the normal range (1.4-2.3 mmol/L)<sup>66</sup> 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<sup>67</sup> 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.<sup>68</sup> 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.<sup>69</sup> 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<sup>70</sup> 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.<sup>71,72</sup> Jones and colleagues<sup>73</sup> 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).<sup>74</sup> 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.<sup>32,33</sup> Accordingly, they should generally be used together and in conjunction with other tools such as echocardiography<sup>75,76</sup> or venoarterial carbon dioxide difference<sup>77-79</sup> 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<sup>80</sup> 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,<sup>81</sup> protein C<sup>82</sup>). 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.<sup>48</sup> For example, administration of epinephrine in septic shock is associated with as much as a doubling of lactate concentration compared with norepinephrine.<sup>83,84</sup> Choosing a vasopressor with less beta-adrenergic activity may also be helpful by reducing the incidence of arrhythmias.<sup>85</sup> 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.<sup>86</sup> Administration of thiamine may increase aerobic metabolism<sup>87</sup> 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.<sup>88</sup> 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).<sup>61</sup>

**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.<sup>89</sup> 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.<sup>90</sup>

## 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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## References

1. Mizock BA, Falk JL. Lactic acidosis in critical illness. *Crit Care Med*. 1992;1(20):80-93.
2. Gladden LB. Lactate metabolism – a new paradigm for the third millennium. *J Physiol*. 2004;558:5-30.
3. Fuller BM, Dellinger RP. Lactate as a hemodynamic marker in the critically ill. *Curr Opin Crit Care*. 2012;18(3):267-272.
4. Kompanje EJ, Jansen TC, van der Hoven B, Bakker J. The first demonstration of lactic acid in human blood in shock by Johann Joseph Scherer (1814-1869) in January 1843. *Intensive Care Med*. 2007;33(11):1967-1971.
5. Huckabee WE. Abnormal resting blood lactate. I. The significance of hyperlactatemia in hospitalized patients. *Am J Med*. 1961;30:833-839.
6. Huckabee WE. Abnormal resting blood lactate. II. Lactic acidosis. *Am J Med*. 1961;30:840-848.
7. Cohen RD, Woods HF. *Clinical and Biochemical Aspects of Lactic Acidosis*. Oxford, UK: Blackwell Scientific; 1976.
8. Brooks GA. Cell-cell and intracellular lactate shuttles. *J Physiol*. 2009;587(23):5591-5600.
9. Brooks GA. Intra- and extra-cellular lactate shuttles. *Med Sci Sports Exerc*. 2000;32(4):790-799.
10. Leverve XM, Mustafa I. Lactate: a key metabolite in the intercellular metabolic interplay. *Crit Care*. 2002;6(4):284-285.
11. Van Hall G. Lactate as a fuel for mitochondrial respiration. *Acta Physiol Scand*. 2000;168(4):643-656.
12. Levy B. Lactate and shock state: the metabolic view. *Curr Opin Crit Care*. 2006;12(4):315-321.
13. Kellum JA, Kramer DJ, Lee K, Mankad S, Bellomo R, Pinsky MR. Release of lactate by the lung in acute lung injury. *Chest*. 1997; 111(5):1301-1305.
14. Iscra F, Gullo A, Biolo G. Bench-to bedside review: lactate and the lung. *Crit Care*. 2002;6(4):327-329.
15. Borregaard N, Herlin T. Energy metabolism of human neutrophils during phagocytosis. *J Clin Invest*. 1982;70(3):550-557.
16. Bar-Even A, Flahholz A, Noor E, Milo R. Rethinking glycolysis: on the biochemical logic of metabolic pathways. *Nat Chem Biol*. 2012;8(6):509-517.
17. Stanley WC. Myocardial lactate metabolism during exercise. *Med Sci Sports Exerc*. 1991;23(8):920-924.
18. Kline JA, Thornton LR, Lopaschuk GD, Barbee RW, Watts JA. Lactate improves cardiac efficiency after hemorrhagic shock. *Shock*. 2000;14:215-221.
19. van Hall G, Stromstad M, Rasmussen P, et al. Blood lactate is an important energy source for the human brain. *J Cerebr Blood Flow Metab*. 2009;29:1121-1129.
20. Juneja D, Singh O, Dang R. Admission hyperlactatemia: causes, incidence, and impact on outcome of patients admitted in a general medical intensive care unit. *J Crit Care*. 2011;26(3):316-320.
21. Dugas AF, Mackenhauer J, Saliccioli JD, Cocchi MN, Gautam S, Donnino MW. Prevalence and characteristics of nonlactate and lactate expressors in septic shock. *J Crit Care*. 2012;27(4):344-350.
