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Sepsis-associated pulmonary complications in emergency department patients monitored with serial lactate: An observational cohort study

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ABSTRACT

Purpose: Patients with severe sepsis and septic shock are at high risk for development of pulmonary complications, including acute respiratory distress syndrome (ARDS). Serial lactate monitoring is a useful tool to gauge global tissue hypoxia in emergency department (ED) patients with sepsis. We hypothesized that patients undergoing serial lactate monitoring (SL) would demonstrate a decreased incidence of pulmonary complications.
Methods: This is a retrospective observational cohort study of adult severe sepsis and septic shock patients with elevated lactate presenting to a large academic ED. A total of 243 patients were assigned to SL (n = 132) or no serial lactate monitoring (NL; n = 111). The primary outcome was a composite of pulmonary complications: (1) ARDS development and (2) respiratory failure.
Results: Twenty-eight patients (21%) in the SL group and 37 patients (33%) in the NL group developed the primary outcome ($P = .03$). Multivariate analysis demonstrated an association between the NL group and development of pulmonary complications (adjusted odds ratio [aOR], 2.1; confidence interval [CI], 1.15-3.78). Emergency department mechanical ventilation was independently associated with development of ARDS (aOR, 3.5; 1.8-7.0). In the a priori subgroup of patients mechanically ventilated in the ED (n = 97), those who developed ARDS received higher tidal volumes compared to patients who did not develop ARDS (8.7 mL/kg predicted body weight [interquartile range, 7.6-9.5] vs 7.6 [interquartile range, 6.8-9.0]; $P < .01$).
Conclusions: Serial lactate monitoring is associated with a decrease in major pulmonary complications in severe sepsis and septic shock. Acute respiratory distress syndrome incidence is also influenced by ED-based mechanical ventilation. These results provide 2 potentially modifiable variables to be targeted in future studies to prevent pulmonary complications in this patient subset.

1. Introduction

Severe sepsis and septic shock are increasing in incidence and are associated with high morbidity and mortality [1]. The development of respiratory failure and acute respiratory distress syndrome (ARDS) is a common manifestation of sepsis-associated organ dysfunction [2,3]. Progression to ARDS during the course of sepsis is associated with an increase in mortality and organ failure [2,4]. As such, prevention has become a central focus of reducing the public health burden of ARDS in critical illness [5,6].

Acute respiratory distress syndrome is caused by vascular permeability leading to noncardiogenic alveolar edema. Multiple studies have demonstrated an association between positive fluid balance and ARDS incidence [7-10]. Quantitative resuscitation strategies, conversely, are typically associated with larger fluid resuscitation volumes. This approach may serve to worsen alveolar edema in the setting of systemic inflammation, yet quantitative resuscitation reduces inflammatory biomarkers and improves clinical outcomes even in mechanically ventilated ARDS patients [11-14]. This suggests that early reversal of global tissue hypoxia promotes pulmonary integrity at an endothelial and epithelial level and that quantitative resuscitation strategies may decrease ARDS incidence.

Data from the emergency department (ED) suggest that modifiable factors (eg, shock and high tidal volume ventilation) could be targeted to decrease the incidence of ARDS [4,5]. In the setting of sepsis, evidence of hypoperfusion (elevated lactate level) has also been directly associated with ARDS progression in ED patients [15]. Lactate clearance is associated with improved outcome in critically ill patients, and serial lactate monitoring (SL) has been shown to be a strategy associated with improved outcomes [16-19]. These data provide rationale for SL as a possible therapeutic target for ARDS prevention [19]. However, the impact of SL on the incidence of ARDS has not been investigated.

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In this study, we aimed to determine whether SL in the ED was associated with a reduction in pulmonary complications (eg, ARDS and new respiratory failure) for patients with severe sepsis and septic shock. We hypothesized that SL would be associated with a decrease in incidence of pulmonary complications when compared to patients resuscitated without the use of SL.

2. Materials and methods

This was a retrospective observational cohort study and preplanned secondary analysis of previously published data, reported in accordance with The Strengthening the Reporting of Observational Studies in Epidemiology Statement: Guidelines for Reporting Observational Studies [19,20]. This study was approved by the Human Research Protection Office at the principal investigator's institution with waiver of informed consent (approval no. 201206130).

This study was conducted at a university-affiliated, 1250-bed urban teaching hospital with an annual ED census of 95 000 patients. The total study period was 16 months (January-December 2011; December 2012-March 2013). Adult patients with severe sepsis or septic shock and an initial ED lactate level greater than or equal to 4 mmol/L were eligible for inclusion [1]. Patients were excluded for ED length of stay less than 2 hours, do-not-resuscitate (DNR)/do-not-intubate (DNI) status, and transfer outside of hospital network.

Qualifying patients with severe sepsis or septic shock and lactate greater than or equal to 4 mmol/L were identified by query of the electronic medical record. To ensure uniform data collection and accuracy, all variables were defined before data extraction and placed in a standardized format during the data collection process. Regular meetings and monitoring of data collection were performed. Data were cross-checked for accuracy with the electronic medical record before final data entry.

