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Early lactate clearance in septic patients with elevated lactate levels admitted from the emergency department to intensive care: Time to aim higher?☆,☆☆,★,★★

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Abstract

Purpose: Septic patients with hyperlactatemia have increased mortality rates, irrespective of hemodynamic and oxygen-derived variables. The aims of the study are the following: (1) to ascertain whether lactate clearance (LC) (percentage change in lactate over unit time) predicts mortality in septic patients admitted to intensive care directly from the emergency department and (2) to calculate the optimal "cut-off" value for mortality prediction.

Methods: Three-year retrospective observational study of consecutive patients with severe sepsis and septic shock admitted to intensive care from the emergency department of a tertiary UK hospital. We calculated 6-hour LC, performed receiver operating characteristic analyses to calculate optimal cut-off values for initial lactate and LC, dichotomized patients according to the LC cut-off, and calculated hazard ratios using a Cox proportional hazards model.

Results: One hundred six patients were identified; 78, after exclusions. Lactate clearance was independently associated with 30-day mortality ($P < .04$); optimal cut-off, 36%. Mortality rates were 61.1% and 10.7% for patients with 6-hour LC 36% or less and greater than 36%, respectively. Hazard ratio for death with LC 36% or less was 7.33 (95% confidence interval, 2.17-24.73; $P < .001$).

Conclusions: Six-hour LC was independently associated with mortality, and the optimal cut-off value was 36%, significantly higher than previously reported. We would support further research investigating this higher LC as a distinct resuscitation end point in patients with severe sepsis and septic shock.

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★ CW conceived the study, performed data collection, assisted with the statistical analyses, drafted the initial manuscript, and participated in all manuscript revisions. CW is the corresponding author. DG participated in the study design, performed the statistical analyses, drafted the statistical methods and results sections, and participated in all manuscript revisions. DD performed data collection and participated in all manuscript revisions. AG joint supervised the study and participated in all manuscript revisions. AH joint supervised the study, assisted with the statistical analyses, and participated in all manuscript revisions.

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1. Introduction

Sepsis is an increasingly common reason for hospital admission. A prospective observational study of 198 intensive care units (ICUs) across 24 European countries in 2002 revealed that 24.7% had a diagnosis of sepsis on unit admission [1]. The mortality rate was 27% for patients with sepsis, increasing to 54.1% in patients with septic shock. Epidemiological data from the United States demonstrate that sepsis is a major and growing public health problem. Over a 22-year study period, Martin and colleagues demonstrated that sepsis accounted for more than 10 million hospital admissions, rising steadily from approximately 164 000 in 1979 to 660 000 in 2000 [2].

Recent studies have shown that outcome from sepsis may be improved with optimal resuscitation. When oxygen demand exceeds oxygen delivery, anaerobic metabolism ensues and results in increased lactate production. Septic patients with high initial serum lactate have a higher mortality rate, and this is independent of other organ failure indicators [3-5]. Bakker et al [3] identified, over 2 decades ago, that lactate was superior to oxygen-derived variables in predicting outcome in patients with septic shock.

In 2001, the single-center randomized controlled trial of Rivers et al [6] demonstrated that early goal-directed therapy (EGDT) improved outcome in severe sepsis.

Early goal-directed therapy has now become routine practice and is endorsed in the Surviving Sepsis Guidelines [7]. There are currently 3 international multicenter trials recruiting septic patients to EGDT. There is ongoing debate regarding optimal resuscitation targets. Although Rivers et al [8] used central venous saturations ($ScvO_2$), others have advocated targeting lactate clearance (LC) as a resuscitation end point.

In 2004, Nguyen et al [9] demonstrated that LC at 6 hours was an independent predictor of survival in severe sepsis and septic shock; an LC of more than 10% at 6 hours was reported as the best cut-off value to predict survival. EMShockNet Investigators subsequently used a target of 10% LC at 6 hours in an EGDT trial comparing LC and $ScvO_2$ [8].

We believe that this LC target may be too low. Nguyen et al [9] identified a mean LC of 12% in nonsurvivors, which suggests that a large proportion of these nonsurvivors had an LC greater than 10%. In addition, in a separate EMShockNet trial, only 9% (15/166) of septic patients failed to attain 10% LC at 6 hours [5].

The objectives of our study were (1) to ascertain whether LC predicts mortality in our population of septic patients admitted to the ICU directly from the emergency department (ED) and (2) to calculate the optimal "cut-off" value for LC using receiver operating characteristic (ROC) analysis.

2. Methods

2.1. Design and setting

We performed a 3-year (January 1, 2008, to December 31, 2010) single-center retrospective observational study of consecutive adults (≥16 years) with sepsis admitted directly from the ED to the ICU of a tertiary UK hospital. The ICU admits more than 1000 level 3 patients per annum [10].

2.2. Inclusion and exclusion criteria

The Scottish critical care tracking and audit program, Ward Watcher [11], was interrogated to identify the following: (i) patients admitted between January 1, 2008, and December 31, 2010, (ii) admitted directly from the ED, or (iii) with an admission ICU diagnosis or primary diagnosis (the latter being completed on discharge from ICU for all patients) of infection or sepsis (Fig. 1). The hospital records were obtained and searched manually to confirm that the presentation diagnosis of sepsis was correct.

Patients were excluded if (i) there was no record of arterial lactate measurement in the ED or (ii) the confirmed diagnosis on review of medical notes was not sepsis or infection or (iii) the hospital written records were unobtainable (for >6 months).

2.3. Data collection

The Ward Watcher database, hospital, and ED records were interrogated, and the following data collected: patient age and sex, infection type, initial ED lactate, 6-hour lactate, Acute Physiology and Chronic Health Evaluation (APACHE) II scores at 24 hours after hospital admission, and 30-day survival.

2.4. Lactate clearance definition

Percentage LC was calculated as shown below to allow comparison with previous studies [5,8,9]:

$$\text{Lactate clearance} = \frac{\left(\text{Lactate}^{\text{ED presentation}} - \text{Lactate}^{6\text{ hours}}\right) \times 100}{\text{Lactate}^{\text{ED Presentation}}}$$

2.5. Statistical analysis

Using logistic regression, the relationship between LC and death was investigated. Using univariate analysis, the potential confounders of age, sex, APACHE II score, and initial lactate were tested to determine if they were related to 30-day mortality. Those factors found to be significant ($P < .05$) on univariate testing were included in a multivariate logistic regression model with LC to determine if LC is significantly associated with death after adjusting for these confounders. To test for interaction between initial lactate and LC, an interaction term was included in the model.

For patients who had an abnormal initial lactate concentration (≥2 mmol/L), ROC curves were constructed for initial lactate and LC to test the ability to predict mortality at 30 days. To facilitate ROC analysis, LC was converted