

ORIGINAL CONTRIBUTION

Diagnostic Characteristics of a Clinical Screening Tool in Combination With Measuring Bedside Lactate Level in Emergency Department Patients With Suspected Sepsis

Adam J. Singer, MD, Merry Taylor, RN, Anna Domingo, Saad Ghazipura, Adam Khorasonchi, Henry C. Thode, Jr., PhD, and Nathan I. Shapiro, MD, MPH

Abstract

Background: Early identification of sepsis and initiation of aggressive treatment saves lives. However, the diagnosis of sepsis may be delayed in patients without overt deterioration. Clinical screening tools and lactate levels may help identify sepsis patients at risk for adverse outcomes.

Objectives: The objective was to determine the diagnostic characteristics of a clinical screening tool in combination with measuring early bedside point-of-care (POC) lactate levels in emergency department (ED) patients with suspected sepsis.

Methods: This was a prospective, observational study set at a suburban academic ED with an annual census of 90,000. A convenience sample of adult ED patients with suspected infection were screened with a sepsis screening tool for the presence of at least one of the following: temperature greater than 38°C or less than 36°C, heart rate greater than 90 beats/min, respiratory rate greater than 20 breaths/min, or altered mental status. Patients meeting criteria had bedside POC lactate testing following triage, which was immediately reported to the treating physician if ≥ 2.0 mmol/L. Demographic and clinical information, including lactate levels, ED interventions, and final diagnosis, were recorded. Outcomes included presence or absence of sepsis using the American College of Chest Physicians/Society of Critical Care Medicine consensus conference definitions and intensive care unit (ICU) admissions, use of vasopressors, and mortality. Diagnostic test characteristics were calculated using 2-by-2 tables with their 95% confidence intervals (CIs). The association between bedside lactate and ICU admissions, use of vasopressors, and mortality was determined using logistic regression.

Results: A total of 258 patients were screened for sepsis. Their mean ($\pm$ standard deviation [SD]) age was 64 (± 19) years; 46% were female, and 82% were white. Lactate levels were 2.0 mmol/L or greater in 80 (31%) patients. Patients were confirmed to meet sepsis criteria in 208 patients (81%). The diagnostic characteristics for sepsis of the combined clinical screening tool and bedside lactates were sensitivity 34% (95% CI = 28% to 41%), specificity 82% (95% CI = 69% to 90%), positive predictive value 89% (95% CI = 80% to 94%), and negative predictive value 23% (95% CI = 17% to 30%). Bedside lactate levels were associated with sepsis severity ($p < 0.001$), ICU admission (odds ratio [OR] = 2.01; 95% CI = 1.53 to 2.63), and need for vasopressors (OR = 1.54; 95% CI = 1.13 to 2.12).

Conclusions: Use of a clinical screening tool in combination with early bedside POC lactates has moderate to good specificity but low sensitivity in adult ED patients with suspected sepsis. Elevated bedside lactate levels are associated with poor outcomes.

ACADEMIC EMERGENCY MEDICINE 2014;21:853-857 © 2014 by the Society for Academic Emergency Medicine

From the Department of Emergency Medicine, Stony Brook Medicine (AJS, MT, AD, SG, AK, HCT), Stony Brook, NY; and the Department of Emergency Medicine, Beth Israel Deaconess Medical Center (NIS), Boston, MA.

Received December 30, 2013; revision received February 26, 2014; accepted April 4, 2014.

The study was funded by Abbott Point of Care (Princeton, NJ); AJS is on the Speaker's Bureau of Abbott Point of Care. The authors have no potential conflicts of interest to disclose.

Presented at the Society for Academic Emergency Medicine Annual Meeting, Atlanta, GA, May 2013.

Supervising Editor: Timothy Jang, MD.

Address for correspondence and reprints: Adam J. Singer, MD; e-mail: adam.singer@stonybrook.edu.

With over 750,000 cases a year in the United States alone, sepsis is one of the most common causes of emergency department (ED) visits.^{1,2} Despite advances in the understanding and care of sepsis, mortality remains as high as 25% to 50%.^{3,4} Given the high mortality of sepsis and the importance of early and aggressive treatment strategies such as goal-directed therapy, early recognition of sepsis is of paramount importance.⁵⁻⁷ To improve early recognition of sepsis a number of clinical screening tools and biomarkers have been investigated.

