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ORIGINAL RESEARCH CONTRIBUTION

The Utility of Early Lactate Testing in Undifferentiated Pediatric Systemic Inflammatory Response Syndrome

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Abstract

Objectives: Failure to recognize shock contributes to inadequate early resuscitation in many children with sepsis. Serum lactate levels are used to identify adult patients with septic shock, but physical examination diagnosis alone is recommended in pediatric sepsis. The authors sought to test the utility of lactate testing in pediatric emergency department (ED) patients with systemic inflammatory response syndrome (SIRS). The hypothesis was that early hyperlactatemia (serum lactate $\geq$ 4.0 mmol/L) would be associated with increased risk of organ dysfunction.

Methods: This was a prospective cohort study of children younger than 19 years with SIRS presenting to a pediatric ED. The primary outcome was organ dysfunction within 24 hours of triage; secondary outcomes included disposition, serious bacterial infection (SBI), treatments, and mortality. Study personnel measured venous lactate level on a point-of-care meter, with clinicians blinded to results, and patients received usual care.

Results: A total of 239 subjects were enrolled; 18 had hyperlactatemia. The hyperlactatemia group had a relative risk of 5.5 (95% confidence interval [CI] = 1.9 to 16.0) of developing 24-hour organ dysfunction. As a test for organ dysfunction, hyperlactatemia had a positive likelihood ratio of 5.0, a sensitivity of 31% (95% CI = 13% to 58%), and specificity of 94% (95% CI = 90% to 96%). Subjects with hyperlactatemia were significantly more likely to receive intravenous (IV) antibiotics and fluid boluses; despite increased therapy, they were at significantly increased risk for intensive care unit (ICU) admission and bacterial infection.

Conclusions: Among undifferentiated children with SIRS, early hyperlactatemia is significantly associated with increased risk of organ dysfunction, resuscitative therapies, and critical illness. The addition of serum lactate testing to the currently recommended clinical assessment may improve early identification of pediatric sepsis requiring resuscitation.

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Severe sepsis affects more than 20,000 children yearly in the United States, with mortality rates as high as 13%.[1] These patients must be distinguished from the millions of children who present to emergency departments (ED) with benign infectious illnesses. Recognition failure is a leading reason for noncompliance with American College of Critical Care Medicine (ACCM)/Pediatric Advanced Life Support septic shock guidelines; compliance is as low as 30%.[2] Use of these guidelines reduces mortality; thus, rapid and

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accurate diagnosis is a critical component of sepsis survival in children.[2] The ACCM guidelines recommend physical examination to diagnose septic shock and cite inadequate data to support the use of laboratory tests, including serum lactate.[3]

Lactate is produced during anaerobic metabolism and increases with tissue hypoperfusion. In adult septic shock, early lactate levels prognosticate mortality.[4] A serum lactate level of $\geq$ 4 mmol/L triggers aggressive sepsis therapy in the Surviving Sepsis Campaign, which has reduced sepsis mortality in adults. Pediatric studies of hyperlactatemia show it is a specific predictor of serious bacterial infection (SBI) in the ED, and predicts mortality in sepsis in the intensive care unit (ICU).[5,6] The ability of ED serum lactate levels to predict the development of severe sepsis in children is unknown.

In this investigation, we studied whether measurement of an initial lactate level in an undifferentiated ED population of children with systemic inflammatory response syndrome (SIRS) identifies risk of severe illness. We hypothesized that ED hyperlactatemia, defined as serum lactate level of $\geq$ 4.0 mmol/L, would be associated with increased risk of organ dysfunction within 24 hours.

METHODS

Study Design

This was a prospective observational cohort study. The institutional review board approved this study and granted a waiver of informed consent. The funding sources for this study, the Academic Pediatric Association Region 2 Young Investigator Grant and the Nicholas Crognale Endowed Chair for Emergency Medicine at the Children's Hospital of Philadelphia, had no role in the design, conduct, or reporting of the study.

