Lactate Clearance and Normalization and Prolonged Organ Dysfunction in Pediatric Sepsis

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Objectives To evaluate whether lactate clearance and normalization during emergency care of pediatric sepsis is associated with lower rates of persistent organ dysfunction.

Study design This was a prospective cohort study of 77 children <18 years of age in the emergency department with infection and acute organ dysfunction per consensus definitions. In consented patients, lactate was measured 2 and/or 4 hours after an initial lactate; persistent organ dysfunction was assessed through laboratory and physician evaluation at 48 hours. A decrease of ≥10% from initial to final level was considered lactate clearance; a final level <2 mmol/L was considered lactate normalization. Relative risk (RR) with 95% CIs, adjusted in a log-binomial model, was used to evaluate associations between lactate clearance/normalization and organ dysfunction.

Results Lactate normalized in 62 (81%) patients and cleared in 70 (91%). The primary outcome, persistent 48-hour organ dysfunction, was present in 32 (42%). Lactate normalization was associated with decreased risk of persistent organ dysfunction (RR 0.46, 0.29-0.73; adjusted RR 0.47, 0.29-0.78); lactate clearance was not (RR 0.70, 0.35-1.41; adjusted RR 0.75, 0.38-1.50). The association between lactate normalization and decreased risk of persistent organ dysfunction was retained in the subgroups with initial lactate ≥2 mmol/L and hypotension.

Conclusions In children with sepsis and organ dysfunction, lactate normalization within 4 hours was associated with decreased persistent organ dysfunction. Serial lactate level measurement may provide a useful prognostic tool during the first hours of resuscitation in pediatric sepsis. *(J Pediatr 2016;170:149-55)*.

More than 75 000 US children develop severe sepsis yearly, with US pediatric mortality rates of 10%-20%.[1,2] Failure to recognize and adequately resuscitate shock have been identified as causes of preventable morbidity.[3,4] The ability to initially identify the highest-risk children and to objectively monitor the progression of disease and success of therapy at bedside is critical to the quality of sepsis care.

Elevated lactate, a byproduct of anaerobic metabolism, is associated with poor prognosis in sepsis, and changes in real time in response to pathophysiology and resuscitation.[5-8] Measuring and re-measuring lactate levels comprise 2 of 7 surviving sepsis bundle elements whose implementation in adults has decreased mortality.[9,10] A single elevated serum lactate level at the start of emergency department (ED) care in pediatric sepsis is associated with a 5-fold increase in organ dysfunction risk, but no studies have evaluated lactate clearance or normalization in early pediatric sepsis.[6] Thus, this study sought to test whether a decrease in serum lactate level during the first 4 hours of care is associated with lower rates of persistent organ dysfunction at 48 hours, among pediatric ED patients with infection and acute organ dysfunction. The hypothesis was that patients with lactate clearance and normalization would have lower rates of persistent organ dysfunction at 48 hours.

Methods

This was a prospective cohort study conducted at Children's Hospital Colorado, an academic pediatric referral center that treats >70 000 patients yearly in the ED. The ED uses a sepsis resuscitation system, in which ED clinicians may activate a coordinated, standardized, resuscitation response via page when they clinically determine that a patient has suspected sepsis with decreased mental status or perfusion. Measuring a lactate level is recommended but not required in cases of suspected septic shock. Internal continuous quality improvement data show that lactate is tested in 60% of cases of suspected sepsis and 75% of cases of septic

ED	Emergency department
ICU	Intensive care unit
PELOD	Pediatric Logistic Organ Dysfunction
REDCap	Research Electronic Data Capture
RR	Relative risk

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shock with hypotension.[11] Children who presented for care to the ED were eligible if they were <18 years old, had a lactate level measured by their treating physician, had suspected infection as identified by their treating physician, and met organ dysfunction criteria in the ED. Published consensus definitions for organ dysfunction were used (**Table I**; available at www.jpeds.com).[12] Children with inborn errors of metabolism and children whose ED care occurred between 1:00 a.m. and 7:00 a.m., which was outside of enrollment hours, were excluded. Activation of the sepsis resuscitation system was not required for enrollment in the study. This study was approved by the Colorado Multiple Institutional Review Board.

