Editorial
http://dx.doi.org/10.3947/ic.2016.48.3.252
Infect Chemother 2016;48(3):252-253
ISSN 2093-2340 (Print) · ISSN 2092-6448 (Online)

Infection & Chemotherapy

Lactate as a Biomarker for Sepsis Prognosis?

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Blood lactate concentrations reflect the balance between lactate production and clearance. During glycolysis in resting state, most glucose is converted to pyruvate. Pyruvate is metabolized through the aerobic pathway, to acetyl-CoA by pyruvate dehydrogenase (PDH) to enter the tricarboxylic acid cycle that is the main source of energy for cellular metabolism. In times of stress, tissue oxygen (O_2) needs are no longer met by O_2 delivery, which results in cellular hypoxia. Cell hypoxia induces a switch from aerobic metabolism to the less efficient anaerobic metabolism in which PDH is inhibited and lactate formation from pyruvate by lactate dehydrogenase (LDH) is favored. On the other hand, high inflammatory states such as sepsis accelerated glycolysis leads to overproduction of lactate [1]. However, as lactate is a normal product of glucose metabolism, many other factors could increase lactate levels in the absence of tissue hypoperfusion due to malignancy, liver disease, or mitochondrial disorder. Normally, the liver removes 70% of lactate. When hepatic blood flow decreases to 25% of normal, the capacity of the liver to metabolize lactate is diminished and lactate clearance is reduced [2]. Although overproduction of lactate in response to endotoxin or tissue hypoxia accounts for some of the rise in lactate in septic states, a decrease in hepatic lactate extraction and utilization also occurs.

Hyperlactatemia (most commonly ≥4 mmol/L,) is a marker of sepsis-induced hypoperfusion and the threshold was incorporated into the Surviving Sepsis Campaign (SSC) guidelines for early identification of sepsis [3]. It is reasonable, therefore, to assume that hyperlactatemia is very clearly associated with increased risk for mortality in patients with sepsis, in both the intensive care unit (ICU) and emergency department (ED) setting [4, 5]. A recent analysis of the Surviving Sepsis Campaign database reported that elevated lactate ≥4 mmol/L was independently associated with mortality [4]. Interestingly, the prognostic value of lactate levels seems to be independent from the underlying critical illness or the presence of shock or organ failure [6]. In line with these studies, Song *et al.* [7] reported high lactate level (≥4 mmol/L) was an independent risk factor for 7- and 28-day mortality (odds ratio, 1.286 and 1.346, respectively) in septic shock patients who received treatments following SSC bundles in the ED.

In addition to the importance of baseline lactate level, the clearance of lactate during the early phase of resuscitation is associated with mortality. Lactate clearance usually occurs after successful resuscitation which indicates adequate tissue perfusion. According to this concept, lactate clearance has been proposed as alternative goal of resuscitation in patients with sepsis. A recently published study showed a 17% mortali-

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ty rate in subjects randomized to lactate clearance-guided resuscitation versus 23% in those randomized to central venous oxygen saturation-guided resuscitation [8]. The authors concluded that lactate clearance resuscitation goal was noninferior and led to very similar early fluid resuscitation [8]. Another study that randomized patients to routine early goal-directed therapy or to lactate measurement every 2 hours for the first 8 hours showed that the lactate group had a significantly favorable impact on outcome after adjustment for severity of illness [9]. A meta-anlaysis of four randomized trials including above the two studies showed that compared to the control group, early lactate clearance guided control was associated with a reduction in mortality (relative risk, 0.65, 95% confidence interval 0.49-0.85) [10]. However, persistent hyperlactatemia may represent not only increased production of lactate (either aerobic or anaerobic) but also its impaired clearance. We should consider the toxicity of overresuscitation if lactate normalization is pursuing through further resuscitation with fluids and inotropes even after other signs of tissue hypoperfusion have disappeared. Therefore, measurement of 6-hour lactate clearance was weakly recommended in the 2012 Surviving Sepsis guidelines [3].

Lactate metabolism is complex in critically ill patients, and tissue hypoxia has a significant contribution to hyperlactatemia which is an independent predictor of mortality. Currently, lactate clearance is not clearly identified as a variable that can be used to determine the therapeutic endpoint for patients with sepsis. However, monitoring serum lactate levels over time could help to insure that treatment was effective and provide valuable information regarding a patient's response to therapy.

Conflicts of Interest

No conflicts of interest.

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