Paediatrica Indonesiana

VOLUME 54 May • 2014 NUMBER 3

Original Article

Serial blood lactate levels as a prognostic factor for sepsis mortality

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Abstract

Background Sepsis is a major health problem in children and a leading cause of death. In recent decades, lactate has been studied as a biomarker for sepsis, and as an indicator of global tissue hypoxia, increased glycolysis, endotoxin effect, and anaerobic metabolism. Many studies have shown both high levels and increased serial blood lactate level measurements to be associated with increased risk of sepsis mortality.

Objective To evaluate serial blood lactate levels as a prognostic factor for sepsis mortality.

Methods We performed an observational, prospective study in the Pediatric Intensive Care Unit (PICU) at DR. Sardjito Hospital, Yogyakarta from July to November 2012. We collected serial blood lactate specimens of children with sepsis, first at the time of admission, followed by 6 and 24 hours later. The outcome measure was mortality at the end of intensive care. Relative risks and 95% confidence intervals of the factors associated with mortality were calculated using univariate and multivariate analyses.

Results Sepsis was found in 91 (50.3%) patients admitted to the PICU, of whom 75 were included in this study. Five patients (6.7%) died before the 24-hour lactate collection and 39 patients (52.0%) died during the study. Blood lactate levels of ≥ 4 mmol/L at the first and 24-hour specimens were associated with mortality (RR 2.9; 95%CI 1.09 to 7.66 and RR 4.92; 95%CI 1.77 to 13.65, respectively). Lactate clearance of less than 10% at 24 hours (adjusted RR 5.3; 95% CI 1.1 to 24.5) had a significantly greater risk followed by septic shock (adjusted RR 1.54; 95%CI 1.36 to 6.47) due to mortality.

Conclusion In children with sepsis there is a greater risk of mortality in those with increasing or persistently high serial blood lactate levels, as shown by less than 10% lactate clearance at 24-hours after PICU admission. **[Paediatr Indones. 2014;54:168-73.]**

Keywords: *sepsis, serial blood lactate, lactate clearance, mortality*

According to the *International Pediatrics Sepsis Consensus Conference* in 2005, sepsis is a systemic inflammatory response syndrome (SIRS) associated with an infection.[1] Sepsis remains a major health problem, as a leading cause of mortality in infants and children. In the United States, more than 42,000 cases per year of severe sepsis in children (aged <18 years) have been reported, with a mortality rate of 10.3%.[2] In Indonesia, mortality rates due to sepsis remain high, at approximately 43% in the PICU of Sardjito Hospital, Yogyakarta in 2010 and 54% in the PICU of Cipto Mangunkusumo Hospital, Jakarta.[3,4] Early detection, prompt treatment, monitoring and stratification of mortality risk is important.

Several biomarkers for pediatric sepsis have been studied. In the last decade, lactate had been studied as a biomarker of tissue hypoxia in patients with critical illness, trauma, and sepsis.[5-10] In sepsis, the increased lactate level is generally thought to be related to global tissue hypoxia, increased glycolysis, anaerobic metabolism, and a role of endotoxin in cells, resulting from systemic responses to infection,

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cardiopulmonary failure, and multiple organ dysfunction leading to death.[5,10-13]

Previous studies have reported blood lactate level to be a prognostic marker and predictor of sepsis mortality.[1,14-16] Shapiro *et al.* and Nguyen et *al.* reported that blood lactate level ≥4 mmol/L and lactate clearance of less than 10% increased the risk of sepsis mortality.[14,16-17] The aim of this study was to evaluate serial blood lactate levels and the other factors as a prognostic indicators for sepsis mortality in our hospital setting.

Methods

We conducted a prospective cohort study in the PICU of Sardjito Hospital, Yogyakarta from July to November 2012. Children aged 1 month to 18 years who met the criteria of sepsis according to the *International Pediatrics Sepsis Consensus Conference* 2005[1] definition and whose parents consented to participation were eligible for this study. We excluded patients with major congenital anomalies, cyanotic congenital heart diseases, trauma, burns, severe malnutrition, asthmatic and epileptic status, or pulmonary edema. Patients with HIV infection receiving anti-retroviral therapy or those with diabetes mellitus using anti-diabetic oral medication were also excluded.