22. Casserly B, Phillips GS, Schorr C, et al. Lactate measurements in sepsis-induced tissue hypoperfusion: results from the Surviving Sepsis Campaign Database. *Crit Care Med*. 2015;43(3):567-573.
23. Ronco JJ, Fenwick JC, Tweeddalle MG, et al. Identification of the critical oxygen delivery for anaerobic metabolism in critically ill septic and nonseptic humans. *JAMA*. 1993;270(14):1724-1730.
24. Astiz ME, Rackow EC, Falk JL, Kaufman BS, Weil MH. Oxygen delivery and consumption in patients with hyperdynamic septic shock. *Crit Care Med*. 1987;15:26-28.
25. Friedman G, De Backer D, Shahla M, Vincent JL. Oxygen supply dependency can characterize septic shock. *Intensive Care Med*. 1998;24(2):118-123.
26. Hayes MA, Timmins AC, Yau EH, Palazzo M, Hinds CJ, Watson D. Elevation of systemic oxygen delivery in the treatment of critically ill patients. *N Engl J Med*. 1994;330(24):1717-1722.
27. Suistomaa M, Ruokonen E, Kari A, Takala J. Time-pattern of lactate and lactate to pyruvate ratio in the first 24 hours of intensive care emergency admissions. *Shock*. 2000;14(1):8-12.
28. Levy B, Sadoune LO, Gelot AM, Bollaert PE, Nabet P, Larcen A. Evolution of lactate/pyruvate and arterial ketone body ratios in the early course of catecholamine-treated septic shock. *Crit Care Med*. 2000;28(1):114-119.
29. Gallet D, Goudable J, Vedrinne JM, Viale JP, Annat G. Increased lactate/pyruvate ratio with normal beta-hydroxybutyrate/ acetoacetate ratio and lack of oxygen supply dependency in a patient with fatal septic shock. *Intensive Care Med*. 1997;23(1): 114-116.
30. Dugas MA, Proulx F, de Jaeger A, Lacroix J, Lambert M. Markers of tissue hypoperfusion in pediatric septic shock. *Intensive Care Med*. 2000;26(1):75-83.
31. Rimachi R, Bruzzi de Carvahlo F, et al. Lactate/pyruvate ratio as a marker of tissue hypoxia in circulatory and septic shock. *Anaesth Intensive Care*. 2012;40(3):427-432.
32. ProCESS Investigators, Yealy DM, Kellum JA, Huang DT, et al. A randomized trial of protocol-based care for early septic shock. *N Engl J Med*. 2014;370(18):1683-1693.
33. ARISE Investigators; ANZICS Clinical Trials Group, Peake SL, Delaney A, Bailey M, et al. Goal-directed resuscitation for patients with early septic shock. *N Engl J Med*. 2014;371(16):1496-1506.
34. Astiz ME, Rackow EC, Kaufman B, Falk JL, Weil MH. Relationship of oxygen delivery and mixed venous oxygenation to lactic acidosis in patients with sepsis and acute myocardial infarction. *Crit Care Med*. 1988;16(7):655-658.
35. Sair M, Etherington PJ, Peter Winlove C, Evans TW. Tissue oxygenation and perfusion in patients with systemic sepsis. *Crit Care Med*. 2001;29(7):1343-1349.
36. VanderMeer TJ, Wang H, Fink MP. Endotoxemia causes ileal mucosal acidosis in the absence of mucosal hypoxia in a normodynamic porcine model of septic shock. *Crit Care Med*. 1995;23(7):1217-1226.
37. Opdam H, Bellomo R. Oxygen consumption and lactate release by the lung after cardiopulmonary bypass and during septic shock. *Crit Care Resusc*. 2000;2(3):181-187.



38. Gore DC, Jahoor F, Hibbert JM, DeMaria EJ. Lactic acidosis during sepsis is related to increased pyruvate production, not deficits in tissue oxygen availability. *Ann Surg*. 1996;224(1):97-102.
39. Morelli A, Ertmer C, Westphal M, et al. Effect of heart rate control with esmolol on hemodynamic and clinical outcomes in patients with septic shock: a randomized clinical trial. *JAMA*. 2013;310(16):1683-1691.
40. Schumacker PT, Samsel RW. Oxygen delivery and uptake by peripheral tissues: physiology and pathophysiology. *Crit Care Clin*. 1989;5(2):255-269.
41. Herbertson MJ, Werner HA, Russell JA, Iversen K, Walley KR. Myocardial oxygen extraction ratio is decreased during endotoxemia in pigs. *J Appl Physiol* (1985). 1995;79(2):479-486.
42. Walley KR. Heterogeneity of oxygen delivery impairs oxygen extraction by peripheral tissues: theory. *J Appl Physiol* (1985). 1996;81(2):885-894.