Study Setting and Population

This study was conducted in the ED of a freestanding tertiary care children's hospital with $\geq$ 80,000 annual visits. We enrolled a convenience sample of ED patients over 1 year, during 17 hours of trained research assistant coverage daily. Patients were included if they were < 19 years, met pediatric SIRS criteria with a temperature of > 38.5 or < 36° C and a heart rate greater than two standard deviations (SDs) above normal for age, and underwent phlebotomy or central venous catheter access in the course of their clinical care.[7] We did not use the additional SIRS criteria of leukocyte count, which is unavailable at the time of triage, or respiratory rate, which is less reliably measured and which would select a population with a lower pretest probability of sepsis due to the prevalence of primary respiratory processes such as bronchiolitis and asthma. Patients transferred after receiving care at another facility or with known inborn errors of metabolism were excluded. If lactate was not measured within 15 minutes of IV therapy initiation, patients were excluded.

Study Protocol

Research assistants identified patients with qualifying vital signs, assessed eligibility, and recorded lactate levels. Clinical providers remained blinded to lactate levels, and medical management was conducted as usual. We collected data about ED course and hospitalization from the medical record, using standardized data abstraction forms, which were reviewed for accuracy by study investigators.

Measures

We used a previously validated point-of-care device (LactatePro, Arkray, Inc., Kyoto, Japan) to measure venous lactate level during venipuncture performed for clinical care.[8] There were no restrictions on tourniquet use. Research assistants placed 5 μL of blood on the meter's test strip, ran the meter, and recorded the result on a data collection form placed in a locked box.

Our predictor was the presence of hyperlactatemia, defined as lactate $\geq$ 4 mmol/L. Although there is some debate, lactate levels of < 2 mmol/L are considered normal, levels of 2 to 4 mmol/L are intermediate or somewhat elevated, and levels of $\geq$ 4 mmol/L are considered elevated and shock-defining. Our primary outcome measure was organ dysfunction within 24 hours of triage time, classified following International Pediatric Sepsis Consensus Conference definitions (Table 1).[7] We excluded lactate $\geq$ 4 mmol/L as a criterion for organ dysfunction. We assessed hyperlactatemia as a risk factor for outcomes including SBI, pathogen-positive culture, ED disposition, fluid resuscitation, and IV antibiotic use. SBI was defined as a pathogen-positive blood or cerebrospinal fluid culture, a catheterized urine

Table 1
Study Organ Dysfunction Definitions, Adapted From IPSCC definitions[7]

Cardiovascular dysfunction (any of the following):
Despite isotonic IV bolus $\geq$ 40 mL/kg
Systolic blood pressure < 5% for age or
Need for vasoactive drug (dopamine > 5 μg/kg/min or dobutamine, epinephrine, norepinephrine)
Capillary refill > 5 seconds
Urine output < 0.5 mL/kg/hour
Respiratory dysfunction (any of the following):
PaO_2/FIO_2 < 300 in absence of cyanotic heart disease or preexisting lung disease
$PaCO_2$ > 65 torr or 20 mm Hg over baseline
Proven need for > 50% FIO_2 to maintain saturation $\geq$ 92%
Neurologic dysfunction (any of the following):
Glasgow Coma Scale $\leq$ 11 or acute change $\geq$ 3 points below abnormal baseline
Hematologic dysfunction (any of the following):
Platelets < 80,000 or decline of 50% from highest value over past three days in patients with baseline low platelets
International normalized ratio > 2
Renal dysfunction:
Creatinine $\geq$ 2 times upper limit for age or twofold increase in baseline creatinine in patients with baseline elevations in creatinine
Hepatic dysfunction (any of the following):
Total bilirubin $\geq$ 4 (not applicable to newborn)
Alanine transaminase (ALT) two times upper limit of normal for age or twofold increase in baseline abnormal ALT

FIO_2 = fraction of inspired oxygen; IPSCC = International Pediatric Sepsis Consensus Conference; $PaCO_2$ = partial pressure of carbon dioxide; PaO_2 = partial pressure of oxygen.

specimen with > 100,000 colony-forming units of a pathogen, or an attending radiologist chest radiograph interpretation of definitive infiltrate. Sepsis resuscitation was an outcome defined as receipt of at least 40 mL/kg of isotonic IV fluid and IV antibiotics during the ED course. We created this definition as a minimal indication of intent to perform sepsis resuscitation, without evaluating quality of resuscitation using measures such as time course or patient response to treatment. To assess processes of care for SIRS patients in the absence of lactate testing, we measured time to antibiotic as recorded in the medication record and time to attending physician examination, prospectively recorded by physicians.