One of the most important biomarkers in sepsis is serum lactate. Lactate is not only the end product of anaerobic glycolysis, but is also increased during stress and critical illness, as well as other mechanisms such as increased bacterial load. Elevated levels of lactate are common in sepsis. There is an association between higher levels of lactate and increased mortality.^{8,9} The clearance of lactate after aggressive therapy is associated with improved outcomes.^{10,11} In addition, elevated levels of lactate may precede clinical evidence of hypoperfusion such as hypotension.¹² As a result, early identification of elevated lactate levels may result in early identification of patient at risk of adverse outcomes.

Because identification of hypoperfusion and cryptic shock may be difficult or delayed, we hypothesized that screening for elevated lactate levels in ED patients with suspected sepsis would result in improved sensitivity with reasonable specificity. We also hypothesized that point-of-care (POC) bedside lactate levels would be associated with intensive care unit (ICU) admission, use of vasopressors, and mortality.

METHODS

Study Design

This was a prospective, observational study designed to determine the diagnostic test characteristics of early bedside lactate levels in ED patients with suspected sepsis. The study was approved by the institutional review board and all patients or their legal representatives gave written informed consent.

Study Setting and Population

We conducted the study at a tertiary care, suburban, academic ED with an annual census of 90,000 patients. The ED is also the site of an emergency medicine residency training program. The study institution participates in the Surviving Sepsis Campaign.

A convenience sample of adult ED patients with suspected infection were screened with a sepsis screening tool for the presence of at least one of the following: temperature greater than 38°C or less than 36°C, heart rate greater than 90 beats/min, respiratory rate greater than 20 breaths/min, or altered mental status.¹³ At the time of triage, the ED triage nurse indicated whether infection was suspected on a specific field in the electronic triage form. If this box was checked and the patient had at least two of the criteria for systemic inflammatory response syndrome (SIRS) as indicated above, an electronic message was sent to the research staff who then approached the patient and verified study criteria. Informed consent was then requested

from either the patient or the legal representative. The research staff were present in the ED Monday through Friday from 8 a.m. to 8 p.m.

Study Protocol

Patients meeting inclusion criteria had a bedside POC lactate (i-STAT System, Abbott Point Of Care, Princeton, NJ) performed after triage on room assignment by a trained research staff member. If the lactate level was 2.0 mmol/L or higher, the results were immediately reported to the treating attending physician, regardless of whether the patient had already been seen by any nurse or physician. All further interventions and treatment were at the discretion of the attending physician.

Demographic and clinical information including comorbidities, final diagnosis, and lactate levels were collected on all study patients. The main outcome was the diagnosis of sepsis, severe sepsis, or septic shock, based on the American College of Chest Physicians/Society for Critical Care Medicine consensus conference definitions.¹⁴ Sepsis was defined as suspected or confirmed infection together with at least two SIRS criteria. Severe sepsis was defined as sepsis together with evidence of end organ failure. Septic shock was defined as the presence of sepsis together with hypotension after adequate fluid resuscitation. Verification of the final diagnosis was based on the assessment of two study personnel, one of whom was an attending physician, and included the entire hospital course. The final clinical diagnosis was abstracted, and the agreement between the hospital discharge diagnosis and the investigator-determined diagnosis was determined. Secondary outcomes were ICU admission, use of vasopressors in the ED, and in-hospital mortality. We also determined whether there was an association between the severity of sepsis and both lactate levels and the time to intravenous (IV) antibiotics. The time of initiation of IV antibiotics was recorded by research staff who were present in the patient's room when the antibiotics were actually given.

Data Analysis

We used descriptive statistics to summarize the data. The diagnostic test characteristics of various cutoff levels of lactate were calculated using 2-by-2 tables together with calculation of their 95% confidence intervals (CIs). Lactate cutoffs studied were 2 mmol/L or greater and 4 mmol/L or greater. Diagnostic test characteristics were calculated for all categories of sepsis and for sepsis, severe sepsis, and septic shock individually. Assuming conservatively that half of the patients who screened positive had sepsis, then 250 patients provides sufficient power to obtain CIs of $\pm 10\%$ for sensitivity and specificity. Nonparametric test of medians was used to determine the association between severity of sepsis and time to IV antibiotics. The associations of comorbidities with sepsis severity and lactate level were evaluated using chi-square tests and median tests, respectively. Finally, we used logistic regression to assess the association between lactate levels and the secondary outcomes of ICU admission, use of vasopressors in the ED, and mortality. Multivariate analyses were not performed on the secondary outcomes because most had too few outcomes to provide

unbiased estimates based on the 10 outcome per model parameter convention. All comparisons used a *p*-value of 0.05 as the level of significance. Data analyses were conducted with SPSS for Windows, version 22.0.