43. Humer MF, Phang PT, Friesen BP, Allard MF, Goddard CM, Walley KR. Heterogeneity of gut capillary transit times and impaired gut oxygen extraction in endotoxemic pigs. *J Appl Physiol* (1985). 1996;81(2):895-904.
44. Bateman RM, Walley KR. Microvascular resuscitation as a therapeutic goal in severe sepsis. *Crit Care*. 2005;9(Suppl 4):S27-S32.
45. Kreymann G, Grosser S, Buggisch P, Gottschall C, Matthaei S, Greten H. Oxygen consumption and resting metabolic rate in sepsis, sepsis syndrome, and septic shock. *Crit Care Med*. 1993;21(7):1012-1019.
46. McCarter FD, Nierman SR, James JH, et al. Role of skeletal muscle Na<sup>+</sup>-K<sup>+</sup> ATPase activity in increased lactate production in sub-acute sepsis. *Life Sci*. 2002;70(16):1875-1888.
47. Bundgaard H, Kjeldsen K, Suarez Krabbe K, et al. Endotoxemia stimulates skeletal muscle Na<sup>+</sup>-K<sup>+</sup>-ATPase and raises blood lactate under aerobic conditions in humans. *Am J Physiol Heart Circ Physiol*. 2003;284(3):H1028-H1034.
48. Levy B, Desebbe O, Montemont C, Gibot S. Increased aerobic glycolysis through beta2 stimulation is a common mechanism involved in lactate formation during shock states. *Shock*. 2008;30(4):417-421.
49. Levy B, Gibot S, Franck P, Cravoisy A, Bollaert PE. Relation between muscle Na<sup>+</sup>-K<sup>+</sup> ATPase activity and raised lactate concentrations in septic shock: a prospective study. *Lancet*. 2005;365(9462):871-875.
50. James JH, Fang CH, Schrantz SJ, Hasselgren PO, Paul RJ, Fischer JE. Linkage of aerobic glycolysis to sodium-potassium transport in rat skeletal muscle. Implications for increased muscle lactate production in sepsis. *J Clin Invest*. 1996;98(10):2388-2397.
51. James JH, Wagner KR, King JK, et al. Stimulation of both aerobic glycolysis and Na(+)-K(+)-ATPase activity in skeletal muscle by epinephrine or amylin. *Am J Physiol*. 1999;277:E176-E186.
52. Levraut J, Ciebiera JP, Chave S, et al. Mild hyperlactatemia in stable septic patients is due to impaired lactate clearance rather than overproduction. *Am J Respir Crit Care Med*. 1998;157:1021-1026.
53. Revelly JP, Tappy L, Martinez A, et al. Lactate and glucose metabolism in severe sepsis and cardiogenic shock. *Crit Care Med*. 2005;33(10):2235-2240.
54. Michaeli B, Martinez A, Revelly JP, et al. Effects of endotoxin on lactate metabolism in humans. *Crit Care*. 2012;16(4):R139.
55. Berkman M, Ufberg J, Nathanson LA, Shapiro NI. Anion gap as a screening tool for elevated lactate in patients with an increased risk of developing sepsis in the emergency department. *J Emerg Med*. 2009;36(4):391-394.
56. Iberti TJ, Leibowitz AB, Papadakos PJ, Fischer EP. Low sensitivity of the anion gap as a screen to detect hyperlactatemia in critically ill patients. *Crit Care Med*. 1990;18:275-277.
57. Kraut JA, Madias NE. Serum anion gap: its uses and limitations in clinical medicine. *Clin J Am Soc Nephrol*. 2007;2(1):162-174.
58. Gallagher EJ, Rodriguez K, Touger M. Agreement between peripheral venous and arterial lactate concentrations. *Ann Emerg Med*. 1997;29(4):479-483.
59. Noordally O, Vincent JL. Evaluation of a new, rapid lactate analyzer in critical care. *Intensive Care Med*. 1999;25(5):508-513.
60. Contenti J, Corraze H, Lemoël F, Levraut J. Effectiveness of arterial, venous, and capillary blood lactate as a sepsis triage tool in ED patients. *Am J Emerg Med*. 2015;33(2):167-172.
61. Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med*. 2013;39(2):165-228.
62. Mato AR, Luger SM, Heitjan DF, et al. Elevation in serum lactate at the time of febrile neutropenia (FN) in hemodynamically-stable patients with hematologic malignancies (HM) is associated with the development of septic shock within 48 hours. *Cancer Biol Ther*. 2010;9(8):585-589.
63. 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.
64. Hernandez G, Castro R, Romero C, et al. Persistent sepsis-induced hypotension without hyperlactatemia: is it really septic shock? *J Crit Care*. 2011;26(4):435.e9-e14.
65. Tang Y, Choi J, Kim D, et al. Clinical predictors of adverse outcome in severe sepsis patients with lactate 2-4 mM admitted to the hospital. *QJM*. 2015;108(4):279-287.