Data Analysis

We calculated that a sample size of 151 would be required to detect a relative risk of 2.5 with a power of 0.8 and two-sided alpha of 0.05, given an estimated occurrence of organ dysfunction of 10% in the nonhyperlactatemic SIRS population. We derived estimates from review of a small sample of deidentified institutional data. Given the uncertainty of these estimates due to lack of published data on SIRS or hyperlactatemia in the pediatric ED, this was a minimum sample size with a goal of enrolling as many patients as possible in 1 year.

We calculated relative risk ratios to test our primary hypothesis and secondary severity outcomes and odds ratios (ORs) to measure the association between hyperlactatemia and treatments administered and calculated sensitivity, specificity, and positive likelihood ratio. Data were entered and analyzed using SPSS, version 17.0 (SPSS Inc., IBM Co., Chicago, IL).

RESULTS

A total of 239 evaluable subjects were enrolled. The overall missed eligible rate was 36%, and ED disposition of missed eligible patients was similar to that of enrolled subjects. Fifty-five percent of subjects were 2 to 12 years in age, 28% were 3 months to 2 years, and the remainder were 13 to 18 years or under 3 months. Fifty-four percent of subjects were male, 50% were African American, and 30% were white. Twenty-eight percent of patients had chronic illness, including 8% who were immunocompromised. None of the enrolled patients had hypothermia. Sixty-nine percent of study subjects were admitted to a ward, and 8% were admitted to an ICU. Few patients (2%) had hypotension in the first 24 hours of care; all of these were fluid-refractory. SBI was present in 22%, comprising patients with pneumonia (14%), urinary tract infection (6%), and bacteremia (4%). IV antibiotics were given to 62% of subjects, and IV fluids to 49%; 7% received sepsis resuscitation.

Mean (±SD) lactate in study subjects was 2.0 (±1.2) mmol/L; 8% of subjects had hyperlactatemia. Five percent of all subjects had organ dysfunction within 24 hours of triage; this represented 4% of the low-lactate population and 22% of the hyperlactatemic population. Hyperlactatemia was associated with a higher risk of organ dysfunction, ICU admission, and SBI and with ED therapies, including increased odds of receiving IV antibiotics, multiple fluid boluses, and sepsis resuscitation (Table 2).

Subjects with hyperlactatemia and organ dysfunction demonstrated dysfunction in a median of two systems (interquartile range [IQR] = 1 to 3.8), with a median of 6 (IQR = 2 to 8.5) organ dysfunction days (Table 3). Subjects with organ dysfunction without hyperlactatemia had a median of two (IQR = 1 to 2) systems dysfunctional, with a median of two (IQR = 1.5 to 7.5) organ dysfunction days. As a test for 24-hour organ dysfunction, hyperlactatemia had a positive likelihood

Table 2
Risk of Severe Outcome, ED Treatments Among Subjects With Hyperlactatemia (n = 18) Compared to Subjects Without Hyperlactatemia (n = 221)

Outcome	Lactate, *N* (%)		Relative risk (95% CI)
	≥ 4 mmol/L	<4 mmol/L	
24-hour organ dysfunction	4 (22)	9 (4)	5.5 (1.9–16.0)
SBI	8 (44)	45 (20)	2.2 (1.2–3.9)
Positive culture	6 (33)	16 (7)	4.6 (2.1–10.3)
ICU admission	5 (28)	14 (6)	4.4 (1.8–10.8)
Admission to hospital	17 (94)	166 (75)	1.3 (1.1–1.4)
Treatment			OR (95% CI)
IV antibiotic	17 (94)	132 (59)	11.4 (1.5–88.7)
≥ 40 mL/kg IV fluid	5 (28)	17 (7)	4.6 (1.5–14.5)
≥ 40 mL/kg IV fluid + IV antibiotic	5 (28)	12 (5)	6.7 (2.1–21.9)

ICU = intensive care unit; SBI = serious bacterial infection.