We measured capillary blood lactate levels using a portable hand analyzer (*Accutrend Lactate®*). Accuracy, reliability, and linearity of this device was calibrated against benchmarked laboratory testing.[18] Serial blood lactate examinations were performed at 0 hour, or the time of patient PICU admission (LI), as well as at 6 hours (LII), and 24 hours (LIII) after the first lactate measurement. We categorized serial blood lactate levels at a cut off point of 4 mmol/L, as this level had been shown to have prognostic value.[1,4,13-17] Patients were treated according to local protocols, and lactate levels did not influence procedures or treatment. Subjects were followed until the end of intensive care treatment, and outcomes were classified as survived or died. Lactate clearance was defined as the percent change in lactate level at 6 or 24 hours after the baseline measurement. A persistent or increase in lactate level was defined as lactate clearance of less than 10%.

Factors associated with mortality were recorded. Septic shock was considered to be a condition of sepsis with cardiovascular organ dysfunction, as defined by the *International Pediatric Sepsis Consensus Conference* 2005.[1,19] Lactic acidosis was defined as blood pH <7.35 and lactate level of >2 mmol/L. Hyperglycemia was defined as random glucose >200 mg/dL. Microorganisms found in any specimens such as blood, urine, or other sites of infection were categorized as positive cultures and the time of antibiotic onset was categorized as either <6 hours or ≥6 hours antibiotic onset.

Data were analyzed with Pearson's and Chi square tests to compare distributions of each factor. All prognostic factors with P<0.25 in univariate analysis were included in a multivariable logistic regression model. Relative risk with 95% confidence interval (CI) was calculated for each factor to assess statistical significance.

This study was approved by the Medical and Health Research Ethics Committee, Gadjah Mada University Medical School, Yogyakarta, Indonesia.

Results

Of the 181 patients admitted to the PICU, 91 (50.3%) patients met the inclusion criteria, 16 were excluded, and five subjects died before 24 hours, thus leaving 70 subjects (**Figure 1**). **Table 1** shows the basic characteristics of subjects.

Table 1. Subjects' characteristics

Characteristics	(n=75)
Age	
1-12 months, n (%)	45 (60.0)
>12 months, n (%)	30 (40.0)
Gender	
Male, n (%)	44 (58.7)
Female, n (%)	31 (41.3)
Diagnoses	
Surgical cases, n (%)	18 (24.0)
Non-surgical cases (*medical sepsis*), n (%)	57 (76.0)
Pneumonia, n (%)	25 (33.3)
Intracranial infection, n (%)	17 (22.7)
Diarrhea, n (%)	6 (8.0)
Malignancy, n (%)	5 (6.7)
Kidney disease, n (%)	3 (4.0)
Dengue infection, n (%)	1 (1.3)
Patients with positive cultures, n (%)	43 (57.3)
Septic shock, n (%)	25 (33.3)

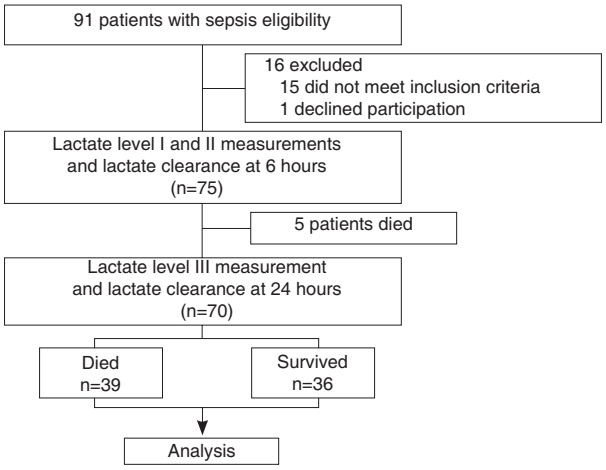

Figure 1. Study flow diagram

Median length of PICU stay was 120 hours, ranging from 9 to 1,295 hours. The most common microorganisms found in the 55 positive cultures from 43 patients were *Staphylococcus sp.* (23.6%) and *Pseudomonas sp.* (21.8%). Thirty-nine patients died (52.0%) at the end of their PICU stay and the most common cause of death was pneumonia (41.0%).

Factors associated with mortality are shown in **Table 2**. Univariate analysis revealed significant results for the following variables: LI, LIII, 24-hour lactate clearance, septic shock and lactic acidosis. Multivariate analysis revealed that lactate clearance of less than 10% at 24 hours and septic shock had statistically significant associations with mortality (**Table 3**).