RESULTS

During the study period, 258 ED patients met the study inclusion criteria and were included. Their mean ($\pm$ standard deviation [SD]) age was 64 ($\pm$ 19) years, 54% were male, and 82% were white. Sepsis was confirmed in 208 patients (81.6%). The numbers of patients in each category of the sepsis spectrum were sepsis 99, severe sepsis 79, and septic shock 30. Underlying infections included pneumonia (*n* = 84), urinary tract infection (*n* = 74), and skin and soft tissue infections (*n* = 7).

The median lactate level for the entire study group was 1.5 mmol/L (interquartile range [IQR] = 1 to 2.2 mmol/L). Lactate levels were 2.0 mmol/L or greater in 80 (31%) patients and 4.0 mmol/L or greater in 15 (6%) patients. Patients with confirmed sepsis had higher median lactate levels (1.48 mmol/L, IQR = 1.06 to 2.32 vs. 1.35 mmol/L, IQR = 0.81 to 1.89; *p* = 0.05), but were similar in age (64 years vs. 62 years, *p* = 0.36) to patients in whom sepsis was not confirmed. Lactate lev-

els were associated with sepsis severity with increasing lactate levels in the more severe categories (*p* < 0.001, Figure 1).

A summary of the diagnostic tests characteristics of various cutoffs for lactate levels by the severity of sepsis is presented in Table 1. The areas under the receiver operating characteristic curves levels for detecting the main outcomes were sepsis, 0.59 (95% CI = 0.51 to 0.68); severe sepsis plus septic shock, 0.81 (95% CI = 0.75 to 0.87); and septic shock, 0.66 (95% CI = 0.54 to 0.78).

Comorbidities which were examined included diabetes mellitus, chronic obstructive pulmonary disease (COPD), congestive heart failure, coronary artery disease, HIV, end-stage renal disease, active malignancy, organ transplant, indwelling vascular line, and resident of a nursing home. All of the comorbidities except HIV, organ transplant, and indwelling vascular line showed significantly increased prevalence with increased sepsis severity (data not shown). Patients with diabetes or COPD had significantly higher levels of lactate compared to those without those comorbidities.

Of 258 patients in the study, 212 (82%) received antibiotics while in the ED. Median time from triage to antibiotics was 109 minutes (IQR = 71 to 200 minutes). The percentage of patients receiving IV antibiotics while still in the ED was associated with sepsis severity (Table 2). The median time from triage to IV antibiotics among the various categories of sepsis varied significantly, with increasingly shorter times with increased severity of sepsis (*p* = 0.04; Table 2 and Figure 2).

Comparison of outcomes across the various categories of sepsis demonstrated that increasing severity was associated with use of vasopressors, hospital admission, ICU admission, and in-hospital mortality (Table 3). Increasing levels of bedside lactate were associated with increased likelihood of ICU admission and use of vasopressors (Table 4).

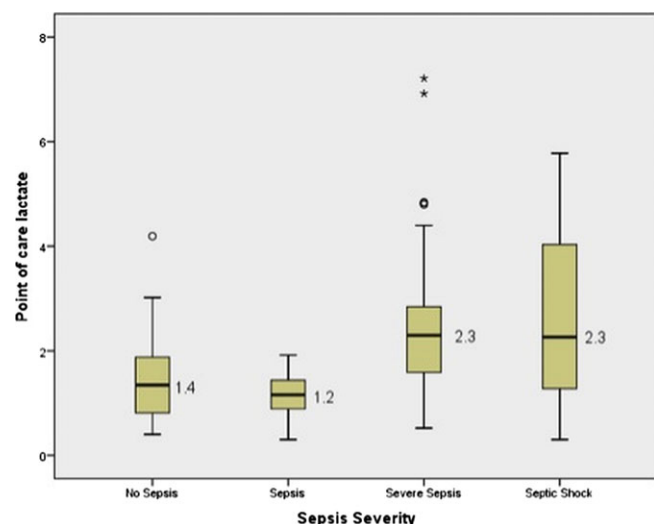


Figure 1. Association between lactate levels and sepsis severity. * denotes outliers.

