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Clearing Lactate is Clearly Better.....But How Much?

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In this month's edition of Critical Care Medicine, Zhang and Xu¹ present a comprehensive and well conducted systematic review and meta-analysis of the prognostic potential of lactate clearance to predict survivors and non-survivors among patients with critical illness. The results confirm in aggregate what each of the smaller studies suggest, that failure of lactate to decrease or clear is associated with a worse prognosis and higher mortality rate. An examination of the Forest plot (Figure 2) clearly shows that all included studies, whether among patients with sepsis or non-sepsis and taking place in either the emergency department or intensive care unit, all have relative risk reduction and 95% confidence intervals that do not cross 1. This clearly demonstrates a better prognosis associated with lactate clearance. Thus the only real question is “how much” – how much of a risk reduction is there, how much lactate clearance is superior, and how much should we try to drive lactate clearance?

How much of a risk reduction is there?

Compared to failure of lactate clearance (variably defined in each of the studies), lactate clearance is associated with a relative risk reduction (RR) of 0.34 (95% CI 0.34-0.53) in non-sepsis patients compared to a slightly different RR of 0.41 (95% CI 0.28-0.60) in patients with sepsis. The study by Jansen et al² was analyzed in the non-sepsis group, despite the fact that 40% of this study represented patients with sepsis. Surprisingly, the authors conclude that “LC...is of limited value in patients with sepsis or septic shock.” However, given the data presented we strongly disagree with this conclusion. Their data actually support the prognostic value of lactate clearance in any of these clinical scenarios.

How much lactate clearance is superior?

Two critical questions remain for clinicians: 1) What degree of lactate clearance is superior?; and 2) In what time frame should that superior lactate clearance target be achieved? Unfortunately, this study adds little to this discussion as authors do not provide a summary analysis comparing the prognostic ability of various levels of lactate clearance, nor any additional analyses on clearance time frames or rates of clearance. While the Surviving Sepsis Campaign recommends lactate normalization as a target of sepsis resuscitation, this

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recommendation was based primarily on the lack of consensus between two randomized clinical trials that studied the use of lactate clearance as a resuscitation parameter, in combination with the prevailing wisdom that “normal” is better than “abnormal.” Given this lack of consensus, however, lactate clearance as a resuscitation target received relatively weak 2C recommendation. Since these guidelines were published, work by Puskarich et al³ has suggested that lactate normalization does indeed provide the best predictor of survival compared to any other degree of relative lactate clearance, though the observational design of the study does not answer the question of whether targeting lactate normalization improves patient outcomes.

How much should we try to drive lactate clearance?

Two randomized clinical trials demonstrate that targeting modest (10-20%) lactate clearance is associated with non-inferior or even superior outcomes in critically ill patients^{2,4}. Combined with the current meta-analysis, the evidence is clear that lactate clearance is a useful, non-invasive resuscitation target that should be strongly considered when evaluating critically ill patients, no matter the etiology of their illness. It remains unproven if more aggressive target lactate normalization should indeed be our goal. If lactate results predominantly from ischemia, then rapid reversal of tissue hypoperfusion and normalization of lactate is highly likely to improve outcomes, though this hypothesis remains untested formally. However, if a significant proportion of lactate is results from non-ischemic mechanisms (such as increased glycolysis or mitochondrial dysfunction, as may be the case in certain patients with sepsis), attempting to drive lactate levels down under the assumption lactate is generated solely due to impaired oxygen delivery may have unintended consequences. Specifically, if one attempts to artificially drive lactate clearance through the use of extremely high volume resuscitation or aggressive use of packed red blood transfusions, patient outcomes may actually be worsened. In order to further assess this question, clinical trials explicitly targeting lactate normalization will be necessary to accurately assess the risk to benefit ratio of this therapeutic target. In the meantime, the observations presented by Zhang and Xu¹ support the continually emerging evidence that clearing lactate is good and should be strongly considered as important information in the armamentarium of caring for the critically ill.

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