Blood lactate levels in sepsis: in 8 questions

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Purpose of review
Blood lactate concentrations are frequently measured in critically ill patients and have important prognostic value. Here, we review some key questions related to their clinical use in sepsis.

Recent findings
Despite the metabolic hurdles, measuring lactate concentrations remains very informative in clinical practice. Although blood lactate levels change too slowly to represent the only guide to resuscitation, serial lactate levels can help to define the patient's trajectory and encourage a review of the therapeutic strategy if they remain stable or increase over time.

Summary
Lactate concentrations respond too slowly to be used to guide acute changes in therapy, but can help evaluate overall response. Hyperlactatemia should not be considered as a problem in itself, but as a warning of altered cell function.

Keywords
anaerobic metabolism, microcirculation, pyruvate, tissue hypoxia

INTRODUCTION

Measurement of blood lactate concentrations can be very useful in septic shock, as in other forms of shock, providing a marker of altered tissue perfusion, disease severity, and prognosis [1–4,5▪]. Moreover, the evaluation of serial lactate concentrations can help monitor a patient's response to treatment. The normal blood lactate concentration is about 1 mEq/l (or mMol/l), and an increase to 1.5 mEq/l (hyperlactatemia) or above is an important alarm signal [6]. Septic shock is associated with a lactate concentration above an arbitrary value of 2 mEq/L [7].

In this article, we will provide an up-to-date review on the role of blood lactate measurement in patients with sepsis by providing answers to eight important questions.

Question 1: Does hyperlactatemia always reflect anaerobic metabolism in sepsis?

Answer: No.

Under physiological conditions, lactate is a normal end-product of glucose metabolism via two main pathways: glycolysis and oxidative phosphorylation. Glycolysis is a process that generates small amounts of adenosine triphosphate (ATP), but because of its speed, can create significant energy. Oxidative phosphorylation is the process that involves the Krebs cycle. This is a slower process than glycolysis and requires oxygen to metabolize the pyruvate generated from glucose. In shock, including septic shock, lack of oxygen prohibits the metabolism of pyruvate in the Krebs cycle, and anaerobic metabolism converts it to lactate via the enzyme lactate dehydrogenase. Indeed, hypoxic states are characterized by inadequate oxygen supply to the cells such that supply is unable to match demand. Experimental studies, including models of endotoxin administration or bacterial sepsis, have clearly documented that an acute and profound reduction in global oxygen delivery (DO_2) results in a decrease in oxygen uptake (VO_2) and that the critical DO_2 value at which this occurs is also the

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KEY POINTS

- Lactate concentrations are increased in patients with shock and associated with organ dysfunction and greater mortality.
- Changes in blood lactate concentrations are determined by the balance between production of lactate and its uptake or elimination.
- Hyperlactatemia should be considered a warning sign of altered cell function.
- A decrease in lactate levels during resuscitation of a patient with septic shock suggests likely clinical improvement, but patient management should never be based on one variable alone.
- Serial lactate concentrations change too slowly to help directly guide acute changes in therapy, but can help orient the overall therapeutic strategy.

moment when lactate concentrations start to increase sharply.

In sepsis, the altered microcirculation, with increased heterogeneity of flow, further limits tissue oxygenation [8]. In cardiac surgery patients, who have similar microcirculatory changes to those seen in sepsis, greater severity of microcirculatory impairment was associated with significantly higher blood lactate concentrations [9▪]. In patients with increased lactate production, liver dysfunction, frequently present in patients with sepsis, may reduce the capacity to clear lactate, thus contribute to raised blood lactate concentrations. However, liver failure alone cannot result in hyperlactatemia [10]. The kidneys also metabolize lactate but to a much lesser extent such that renal failure does not have a major impact on blood lactate concentrations.

In addition metabolic changes in sepsis, such as inhibition of pyruvate dehydrogenase and increased Na/K pump activity, may result in increased lactate concentrations despite the presence of adequate tissue oxygen availability. Another possible reason for increased lactate in sepsis is increased glycolysis, a process that is stimulated by beta-adrenergic agents and alkalemia among other causes (Table 1). Other causes of hyperlactatemia, which are less relevant to our discussion in sepsis, also exist. For example, metformin use can cause hyperlactatemia by interfering with oxidative phosphorylation [11▪].

Table 1. Main causes of hyperlactatemia in sepsis

Tissue hypoxia
Increased glycolysis
Adrenergic stimulation
Pyruvate dehydrogenase inhibition
Altered clearance (by the liver)

If there are associated metabolic alterations, the lactate/pyruvate (L/P) ratio will be increased above the normal value of around 10/1, whereas with increased glycolysis, it is the excess pyruvate that can lead to hyperlactatemia, with an unchanged L/P ratio. Separation of hyperlactatemia into hypoxic and nonhypoxic causes based on the L/P ratio has been attempted, but pyruvate measurements are difficult and prone to technical problems. Moreover, the two types (hypoxic and nonhypoxic) usually coexist. Studies have shown that pyruvate concentrations and/or the L/P ratio have limited clinical use.

