

Correlation between interleukin-6 and septic shock in children

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Abstract

Background Sepsis is a life-threatening condition and the most common cause of death in intensive care units in developing countries, such as Indonesia. The first clinical signs of sepsis are usually non-specific. More specific signs and laboratory parameters often occur late and are associated with organ dysfunction and high mortality rates. Interleukin-6 (IL-6) is a biomarker reported to be superior to clinical signs and conventional tests for sepsis. IL-6 levels may indicate microorganism invasion, as well as progression of infection into sepsis, severe sepsis, and septic shock.

Objective To evaluate a correlation between interleukin (IL)-6 and septic shock in children

Methods This cross-sectional study was conducted in the pediatric intensive care unit of Prof. Dr. R.D. Kandou Hospital, Manado, between June to September 2011. Subjects were children with sepsis or septic shock aged 1 month to 13 years, with diagnoses based on the *International Pediatric Sepsis Consensus Conference Criteria* 2005. A one-time measurement of IL-6 plasma levels was done at the time of diagnosis. Data was analyzed by logistic regression test using SPSS version 17 software. A P value of <0.05 indicated statistical significance.

Results The mean IL-6 plasma level in the septic group was 1.68 (95%CI 1.45 to 1.91) pg/mL and that of the septic shock group was 2.33 (95%CI 1.79 to 2.86) pg/mL. Our results showed a strong positive correlation between IL-6 plasma levels with the probability of septic shock in children with sepsis (regression coefficient=1.310, P=0.024).

Conclusion Higher plasma IL-6 levels were associated with a higher risk of septic shock in children with sepsis. [Paediatr Indones. 2012;52:352-5].

Keywords: sepsis, interleukin-6

Sepsis is a systemic disease caused by microbes or toxins in the bloodstream, leading to systemic responses. Sepsis is a major cause of mortality in critically ill patients.¹⁻⁴ It has been defined as the systemic inflammatory response syndrome (SIRS) caused by infection with bacteria, fungi, or viruses, or as a consequence of secreted toxins. However, the most common cause is Gram-negative bacteria.^{5,6} The progression of SIRS usually leads to life-threatening multiple organ dysfunction culminating in multiple organ failure (MOF).⁷ Consequently, there is a demand for a better marker for early recognition of sepsis in clinical circumstances. Recognition should be followed by aggressive, protocolized clinical management in order to improve mortality outcomes. The pathogenesis of sepsis is complex, with several mediators known to be involved.^{8,9} Endotoxin, a component of Gram-negative bacterial cell walls, is the predominant factor responsible for the initiation of sepsis. Also known as lipopolysaccharide (LPS), endotoxin, in addition to other bacterial molecules, trigger a generalized response that involves both cellular and humoral pathways. The generation of cytokines such as tumor

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necrosis factor, interleukin (IL)-1, IL-6, IL-8 and IL-12 act to trigger inflammatory or anti-inflammatory responses.^{1,10-12}

Interleukin-6 was one of the first circulating pro-inflammatory cytokines to be widely evaluated in septic patients.^{13,14} Previous studies found that IL-6 was a good marker for early diagnosis of sepsis.^{15,16} This study was conducted to investigate a correlation between IL-6 plasma levels and septic shock in children, without regard to the underlying cause of IL-6 production and sensitivity.

Methods

This cross-sectional, analytical study was approved by the Prof. Dr. R.D. Kandou Hospital Ethics Committee. Subjects were children aged 1 month to 13 years who were hospitalized for sepsis or septic shock in the pediatric intensive care unit of this hospital in Manado, between June – September 2011. Subjects fulfilled the clinical and laboratory 2005 *International Pediatric Sepsis Consensus Conference criteria* for sepsis or septic shock.⁷ Sepsis was defined as the presence of at least two of the following criteria: temperature of $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$, tachycardia, tachypnea and leukocytosis or more than 10% immature forms on white blood cell differential, known as SIRS, in addition to a focal infection. Septic shock was defined as sepsis accompanied by cardiovascular dysfunction. Patients with severe malnutrition, immunodeficiency, or malignancy were excluded.

Blood specimens were obtained from subjects at the time of diagnosis, after informed consent was given. The blood specimens were collected in sterile tubes, centrifuged, and stored at -20°C until IL-6 measurements were done at a reference laboratory. Interleukin-6 plasma measurements were performed by a sandwich enzyme immunoassay quantitative technique using a *Quantikine HS IL-6* kit.

To determine the probability of shock in sepsis children based on IL-6 plasma levels, we used logistic regression analysis with a significance level of $P < 0.05$; using the formula:

$$P = \frac{1}{1 + e^{-(-3,821 + 1,310 \text{Log}(\text{IL-6}))}}$$

Statistical analyses were performed using the *Statistical Product and Services Solutions* (SPSS) version 17.0.