Table 2. Univariate analysis of prognostic factors for mortality in patients with sepsis

Variables	Died n (%)	Survived n (%)	RR	95% CI	P value
Lactate I					
≥4 mmol/L	29 (61.7)	18 (38.3)	2.90	1.09 to 7.66	0.029
<4 mmol/L	10 (35.7)	18 (64.3)			
Lactate II					
≥4 mmol/L	28 (59.6)	19 (40.4)	2.28	0.88 to 5.93	0.089
<4 mmol/L	11 (39.3)	17 (60.7)			
Lactate III *					
≥4 mmol/L	25 (65.8)	13 (34.2)	4.92	1.77 to 13.65	0.002
<4 mmol/L	9 (28.1)	23 (71.9)			
Lactate clearance in 6 hours					
<10 %	29 (53.7)	25 (46.3)	1.27	0.46 to 3.50	0.636
≥10%	10 (47.6)	11 (52.4)			
Lactate clearance in 24 hours*					
<10 %	26 (68.4)	12 (31.6)	6.50	2.27 to 18.62	0.001
≥10 %	8 (25.0)	24 (75.0)			
Septic shock					
Yes	20 (80.0)	5 (20.0)	6.53	2.09 to 20.29	0.001
No	19 (38.0)	31 (62.0)			
Lactic acidosis					
Yes	27 (62.8)	16 (37.2)	2.81	1.09 to 7.24	0.030
No	12 (37.5)	20 (62.5)			
Antibiotics					
>6 hours	10 (55.6)	8 (44.4)	1.21	0.42 to 3.50	0.602
<6 hours	29 (50.9)	28 (49.1)			
Hyperglycemia					
Yes	9 (56.3)	7 (43.7)	1.24	0.41 to 3.78	0.701
No	30 (50.8)	29 (49.2)			
Microorganism cultures					
Positive	23 (53.5)	20 (46.5)	1.15	0.46 to 2.87	0.765
Negative	16 (50.0)	16 (50.0)			

* n = 70

Table 3. Multivariate analysis of prognostic factors for sepsis mortality

Variables	Adjusted RR	95% CI
Lactate I	0.16	0.03 to 1.72
Lactate II	3.25	0.60 to 17.73
Lactate III	0.73	0.14 to 3.83
Lactate clearance <10% at 24 hours	5.30	1.10 to 24.50
Septic shock	1.54	1.36 to 6.47
Lactic acidosis	0.45	0.12 to 1.71

Discussion

The incidence of sepsis during this study was high, with the mortality rate comparable to that of previous studies.[2-4,15] Most patients were aged less than 12 months, as sepsis is related to immune system immaturity in severe infection.[2,21,22] Sepsis is a systemic response associated with infection by bacteria, fungi, parasites, viruses or other pathogens.[1,20,21] Only 38-40% of cases typically tested positive for pathogenic bacteria, whereas 50-70% of cases usually do not have positive cultures.[3,20-23]

Lactate is a substrate produced by glycolysis in cells and mostly cleared by the liver (50%) and kidneys (20%).[5,8] Lactate accumulation depends on the rate of glycolysis, consumption of lactate, and clearance by tissues.[5] Hyperlactatemia in sepsis is well recognized to be related to global tissue hypoxia, leading to anaerobic metabolism due to hemodynamic alterations.[5-7] In sepsis, the mechanism of hyperlactatemia has been explained as an increased aerobic glycolysis rate triggered by cytokine or catecholamine stimulation, accumulation of pyruvate caused by impaired activity of pyruvate dehydrogenase complex, and an endotoxin role in the alteration of pyruvate transport to the Krebs cycle.[5,10-13] Rather than overproduction, hyperlactatemia in sepsis is also thought to be a sign of altered lactate clearance due to multiple organ dysfunction.[5,12]

Blood lactate levels of ≥4 mmol/L have been reported to be a prognostic marker of severe sepsis.[1,4,5,14,15] In our study, high initial (LI) and 24-hour (LIII) lactate levels were significantly associated with mortality. The 6-hour lactate level (LII) did not have a significant association with mortality. As such, the 6-hour lactate clearance was not associated with mortality (**Table 2**).

