Clinical Practice Statement

Is Lactate Measurement in the Emergency Department Valuable as a Predictor of Poor Outcomes in Adult Patients with Sepsis?

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Recommendation

Are lactate levels (initial, clearance or normalization) measured in the emergency department associated with poor outcomes in adult patients with sepsis?

Answer

Initial lactate:	**Yes; The vast majority of the available evidence reported on initial lactate measurements. There was a consistent association between elevated initial lactate levels with increased in-hospital mortality, 28-30 day mortality, ICU admission and intubation.** **We further sought evidence to support or refute the recent SSC recommendation of obtaining lactate within one hour of arrival to the ED for patients with suspected sepsis.**
Lactate clearance:	**Yes; Nine trials reported a significant association between lactate clearance (variable definitions) and increasing mortality.**
Lactate normalization:	**Yes; Though only a single trial reported on lactate normalization, it was a secondary analysis of a randomized controlled trial which demonstrated that lactate normalization was the strongest predictor of in-hospital survival (superior to initial lactate and lactate clearance).**

Introduction

Current emergency department (ED) management of sepsis includes serial measurements of serum lactate. Since the initial publication of the Surviving Sepsis Campaign Guidelines and the landmark study by Rivers and colleagues in 2001, numerous lactate measurement strategies have been introduced, including lactate clearance and lactate normalization. [1, 2] Although lactate elevation may be due to a number of etiologies including drugs, toxins and underlying disease processes, in sepsis and shock states it represents a metabolic byproduct of cellular ischemia or cytotoxicity. There is abundant literature with regards to the use of lactate

as a marker of disease severity, endpoint of resuscitation, and predictor of mortality. Lactate measurement has been utilized in various ways including initial static measurement, changes in serial lactate measurements (lactate clearance) and normalization of lactate (generally defined as a final lactate of < 2.0-2.2 mmol/L).

Executive Summary

A systematic search of PubMed articles from the last fifteen years through present was performed that evaluated the utility of lactic acid measurement to predict poor outcomes in adult sepsis patients and was limited to [Human, Adult, English and Clinical Trials]. Only studies that reported initial lactate that was acquired in the ED were included. Studies reporting in only subsets of patients, such as HIV or cancer patients were excluded. Articles sampling post-resuscitation lactate as the initial measure were excluded. For the purpose of this review both arterial and venous sources of lactate were acceptable, however, studies that only compared lactate levels or clearance rates to other predictors such as vital signs were not included. Due to the abundance of peer-reviewed published evidence, no abstracts were included in this review.

The PubMed search yielded a total of 107 articles. Forty three articles that reported on lactate measurements (initial, clearance, normalization), were drawn in the ED, and were associated with in-hospital outcomes were selected for this review.[3-45] Twenty-three were prospective observational studies, seventeen were retrospective trials and four studies were secondary analyses of randomized controlled trials. No study specifically reported time to lactate measurement less than 1 hour. The definition of lactate clearance was generally greater than 10% over various intervals but there was no universal standard definition. Varying lactate levels and lactate clearance rates were used as predictors.

The literature is not uniform with respect to which source (arterial or venous) was utilized. Most (forty-two of forty-four) references cited only the use of venous lactate while one reported the use of arterial and one reported both. Initial lactate was reported in thirty-six articles, while any form of lactate clearance was reported in nine. Puskarich et al, in a pre-planned analysis of a randomized controlled trial reported on initial lactate, lactate clearance and lactate normalization.[34] Though this was the only article reporting on the use of lactate normalization, lactate normalization was reported to be the strongest predictor of survival (adjusted OR, 5.2; 95% CI, 1.7-15.8), followed by lactate clearance ≥ 50% (OR, 4.0; 95% CI, 1.6-10.0). Despite the consistent positive association between lactate clearance and poor outcomes there remains no standard definition and some inconsistencies in the literature. For instance Puskarich and colleagues found no association between survival and lactate clearance ≥ 10%, while Nguyen and colleagues reported improved APACHE II scores and 60 days mortality in patients with lactate clearance ≥ 10% compared to lactate clearance < 10%.[31, 34] Though not specifically included in this review, in a recent systematic review of this topic, Puskarich and colleagues reported on the use of intermediate lactate levels in patients with suspected infection.[46] This study includes eight articles, which reported on intermediate lactate levels in patients with confirmed or suspected infection. This cohort of patients was found to have a mortality of 15.1% and 14.9% in the subgroup of normotensive patients.

The literature is uniformly supportive of lactate as an indicator of poorer overall clinical outcomes in sepsis patients. No studies demonstrated any harm related to lactate use and all studies reported a statistically significant association with poor outcomes. More specifically, twelve studies reported an association with 28- or 30-day mortality, twenty-six studies reported an association with in-hospital mortality, and eight studies reported an association of the use of lactate with in-hospital deterioration. Deterioration was most commonly reported as use of mechanical ventilation, vasopressors, non-invasive positive pressure ventilation or admission to an intensive care unit.

There is literature that addresses elevated lactate levels in various sub-populations, including those patients using metformin or beta-blockers and patients with a history of hepatic dysfunction or cirrhosis. This review did not address any subpopulation, but recognizes that lactate kinetics may vary amongst individuals and particularly in these cohorts. Suggested cut-offs for a lactate threshold above which poorer outcomes are

best predicted have been reported, but not uniformly reported. Some literature suggests that it is lactic acidosis and not simple hyperlactatemia that is associated with poorer outcomes.[24]

Conclusions

There is a preponderance of evidence that uniformly supports the use of lactate in all manners measured in the ED as a marker of increasing mortality and poor outcomes in adult sepsis patients. We were unable to find any evidence to support or refute the recent SSC recommendation of obtaining lactate within one hour of arrival to the ED for patients with suspected sepsis.