Results

A total of 40 children were included in this study, consisting of 27 males and 13 females. Five males and 4 females had septic shock. Sepsis subjects' mean age was 3.63 (SD 2.73) years, while that of subjects' with septic shock was 3.43 (SD 3.88) years. Sources of infection in our subjects were bronchopneumonia (17/40), acute diarrhea (10/40), encephalitis (5/40), meningitis (2/40) and acute abdomen (6/40). Mean IL-6 plasma levels were 1.68 (SD 0.62) pg/mL in the sepsis group (95%CI 1.45 to 1.91) and 2.33 (SD 0.69) pg/mL in the septic shock group (95%CI 1.79 to 2.86) (**Table 1**).

Table 1. Characteristics of children with sepsis and septic shock

Characteristics	Groups	
	Sepsis (n=31)	Septic shock (n=9)
Mean age (SD), years	3.63 (2.73)	3.43 (3.88)
Male gender, n	22	5
Sources of infection		
Bronchopneumonia, n	12	5
Acute diarrhea, n	8	2
Encephalitis, n	4	1
Meningitis, n	1	1
Acute abdomen, n	6	0
Mean plasma IL-6 (SD), pg/mL	1.68 (11.13)	2.33 (23.06)

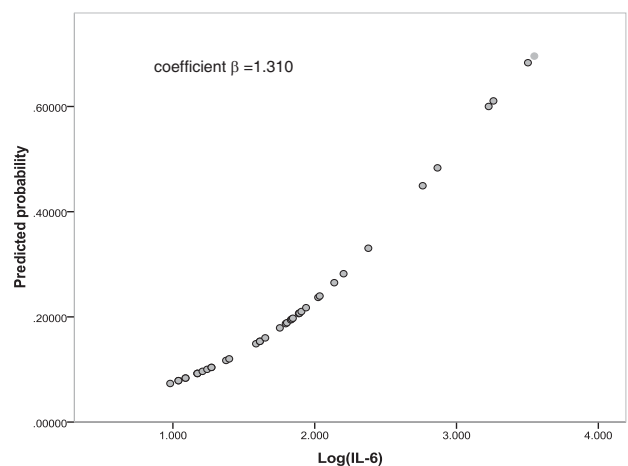


Figure 1. Correlation between IL-6 plasma level and probability of shock in children with sepsis

Logistic regression analysis revealed that at the time of diagnosis, IL-6 plasma level had a significant positive correlation to the probability of shock in children with sepsis, (coefficient $\beta = 1.310$ and $P=0.024$), as shown in **Figure 1**.

Discussion

Bacterial infection continues to be the major cause of morbidity and mortality in children. The prognosis for sepsis depends on early recognition of the condition. A definitive diagnosis may be made by positive blood cultures, but this requires a minimum of 48-72 hours, and they yield positive results in only 30-70% of cases. Therefore, a good marker is needed in order to make a diagnosis of sepsis as early as possible. Interleukin-6 has been reported to be an early indicator of sepsis because of its rapid increase in response to the presence of endotoxin. Also, IL-6 is secreted by monocytes and macrophages in response to bacteremia.¹³⁻¹⁵ Previous studies have shown that IL-6 is a good marker for sepsis and also valuable to determine the prognosis of the disease.¹⁷⁻²⁰

In this study, we found that the mean IL-6 level in the sepsis group was 1.68 (95%CI 1.45 to 1.91) pg/mL, while in that of the septic shock group was 2.33 (95%CI 1.79 to 2.86) pg/mL. Pavare *et al.* found higher mean IL-6 levels: 13.8 pg/mL in the sepsis group and 67.9 pg/mL in the septic shock group.¹⁵ Fioretto *et al.* also found significantly different mean IL-6 levels with 0.86 pg/mL in the sepsis group and 10.85 pg/mL in the septic shock group.²¹ A possible reason for these differences may be that they were conducted in different countries with different patient characteristics and the use of different IL-6 measurement kits.

Logistic regression analysis showed a highly positive significant correlation between higher IL-6 plasma levels and greater probability of shock in children with sepsis ($r = 1.310$, $P=0.024$). This result was consistent with studies by Pavare *et al.*, Fioretto *et al.* and Briassoulis *et al.* which all showed that IL-6 plasma levels in septic shock patients were significantly higher than that of sepsis patients.^{15,21,22}

A limitation of this study was this cross-sectional study design meant that we only collected one blood specimen from each patient at the time of hospital admission for measuring IL-6 plasma levels.

Our subjects were enrolled by consecutive sampling, and consisted of 27 boys and 13 girls. Similarly, Hendra *et al.* showed that sepsis was more common in boys (54.1%) than in girls (45.9%).²³ Likewise, Pavare *et al.*¹⁵ found that of 91 sepsis patients, 53.84% were boys, and Runtunuwu *et al.* in Manado also found that sepsis was more prevalent in boys (58.9%) than in girls (41.1%).²⁴

Bronchopneumonia was the most common source of infection in our subjects, similar to results by Hendra *et al.*²³ and Watson *et al.*²⁵

We found a strong positive correlation between higher plasma IL-6 levels and greater probability of shock in children with sepsis. Based on this study, we recommend investigating plasma IL-6 levels in septic children.

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