Both early and serial lactate levels in patients who died in this study were higher than in patients who survived, similar to results in previous studies.[13,14] A study showed an association between elevated lactate levels and mortality. Patients with ≥4 mmol/L hyperlactatemia had a mortality rate of 28.4% compared to 4.9% in patients with lactate levels of <2.5 mmol/L.[14] Also, another study found that persistent hyperlactatemia at 24 hours of hospitalization was related to 93% mortality. Declining levels of lactate and adequate sepsis management for the first 24 hours had a major role in the reduction risk of mortality.[15]

For predicting mortality, the value of using static vs. dynamic lactate levels remains inconclusive.[24] Some studies have shown dynamic parameter changes in lactate concentrations to be clinically more useful than static indices, as we observed in our study.[24,25] The 24-hour lactate clearance of less than 10% was significantly associated with increased risk of sepsis mortality, similar to others' results.[15-17] The explanation is that an adequate early lactate clearance indicates a resolution of global tissue hypoxia and decreases the risk of mortality.[18,21-23] In contrast, Arnold *et al*. found that hospital mortality was associated with a 6-hour lactate clearance of less than 10%. This difference may be due to the differences in settings and outcome measurements.[26]

The mortality rate of septic shock in previous studies varied from 7-50%.[27-29] Puspanjono *et al*. reported that high initial lactate levels were associated with hypoperfusion and shock in dengue shock syndrome.[30] We did not determine if initial hyperlactatemia was a predictor for the occurrence of septic shock. Mortality caused by prolonged septic shock leads to global tissue hypoxia because of wider-ranging hypoperfusion, causing tissue damage and multiple organ dysfunction.[1,5,11,23] Therefore, early detection of septic shock in children and adequate initial treatment can improve outcomes in patients with septic shock.[1,4,19,31]

Lactate measurements in our study did not affect patient treatment. Monitoring of lactate levels did not change outcomes and the value of lactate as a therapeutic tool remains unclear. An integrated treatment has to provide benefits to patients.[25] Based on previous studies, serial blood lactate monitoring is recommended in critical care settings because it clearly has a place in risk stratification.[16-17,24-27] A limitation of our study was that patients had a wide spectrum of disease, and the first lactate level was measured in the PICU. As such, previous management in the emergency or pediatric ward may have affected the results.

In children with sepsis, increasing or persistently high serial blood lactate, as shown by less than 10% lactate clearance at 24 hours, increases their risk of mortality. In addition, 24-hour lactate clearance and septic shock are also factors affecting mortality in sepsis patients.