66. Wacharasint P, Nakada TA, Boyd JH, Russell JA, Walley KR. Normal-range blood lactate concentration in septic shock is prognostic and predictive. *Shock*. 2012;38(1):4-10.
67. 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(6):752-761.
68. 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(1):55-61.
69. Omar S, Burchard AT, Lundgren AC, Mathivha LR, Dulhunty JM. The relationship between blood lactate and survival following the use of adrenaline in the treatment of septic shock. *Anaesth Intensive Care*. 2011;39(3):449-455.
70. 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(19):1368-1377.
71. Arnold RC, Shapiro NI, Jones AE, et al. Multicenter study of early lactate clearance as a determinant of survival in patients with presumed sepsis. *Shock*. 2009;32(1):35-39.
72. 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(8):1637-1642.
73. Jones AE, Shapiro NI, Trzeciak S, Arnold RC, Claremont HA, Kline JA. Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. *JAMA*. 2010;303(8):739-746.
74. Puskarich MA, Trzeciak S, Shapiro NI, et al. Prognostic value and agreement of achieving lactate clearance or central venous oxygen saturation goals during early sepsis resuscitation. *Acad Emerg Med*. 2012;19(3):252-258.
75. Boyd JH, Walley KR. The role of echocardiography in hemodynamic monitoring. *Curr Opin Crit Care*. 2009;15(3):239-243.
76. Griffie MJ, Merkel MJ, Wei KS. The role of echocardiography in hemodynamic assessment of septic shock. *Crit Care Clin*. 2010;26(2):365-382.
77. Mallat J, Pepy F, Lemyze M, et al. Central venous-to-arterial carbon dioxide partial pressure difference in early resuscitation from septic shock: a prospective observational study. *Eur J Anaesthesiol*. 2014;31(7):371-380.
78. Du W, Liu DW, Wang XT, et al. Combining central venous-to-arterial partial pressure of carbon dioxide difference and central venous oxygen saturation to guide resuscitation in septic shock. *J Crit Care*. 2013;28(6):1110.e1-e5.

79. Vallée F, Vallet B, Mathe O, et al. Central venous-to-arterial carbon dioxide difference: an additional target for goal-directed therapy in septic shock? *Intensive Care Med.* 2008;34(12):2218-2225.
80. Boerma EC, Mathura KR, van der Voort PH, Spronk PE, Ince C. Quantifying bedside-derived imaging of microcirculatory abnormalities in septic patients: a prospective validation study. *Crit Care.* 2005;9(6):R601-R606.
81. Spronk PE, Ince C, Gardien MJ, Mathura KR, Oudemans-van Straaten HM, Zandstra DF. Nitroglycerin in septic shock after intravascular volume resuscitation. *Lancet.* 2002;360(9343):1395-1396.
82. Hoffmann JN, Vollmar B, Laschke MW, et al. Microhemodynamic and cellular mechanisms of activated protein C action during endotoxemia. *Crit Care Med.* 2004;32(4):1011-1017.
83. Myburgh JA, Higgins A, Jovanovska A, Lipman J, Ramakrishnan N, Santamaria J, and the CAT Study Investigators. A comparison of epinephrine and norepinephrine in critically ill patients. *Intens Care Med.* 2008;34(12):2226-2234.
84. Annane D, Vignon P, Renault A, et al; CATS Study Group. Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial. *Lancet.* 2007;370(9588):676-684.
85. De Backer D, Biston P, Devriendt J, et al; SOAP II Investigators. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med.* 2010;362(9):779-789.
86. Russell JA, Walley KR, Singer J, et al; VASST Investigators. Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med.* 2008;358(9):877-887.
87. Berg KM, Gautam S, Saliccioli JD, Giberson T, Saindon B, Donnino MW. Intravenous thiamine is associated with increased oxygen consumption in critically ill patients with preserved cardiac index. *Ann Am Thorac Soc.* 2014;11(10):1597-1601.
88. Cooper DJ, Walley KR, Wiggs BR, Russell JA. Bicarbonate does not improve hemodynamics in critically ill patients who have lactic acidosis. A prospective, controlled clinical study. *Ann Intern Med.* 1990;112(7):492-498.
89. De Corte W, Vuylsteke S, De Waele JJ, et al. Severe lactic acidosis in critically ill patients with acute kidney injury treated with renal replacement therapy. *J Crit Care.* 2014;29(4):650-655.
90. Stacpoole PW, Wright EC, Baumgartner TG, et al. A controlled clinical trial of dichloroacetate for treatment of lactic acidosis in adults. The Dichloroacetate-Lactic Acidosis Study Group. *N Engl J Med.* 1992;327(22):1564-1569.