Research assistants identified potential subjects who had a lactate level measured during their ED care. Treating physicians were then asked to complete a screening form to identify whether infection was suspected and to assess inclusion and exclusion criteria. Patients meeting inclusion criteria were then approached for written informed consent from the parents or guardians of the subjects, and when appropriate, assent was obtained from the children themselves.

After consenting patients were enrolled, serial venous lactate levels were measured. Attempts to collect lactate levels occurred 2 and 4 hours after the original (nonstudy) clinical lactate level was collected. Although both the 2- and 4-hour measurements were preferred, a collection at a minimum of one of these times was considered acceptable for continuation in the study. This approach reflects Surviving Sepsis Guidelines that recommend a repeat lactate measurement during the first 6 hours of care but do not specify a precise timepoint for collection, reflecting clinical realities of acute resuscitation and challenges of vascular access.[9,13] Consistent with prior studies, venous lactate levels were collected by nurses at the same time as collection of other clinical samples, using standard institutional procedures for collection of blood samples, and tourniquets were permitted.[6,13,14] Blood gas syringes for measurement of lactate were immediately placed on ice and levels measured in the Children's Hospital Colorado laboratory, an accredited laboratory with quality control procedures, using the Siemens Rapidlab 1265 (Siemens Healthcare Diagnostics Inc, Tarrytown, New York).

The consensus definitions for organ dysfunction use clinical, laboratory, and physical examination findings.[12] Laboratory tests required to assess organ dysfunction were collected 48 hours after the initial lactate. Physical examination findings required to assess organ dysfunction were recorded on a data collection form by the patient's attending physician at 48 hours. Patients who were discharged from medical care prior to 48 hours had clinical and laboratory assessments for organ dysfunction completed immediately prior to discharge. Additional clinical data including vital signs, laboratory results, hospital course, and treatments were obtained via structured chart abstraction. Study data were collected and managed using Research Electronic Data Capture (REDCap), hosted at the University of Colorado. REDCap is a secure, web-based application designed to support data capture for research studies.[15] Data were then exported for analysis from REDCap to SAS (SAS Institute, Cary, North Carolina).

Clinicians were blinded to laboratory results collected for the study and treatment was performed according to standard of care.

Measures

When both 2- and 4-hour lactate levels were both collected, the 4-hour value was used to determine lactate clearance and lactate normalization status. Lactate clearance was defined according to published definitions as a decrease in serum lactate of ≥10% between first and second measurement in patients with initial lactate ≥2 mmol/L (18 mg/dL), or a second measurement <2 mmol/L (18 mg/dL) in patients with initial lactate <2 mmol/L (18 mg/dL).[13,16] Lactate normalization was a second lactate level that was <2 mmol/L (18 mg/dL).[16] The primary outcome measure was at least one organ dysfunction persisting ≥48 hours after triage time.

Organ dysfunction was defined using international pediatric sepsis consensus definitions (**Table I**).[12] In this study, elevated lactate was not considered part of the outcome of organ dysfunction. The Pediatric Logistic Organ Dysfunction (PELOD) score, a validated measure of organ dysfunction and mortality risk in children, was calculated for the first hospital day to assess severity of presenting illness. PELOD is a score that uses weighted measures of organ dysfunction to predict mortality among pediatric intensive care unit (ICU) patients.[17,18]

Statistical Analyses

Data were summarized using standard descriptive statistics. Continuous outcomes were compared with Wilcoxon rank-sum, including ventilator-days, vasopressor-days, organ-dysfunction-days, and length of stay in hospital and intensive care. Dichotomous outcomes such as mortality, vasopressor requirement, intubation, and disposition to the ICU were compared with the Fisher exact statistic.

The sample size was determined based on the planned analysis for the comparison of presence of 48-hour organ dysfunction between lactate clearance and nonclearance groups, using the Fisher exact statistic. Based on pediatric and adult studies of lactate in sepsis, it was estimated that 33% of subjects would not have lactate clearance and that 40% of those without lactate clearance would have 48-hour organ dysfunction; 5% of the group with lactate clearance would have 48-hour organ dysfunction.[6,13,19] With a sample size of 78 total patients, this would provide 80% power to detect this difference with a 2-tailed alpha of 0.05.

To assess potential confounding effects of select variables on the association of lactate normalization with prolonged organ dysfunction, an adjusted relative risk (RR) was calculated using the log-binomial model with backward elimination. Covariates were selected based on biological plausibility, prior studies, and univariate association with