References

1. Goldstein B, Giroir B, Randolph A, International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med. 2005;6:2-8.
2. Watson RS, Carcillo JA, Linde-Zwirble WT, Clermont G, Lidicker J, Angus DC. The epidemiology of severe sepsis in children in the United State. Am J Respir Crit Care Med. 2003;167:695–701.
3. Nurnaningsih, Setyowireni D, Rusmawatiningtyas D. Microbial pattern in pediatrics septicaemia at pediatric intensive care unit Sardjito Hospital. Paed Indones. 2011;51(S):92.
4. Ikatan Dokter Anak Indonesia (IDAI). Diagnosis dan tata laksana sepsis pada anak. Rekomendasi Ikatan Dokter Anak Indonesia UKK Pediatri Gawat Darurat. Jakarta: BP IDAI; 2010. p. 1-21.
5. Duke T. Dysoxia and lactate. Arch Dis Child. 1999;81:343–50.
6. Bakker J, Coffernils M, Leon M, Gris P, Vincent JL. Blood lactate levels are superior to oxygen-derived variables in predicting outcome in human septic shock. Chest. 1991;99:956-62.
7. Vincent JL. Lactate and biochemical indexes of oxygenation. In: Tobin MJ, editor. Principles and practice of intensive care monitoring. New York: McGraw-Hill; 1998. p. 369-75.
8. Blomkalns AL. Lactate a marker for sepsis and trauma. 2007 [cited 2012 May 21]. Available from http.//www.emcreg.org
9. Bakker J, Jansen TC. Don't take vitals, take a lactate. Intensive Care Med. 2007;33:1863-5.
10. Standage SW, Wong HR. Biomarkers for pediatric sepsis and septic shock. Expert Rev Anti Infect Ther. 2011;9:71-9.
11. Cicarelli DD, Vieira JE, Bensenor FE. Lactate as a predictor of mortality and multiple organ failure in patients with the systemic inflammatory response syndrome. Rev Bras Anestesiol. 2007;57:630-8.
12. Levraut J, Ciebiera JP, Chave S, Rabary O, Jambou P, Carles M, *et al*. Mild hyperlactatemia in stable septic patients is due to impaired lactate clearance rather than overproduction. Am J Respir Crit Care Med. 1998;157:1021-6.
13. Koliski A, Cat I, Giraldi DJ, Cat ML. Blood lactate concentration as prognostic marker in critically ill children. J Pediatr (Rio J). 2005;81:287-92.
14. Shapiro NI, Howell MD, Talmor D, Nathanson LA, Lisbon A, Wolfe RE, *et al*. Serum lactate as a predictor of mortality in emergency department patients with infection. Ann Emerg Med. 2005;45:524–8.
15. Hatherill M, McIntyre AG, Wattie M, Murdoch IA. Early hyperlactataemia in critically ill children. Intensive Care Med. 2000;26:314-8.
16. Nguyen HB, Rivers EP, Knoblich BP, Jacobsen G, Muzzin A, Ressler JA, *et al*. Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. Crit Care Med. 2004;32:1637-42.
17. Nguyen HB, Loomba M, Yang JJ, Jacobsen G, Shah K, Otero RM, *et al*. Early lactate clearance is associated with biomarkers of inflammation, coagulation, apoptosis, organ dysfunction and mortality in severe sepsis and septic shock. J Inflamm. 2010;7:6.
18. Baldari C, Bonavolonta V, Emerenziani GP, Gallotta MC, Silva AJ, Guidetti L. Accuracy, reliability, linearity of Accutrend and Lactate Pro versus EBIO plus analyzer. Eur J Appl Physiol. 2009;107:105-11.
19. Carcillo JA, Fields AI. American College of Critical Care Medicine Task Force Committee Members. Clinical practice parameters for hemodynamic support of pediatric and neonatal patients in septic shock. Crit Care Med. 2002;30:1365–78.
20. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, *et al*. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Intensive Care Med. 2003;29;530-8.

21. Bone RC, Sprung CL, Sibbald WJ. Definitions for sepsis and organ failure. Crit Care Med. 1992; 20:724-6.
22. Reinhart K, Bloos F, Brunkhorst FM. Pathophisiology of sepsis and multiple organ dysfunction. In: Fink MP, Abraham E, Vincent JL, Kochanek PM, editors. Textbook of critical care. 5th ed. Philadelphia: Elsevier Saunders; 2005. p. 1249-58.
23. Parrillo JE, Parker MM, Natanson C, Suffredini AF, Danner RL, Cunnion RE, *et al*. Septic shock in humans. Advances in the understanding of pathogenesis, cardiovascular dysfunction, and therapy. Ann Intern Med. 1990;113:227-42.
24. Jansen TC, van Bommel J, Bakker J. Blood lactate monitoring in critically ill patients: a systemic health technology assessment. Crit Care Med. 2009;37:2827-39.
25. Nichol A, Bailey M, Egi M, Pettilla V, French C, Stachowski E, *et al*. Dynamic lactate indices as predictors of outcome in critically ill patients. Crit Care. 2011;15:R242.
26. Arnold RC, Shapiro NI, Jones AE, Schorr C, Pope J, Casner E, *et al*. Multicenter study of early lactate clearance as a determinant of survival in patients with presumed sepsis. Shock. 2009;32:35-9.
27. Jat KR, Jhamb U, Gupta VK. Serum lactate levels as the predictor of outcome in pediatric septic shock. Indian J Crit Care Med. 2011;15:102–7.
28. Han YY, Carcillo JA, Dragotta MA, Bills DM, Watson RS, Westerman ME, *et al*. Early reversal of pediatric-neonatal septic shock by community physicians is associated with improved outcome. Pediatrics. 2003;112:793–9.
29. Brierley J, Carcillo JA, Choong K, Cornell T, Decaen A, Deymann A, *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.
30. Puspanjono MT, Latief A, Tumbelaka AR, Sastroasmoro S, Gunardi H. Comparison of serial blood lactate level between dengue shock syndrome and dengue hemorrhagic fever (evaluation of prognostic value). Paediatr Indones. 2007;47:150-5.
31. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, *et al*. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med. 2008;36:296–327.