Table 3
Systems Involved in Patients with Organ Dysfunction, by Lactate Level

Number of Systems	Organ Systems	Organ Dysfunction Days
Hyperlactatemic		
1	Resp	1
1	Neuro	9
3	CV,* Resp, Heme	5
4	CV,* Neuro, Renal, Hep	7
Nonhyperlactatemic		
1	Hep	1
1	Hep	1
1	Heme	2
1	Hep	4
2	CV,* Heme	2
2	Heme, Hep	2
2	Resp, Heme	3
2	CV,* Resp	11
2	CV,* Resp	14

CV = cardiovascular; Heme = hematologic; Hep = hepatic; Neuro = neurologic; Resp = respiratory.
*Patients with shock, excluding elevated lactate from definition of shock (CV dysfunction).

ratio of 5.0 (95% CI = 1.9 to 13.0), with a sensitivity of 31% (95% CI = 13% to 58%) and specificity of 94% (95% CI = 90% to 96%).

Receiver operating curve characteristics were calculated for all cut points for lactate, with lactate $\geq$ 4.8 mmol/L having the largest area under the curve of 0.641 (95% CI = 0.460 to 0.822). This differed only slightly from the clinical standard of lactate $\geq$ 4.0 mmol/L, which had the second-largest area under the curve of 0.623 (95% CI = 0.445 to 0.801). Because the receiver operating characteristic curves were driven by so few outcomes, and the alternate cut point offered marginal improvement over the clinical standard, we did not perform separate analyses of test characteristics using 4.8 mmol/L as a cut point.

Patients with chronic illness were at increased risk of organ dysfunction with a relative risk of 3.0 (95% CI = 1.0 to 8.59), and immunosuppressed patients had a relative risk of 5.2 (95% CI = 1.8 to 15.2). Median time to exam by attending physician was 81 (IQR = 43 to 121) minutes, with median time in the patients who developed organ dysfunction of 50 (IQR = 10 to 73) minutes. Of patients who received IV antibiotics, the median time to receipt was 3.2 (IQR = 2.3 to 4.1) hours; in the organ dysfunction population it was 2.2 (IQR: 2.1 to 3.1) hours.

DISCUSSION

To the best of our knowledge, this is the first study to associate serum lactate levels measured in the ED with patient outcome in pediatric SIRS. In children with SIRS, a single elevated lactate level increased risk of organ dysfunction fivefold, despite increased therapy. By all measures, an elevated lactate significantly increased risk for severe disease, including increased risk of intensive care, hospitalization, and SBI.

Current ACCM guidelines recommend that the clinical dyad of hyperthermia/hypothermia and signs of inadequate perfusion be used to diagnose septic shock in pediatric patients, but emergency medicine literature suggests challenges in a purely clinical approach to diagnosis.[3] In one study of children transported to a pediatric ICU with shock present in the ED, only 19% were referred specifically for shock, suggesting that signs of hypoperfusion were underappreciated.[9] Conversely, pediatric EDs prospectively using sepsis protocols have narrowed shock definitions from those proposed in the guidelines, including one group using lactate testing, suggesting a lack of agreement with the recommended criteria.[10] Thus, while published guidelines recommend "early recognition of pediatric septic shock by clinical examination, not biochemical tests," successful implementation of this approach is not robustly supported by data from the ED.[3]

In the ACCM guidelines, two authors dissented from majority opinion of using clinical examination exclusively to diagnose septic shock, suggesting instead that serum lactate measurement may be useful.[3] Lactate offers several advantages of pathophysiology and practicality.