DISCUSSION

An elevated lactate in patients with sepsis is associated with increased mortality^{8,9} and if rapidly cleared it is associated with better outcome.^{10,11} Because not all patients with sepsis appear very ill, lactate is an increasingly well utilized means to screen for occult severe sepsis (also known as cryptic shock) when the patient's

Table 1
Diagnostic Test Characteristics of Lactate

Characteristic	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Lactate > 2 mmol/L				
All sepsis	34 (28–41)	82 (69–90)	89 (80–94)	23 (17–30)
Severe sepsis + septic shock	64 (56–73)	94 (89–97)	89 (80–94)	79 (72–84)
Septic shock	53 (36–70)	72 (66–77)	20 (13–30)	92 (87–95)
Lactate > 4 mmol/L				
All sepsis	7 (4–11)	98 (90–99)	93 (70–99)	20 (16–26)
Severe sepsis + septic shock	13 (8–20)	99 (96–99)	93 (70–99)	61 (55–67)
Septic shock	27 (14–44)	97 (94–99)	53 (30–75)	91 (87–94)

NPV = negative predictive value; PPV = positive predictive value.

Table 2
Antibiotic Administration by Sepsis Severity

Severity	% Receiving Antibiotics in ED* (n/N)	Median Time to Antibiotics (min)†	IQR
No sepsis	42 (21/50)	180	91–357
Sepsis	89 (88/89)	130	79–232
Severe sepsis	94 (74/79)	90	63–168
Septic shock	97 (29/30)	86	50–183

*p < 0.001.
†p = 0.04.

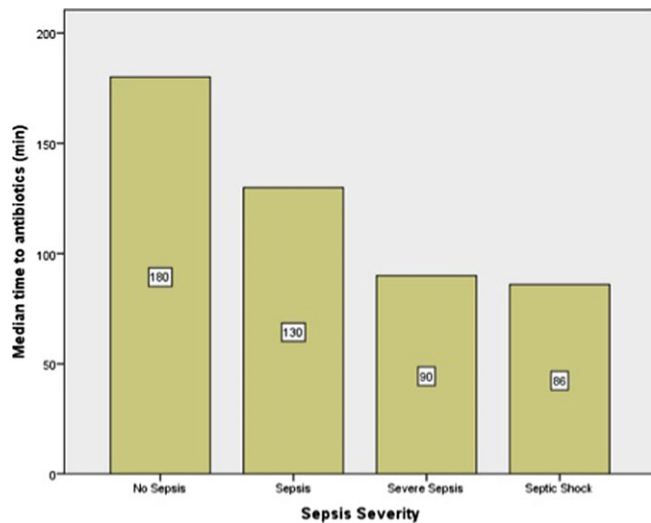


Figure 2. Association between sepsis severity and time from triage to IV antibiotics.

blood pressure and mental status are good, but the patient is still at high risk of death. In the trial by Rivers et al.,^{5,12} almost one-fifth of the patients with severe sepsis had completely normal blood pressures (mean arterial pressure over 100 mm Hg), and almost one-half of the patients did not have systolic blood pressures below 90 mm Hg when their lactate was discovered to be high. Using traditional central laboratory testing, the results of serum lactate may be delayed, leading to an increased time to the recognition of cryptic shock and initiation of necessary early goal-directed therapies. A recent study by Goyal et al.¹⁵ demonstrated that the time to lactate results was significantly reduced with

Table 4
Association Between Initial Bedside Lactate and Outcomes (n = 258)

Outcome	N With Outcome (Sample Size)	Odds Ratio	95% CI	p-value
Vasopressor	18 (213)	1.54	1.13–2.12	0.007
ICU admission	48 (258)	2.01	1.53–2.63	<0.001
Died	10 (246)	1.47	0.99–2.19	0.06

POC testing compared with central laboratory testing (21 minutes vs. 172 minutes), with a median difference of 2.5 hours. This led us to introduce bedside POC lactate measurements as early as possible in patient care, preferably immediately after triage.

The results of our current study demonstrate that early measurement of bedside POC lactate in ED patients with suspected sepsis has low sensitivity to identify all stages of sepsis, even using a cutoff as low as 2 mmol/L. In contrast, an elevated lactate level, especially when greater than 4 mmol/L, has high to very high specificity. The clinical take-home point of our study is that a normal lactate should not be used to exclude sepsis (even severe sepsis), while an elevated lactate level, especially when greater than 4 mmol/L, is highly specific for any and all stages of the sepsis spectrum. Indeed, several study patients presented in septic shock unresponsive to fluid resuscitation despite normal initial lactate levels. It is possible that in these patients lactate levels were measured very early on in the disease process and therefore tissue hypoperfusion had not been present long enough for lactate levels to rise significantly. On the other hand, elevated initial bedside lactate levels were clearly associated with poor outcomes including ICU admission and need for vasopressors. The clinical sepsis screening tool is of value because it helps identify those patients that require POC lactate testing.