Baseline patient characteristics included age, sex, race, weight, height, predicted body weight (PBW), body mass index, comorbidities, vital signs, laboratory values, Sequential Organ Failure Assessment (SOFA) score, suspected source of infection, and ED length of stay. Predicted body weight in kilograms was calculated according to the formula: males, 50 + 2.3 [height (inches) − 60]; females, 45.5 + 2.3 [height (inches) − 60].

Emergency department process-of-care variables included time to antibiotics, intravenous crystalloid volume administered, vasopressor use, packed red blood cell transfusion, corticosteroids, and use of mechanical ventilation. Ventilator-related variables included tidal volume, tidal volume indexed to PBW, peak pressure, and inspiratory plateau pressure.

2.1. Definitions

Sepsis was defined as previously described [1]. Suspected source of infection was extracted from the inpatient medical record. The SL cohort was defined as patients who had a second lactate checked while in the ED. The NL cohort was defined as patients who did not have a second lactate checked while in the ED. Lactate clearance was calculated as a percentage and defined as initial lactate value minus second value divided by initial lactate, then multiplied by 100 $\{[(\text{lactate}^{\text{initial}} - \text{lactate}^{\text{second}})/\text{lactate}^{\text{initial}}] \times 100\}$. *Lactate clearance* was defined as a decrease in lactate of greater than or equal to 20% between the 2 measured lactate values.

Sequential Organ Failure Assessment score was assessed as previously described [21]. A modified SOFA score was used, which omits the neurologic function component of the score [22]. When more than 1 value was present, SOFA scores were calculated from the most abnormal value. For the calculation of initial SOFA score, if a value was not measured in the ED, then the first value after hospital admission was used to calculate initial SOFA score (only applicable to the bilirubin component of the score). *Do not resuscitate/DNI* was defined as documentation of "DNR," "DNI," or "comfort care" in the ED record.

2.2. Outcomes

The primary outcome of interest was a composite of major pulmonary complications: the development of ARDS or respiratory failure requiring mechanical ventilation after hospital admission. Acute respiratory distress syndrome was defined according to the Berlin definition [23]. *Respiratory failure* was defined as the initiation of mechanical ventilation after hospital admission. Outcomes were assessed over the first 5 days after admission. This was done to establish a temporal trend relative to admission from the ED, and previous data indicate that pulmonary complications occur early during intensive care unit stay [24]. An a priori subgroup of interest consisted of patients mechanically ventilated in the ED.

Each investigator reviewed a set of training radiographs before the ARDS adjudication process [25]. Study radiographs were then reviewed and categorized as consistent, inconsistent, or equivocal for the diagnosis of ARDS. When agreement existed between investigators, the patient was then deemed acceptable for ARDS adjudication status. When disagreement existed, a third investigator (the study primary investigator) further reviewed the images independently, and agreement was made by consensus. To limit ascertainment bias, each investigator was blinded to all other ARDS adjudication decisions.

2.3. Analysis

Descriptive statistics, including mean (±SD), median (interquartile range [IQR]), and frequency distributions were used to assess the characteristics of the patient cohort. Normality of distribution was tested for by inspection of histograms, testing for skewness and kurtosis in the data, and the Kolmogorov-Smirnov test. Continuous and categorical data were compared using an unpaired *t* test, Mann-Whitney *U* test (for nonnormally distributed data), χ^2 test, or Fisher exact test as appropriate.

To test predictors of the primary outcome, continuous and categorical variables were compared using an unpaired *t* test, Mann-Whitney *U* test, χ^2 test, or Fisher exact test, as appropriate. A multivariable model was created to assess predictors of outcome. A priori variables selected for the model included (1) those related to illness severity and (2) those shown in prior studies to be predictors of ARDS in critically ill ED patients. These variables included SOFA score, lactate, vasopressor use, and body mass index [4,15]. Other candidate variables for inclusion in the backward stepwise, multivariable, logistic regression analysis included biologically plausible variables without missing data and statistically significant in univariable analysis at a $P \le .05$ level. The stepwise regression method selected variables for inclusion or exclusion from the model in a sequential fashion based on a significance level of 0.05 for entry and 0.05 for removal. Goodness of fit of the model was assessed with the Hosmer-Lemeshow test, and residual statistics were examined. Statistical interactions were assessed. Collinearity diagnostics were assessed to test the assumption of no multicollinearity. The model used variables that contributed information that was statistically independent of the other variables in the model. Adjusted odds ratios (aORs) and corresponding 95% confidence intervals (CIs) are reported for variables in the multivariable model, adjusted for all variables in the model. The analysis of mechanical ventilator variables as predictors was restricted to the subgroup patients who were mechanically ventilated in the ED. All tests were 2 tailed, and $P < .05$ was considered statistically significant. As this was a preplanned secondary analysis of previously reported data, we began with a sample size of 243 patients. From previous data, we expected an event rate of approximately 30% for the primary outcome [4,15]. We aimed for an absolute reduction in the primary outcome from 10% to 15%. Therefore, with a total sample size of 243 patients, we were reasonably assured of an adequate sample. Analyses were performed using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp; Armonk, NY).