Question 2: Does vasoactive drug therapy contribute to increased lactate concentrations?

Answer: Yes and no.

Catecholamines with strong beta-adrenergic activity can stimulate cellular metabolism and thereby increase lactate concentrations. This is particularly the case with administration of epinephrine, which is now relatively uncommon. Any changes in lactate concentration associated with vasoactive drug administration would, however, only amplify the alarm signal, because the sicker the patient, the greater the need for vasoactive agents and the higher the lactate concentrations. It would be a clinical error to overestimate this phenomenon and to assume that a patient's hyperlactatemia is solely the result of administration of adrenergic agents without an associated decrease in tissue perfusion.

Question 3: Can blood lactate concentrations be considered as markers of sepsis?

Answer: No.

Lactate concentrations are increased in *all* forms of shock [12], whether the main underlying pathophysiologic alteration is hypovolemic, cardiogenic, obstructive or distributive. The presence of hyperlactatemia does not provide any information about the cause or type of the underlying shock.

Despite the contribution of cellular alterations to sepsis-related hyperlactatemia, few patients with sepsis will have elevated lactate concentrations if their tissue perfusion is normal, except perhaps if lactate concentrations remain above normal values in a patient who has been fully resuscitated, because they have not yet had time to return to normal [6,13]. Hyperlactatemia should not be considered

as being due to cellular alterations alone; reduced tissue perfusion is an important factor.

Question 4: Can lactate concentrations predict outcome?

Answer: Yes, definitely.

Numerous studies have shown that lactate concentrations are associated with patient survival and/or organ failure in both adult and pediatric sepsis [1,3,4,5▪]. Importantly, even early measurements are predictive of outcome [3].

Question 5: Should we combine lactate and SvO_2 concentrations?

Answer: Yes and no.

Patient management should never be based on one variable alone, and adding mixed (SvO_2) or central ($ScvO_2$) venous oxygen saturation values, a marker of inadequate oxygen delivery, to lactate concentrations can help identify tissue hypoperfusion and may lead to beneficial clinical interventions. However, one cannot expect lactate and $S(c)vO_2$ to be correlated [14]. During resuscitation, changes in $S(c)vO_2$ during an increase in DO_2 (e.g., with fluids or dobutamine administration) are much faster than changes in lactate concentrations, so that the relationship between the two is difficult to interpret [15]; combining these two variables is therefore not straightforward.

It may be attractive to consider that a high SvO_2 (or $ScvO_2$ when only a central venous catheter is available) in the presence of elevated lactate concentrations could reflect a severe alteration in cellular function, wherein the cells can no longer use oxygen (a process sometimes called 'cytopathic hypoxia'). Unfortunately, a high SvO_2 can also be due to microvascular alterations. One may consider that an increase in DO_2 will increase cellular metabolism in the presence of hemodynamic alterations and not in the presence of cellular alterations. The former is indeed what characterizes VO_2/DO_2 dependency in shock states. Unfortunately, these measurements are not easily applied at the bedside.

Question 6: Is it valuable to repeat the measurement of blood lactate concentrations?

Answer: Yes, definitely.

Following the time course of blood lactate concentrations can provide valuable information, especially when the evolution of the patient's condition is uncertain. Some people have used the term 'lactate clearance' to describe the decrease in lactate concentrations over time, but this is inappropriate, because hyperlactatemia is determined more by increased production than by decreased elimination [16]. A recent study showed that increased production and decreased elimination can coexist also in malaria [17]. Reference to lactate clearance can also lead to confusion when a patient is receiving renal replacement therapy. Moreover, an increase in lactate concentrations over time would represent 'negative clearance' [6]. To separate the effects of decreased lactate elimination from increased production would require infusion of a highly concentrated lactate solution or the administration of radiolabeled lactate [18▪], which, although potentially of interest to study the mechanisms of lactate kinetics, would be of little practical use in routine patient care.

Lactate concentrations change relatively slowly, because lactate metabolism takes time. The first study on serial lactate concentrations in 1993 [13] showed that in the best case scenario of a rapid response to fluid therapy, lactate concentrations decreased by 10% in one hour; higher rates of decline are therefore unlikely. Therefore, measurement of lactate concentrations every one or two hours is recommended [6]. Some monitoring systems may allow more frequent assessment of blood lactate concentrations, but it is unclear whether this holds any advantage over hourly measurements. Importantly, because the majority of lactate is metabolized in the liver, evaluating the time course in patients with advanced liver dysfunction is more complex.