Although other markers have been identified for prediction of SBI in children, lactate reflects pathophysiologic processes requiring immediate resuscitation, rather than source of infection. As such it may be particularly useful in children, in whom hypotension is frequently a late finding in shock. Lactate is a byproduct of glycolysis under anaerobic conditions, reflecting tissue oxygen delivery. Because lactate is metabolized by the liver and kidney, hepatic and renal insufficiency also increase lactate levels. By reflecting both tissue oxygen delivery and organ function, lactate levels detect shock processes, regardless of a patient's gross hemodynamics. Our findings that elevated lactate levels correspond with organ dysfunction, ICU admission, and resuscitation administered demonstrate its potential utility as an early indicator of resuscitation requirement in children. Lactate may also increase in patients with inborn errors of metabolism, toxin ingestion, increased exogenous or endogenous catecholamines, and lung injury. In our study, known inborn errors of metabolism were excluded, no patients were diagnosed with toxin ingestion, and none were treated with epinephrine at the time of lactate measurement; these confounders must be kept in mind by clinicians as well.

Lactate offers practical advantages over clinical examination. It is an objective measure that may facilitate communication among providers in prehospital, nonpediatric, and referral center settings, particularly important because most children present for emergency care to centers without pediatric intensive care facilities. Our study suggests that a well-honed clinical acumen can similarly detect sepsis requiring acute intervention over the course of an ED visit, since clinicians who were blinded to lactate levels were nonetheless more likely to treat patients with hyperlactatemia with IV antibiotics and fluid resuscitation, and faster times to antibiotics were seen among patients with organ dysfunction. However, anyone can measure lactate and detect increased risk in minutes, while it took over an hour to be examined by an attending physician in our study and over two hours for antibiotics to be administered in patients with organ dysfunction.

Previous studies of lactate in septic shock in children have been conducted in ICU patients, where levels were elevated in nonsurvivors, and mean levels were high.[6] Our study examines lactate in a mixed-severity population, with a mean lactate of 2 mmol/L, and finds that lactate retains utility in identifying severe illness.

LIMITATIONS

Our population was intentionally undifferentiated, and the lower than expected number of patients with our primary predictor and primary outcome limited our precision. Compared to published studies of pediatric ICU patients with sepsis, or pediatric ED patients treated according to septic shock protocols, the proportion of our population with chronic illness was low.[2,10] The low rates of severe sepsis in the general SIRS population highlight the necessity of early tests to identify higher risk patients. Larger studies of lactate in children in the ED will be needed to refine our understanding of its test characteristics.

CONCLUSIONS

The ability to distinguish a child with an innocent febrile illness from one with impending sepsis with organ dysfunction remains a vital consideration for acute care providers for children. We found that serum lactate measurement identifies a population at higher risk for severe outcomes than the broader pediatric ED population with fever and tachycardia and would be a useful addition to clinical assessment in pediatric sepsis clinical and research protocols.

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References

1. Odetola FO, Gebremariam A, Freed GL. Patient and hospital correlates of clinical outcomes and resource utilization in severe pediatric sepsis. Pediatrics. 2007; 119:487–94.
2. Han YY, Carcillo JA, Dragotta MA, et al. Early reversal of pediatric-neonatal septic shock by community physicians is associated with improved outcome. Pediatrics. 2003; 112:793–9.
3. Brierley J, Carcillo JA, Choong K, et al. Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. Crit Care Med. 2009; 37:666–88.
4. Trzeciak S, Dellinger RP, Chansky ME, et al. Serum lactate as a predictor of mortality in patients with infection. Intensive Care Med. 2007; 33:970–7.
5. Vorwerk C, Manias K, Davies F, Coats TJ. Prediction of severe bacterial infection in children with an emergency department diagnosis of infection. Emerg Med J. 2011; 28:948–51.
6. Duke TD, Butt W, South M. Predictors of mortality and multiple organ failure in children with sepsis. Intensive Care Med. 1997; 23:684–92.
7. Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med. 2005; 6:2–8.
8. Saunders AC, Feldman HA, Correia CE, Weinstein DA. Clinical evaluation of a portable lactate meter in type I glycogen storage disease. J Inherit Metab Dis. 2005; 28:695–701.
9. Carcillo JA, Kuch BA, Han YY, et al. Mortality and functional morbidity after use of PALS/APLS by community physicians. Pediatrics. 2009; 124:500–8.
10. Larsen GY, Mecham N, Greenberg R. An emergency department septic shock protocol and care guideline for children initiated at triage. Pediatrics. 2011; 127:e1585–92.