The utility of early measurement of lactate in patients with suspected sepsis was recently studied in a prospective observational study of 239 children presenting to the ED with SIRS.¹⁶ Among all study patients, 18 had serum lactates greater than 4 mmol/L. Patients with high lactate levels had a greater than fivefold increased risk of developing organ dysfunction within the first 24 hours of admission. In contrast to our study, the treating physicians were masked to the results of the POC lactate. It is also unclear how early in the course of the ED visits the lactate levels were obtained. Of note,

Table 3
Comparison of Outcomes

Outcomes	No Sepsis	Sepsis	Severe Sepsis	Septic Shock	p-value
Admissions	73 (35/48)	71 (67/95)	97 (75/76)	100 (29/29)	<0.001
ICU admissions	6 (3/50)	7 (7/99)	20 (16/79)	73 (22/30)	<0.001
Vasopressors	2 (2/42)	0 (0/86)	0 (3/75)	50 (14/28)	<0.001
Mortality	2.1 (1/49)	0 (0/91)	2.5 (2/29)	25 (7/28)	<0.001

Data are reported as % (n/N).

the sensitivity and specificity of a lactate greater than 4 mmol/L for identifying severe sepsis with organ dysfunction in the pediatric study were 31% (95% CI = 13% to 58%) and 94% (95% CI = 90% to 96%), which are somewhat similar to our reported results. Finally, not surprisingly, the time from triage to initiation of IV antibiotics was associated with severity of sepsis, with shorter time delays in more severe cases.

LIMITATIONS

The sample size was relatively small, with few patients in the septic shock group. As a result the 95% CIs around the point estimates are rather wide. Second, our study is limited to a single academic medical center that may not be representative of other settings. Third, the study patients represent a convenience sample when an investigator was present, mostly during traditional business hours. It is possible that patients who present during other times of the day may differ in some way.

CONCLUSIONS

Our study demonstrates relatively low sensitivity for early measurement of bedside point-of-care lactate levels in ED patients presenting with suspected sepsis. Specificity increased and was very high in patients with the most severe forms of sepsis, especially using a higher cutoff of a lactate level greater than 4 mmol/L. When elevated, lactate levels were associated with poor outcomes such as intensive care unit admission and need for vasopressors. While early measurement of bedside point-of-care lactate may be helpful in some patients, clinical recognition of the spectrum of sepsis remains the mainstay of diagnosis.

References

1. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001;29:1303–10.
2. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med* 2003;348:1546–54.
3. Lever A, Mackenzie I. Sepsis: definition, epidemiology, and diagnosis. *BMJ* 2007;335:879–83.
4. Dombrovskiy VY, Martin AA, Sunderram J, et al. Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: a trend analysis from 1993 to 2003. *Crit Care Med* 2007;35:1244–50.
5. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;345:1368–77.
6. Russell JA. Management of sepsis. *N Engl J Med* 2006;355:1699–713.
7. Dellinger RP, Levy MM, Rhodes A, and the Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013;41:580–637.
8. Poeze M, Solberg BC, Greeve JW, Ramsay G. Monitoring global volume-related hemodynamic or regional variables after initial resuscitation: what is the better predictor of outcome in critically ill septic patients? *Crit Care Med* 2005;33:2494–500.
9. Shapiro NI, Howell MD, Talmor D, et al. Serum lactate as a predictor of mortality in emergency department patients with infection. *Ann Emerg Med* 2005;45:524–8.
10. Nguyen HB, Rivers EP, Knoblich BP, et al. Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. *Crit Care Med* 2004;32:1637–42.
11. Jones AE, Shapiro MI, Trzeciak S, et al. Lactate clearance vs. central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. *JAMA* 2010;303:739–46.
12. Donnino M, Nguyen B, Jacobsen G, Tomplanovich M, Rivers E. Cryptic septic shock: a sub-analysis of early, goal-directed therapy [abstract]. *Chest* 2003; 124:90S.
13. Robson W, Nutbeam T, Daniels R. Sepsis: a need for prehospital intervention? *Emerg Med J* 2009; 26:535–8.
14. Levy MM, Fink MP, Marshal JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 2003;31:1250–6.
15. Goyal M, Pines JM, Drumheller BC, Gaieski DF. Point of care testing at triage decreases time to lactate levels in septic patients. *J Emerg Med* 2010;38:578–81.
16. Scott HF, Donoghue AJ, Gaieski DF, Marchese RF, Mistry RD. The utility of early lactate testing in undifferentiated pediatric systemic inflammatory response syndrome. *Acad Emerg Med* 2012;19: 1276–80.