Question 7: Can assessment of serial lactate concentrations be used to guide therapy?

Answer: Yes and no.

Jansen *et al.* [19] showed that evaluating lactate kinetics over time could be used to influence therapy, but, as already stated, one should not focus on a single variable to guide therapy, and this applies to lactate as well as to other variables. Because changes in lactate concentrations over time are slow and variable, they are of little use alone to guide therapy in the critically ill patient in whom rapid therapeutic decisions are often needed as hemodynamic status alters quickly. In a post hoc analysis of the ANDROMEDA-SHOCK study, resuscitation guided by blood lactate levels in patients with normal capillary refill time, a much more rapid indicator of tissue perfusion than lactate,

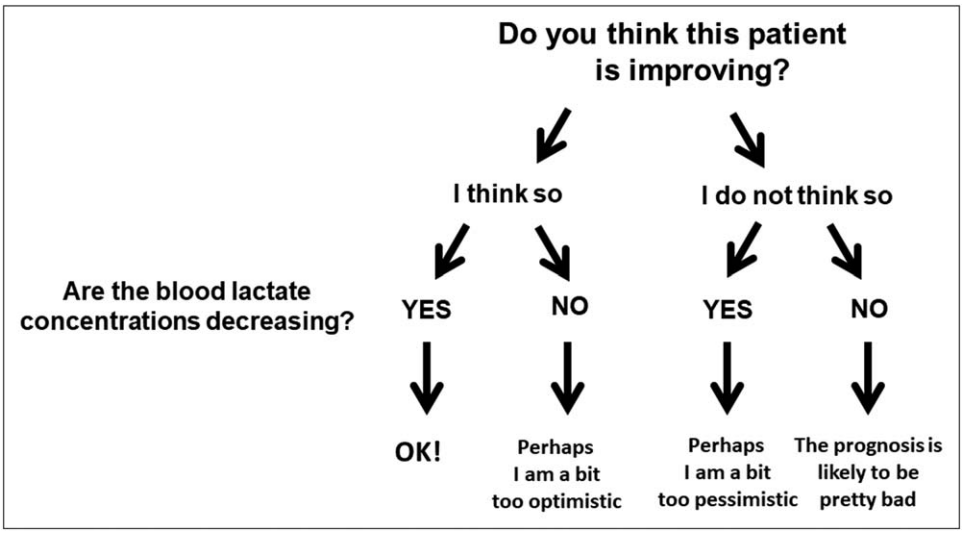

FIGURE 1. A pragmatic approach to help guide therapy in critically ill patients by measuring lactate concentrations.

was associated with more organ dysfunction [20▪▪]. Nevertheless, trends in lactate concentrations in combination with other variables can help indicate response to treatment. A pragmatic approach to use of lactate concentrations to help guide therapy in critically ill patients is proposed in Fig. 1.

Question 8: Is lactate toxic?

Answer: Not really.

Lactate in and of itself is not a toxic molecule and is used as a fuel for cells via the mono-carboxylate transporters; it may even have important beneficial regulatory properties [21▪]. When lactate concentrations increase in the blood, they increase also in the cells and influence their function. Lactate increases T helper 1 cell differentiation and the production of interferon-γ and modifies macrophage function. These effects may also have some immunosuppressive action [22], and may therefore contribute to the acquired immunosuppression (sometimes called 'immunoparalysis') of sepsis, although the implications of this possible effect in patients with sepsis are not well-defined.

It is unclear whether improving lactate metabolism can improve outcome. The administration of dichloroacetate can decrease lactate concentrations, but this was not associated with improved hemodynamics or survival [23]. There was no correlation between thiamine, a co-factor in aerobic metabolism, and lactate concentrations [24] and thiamine supplementation was not associated with improved outcomes in a small pilot study of patients with septic shock [25]. There has been some recent interest in the administration of hypertonic lactate. In experimental sepsis, it was suggested that hypertonic lactate infusion could improve the microcirculation [26], but in a larger animal model of hyperdynamic sepsis, Su *et al.* [27] observed harmful effects.

The goal of therapy should not *per se* be to decrease lactate concentrations, but to intervene in the process that leads to increased lactate concentrations if this process is likely to be harmful to the patient, for example, tissue hypoxia.

CONCLUSION

Measuring lactate concentrations in sepsis provides important and useful information in terms of prognosis and a patient's response to treatment. Serial lactate concentrations may not help directly guide acute changes in therapy, but may help orient the overall therapeutic strategy. Hyperlactatemia should not be considered as a problem in itself but as a reflection of altered cell function where the cause of this alteration relates to the clinical actions needed to improve the patient's condition and outcome.

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Conflicts of interest

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- ■ of special interest
- ■■ of outstanding interest

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