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Original Article

Procalcitonin levels in children aged 3-36 months with suspected serious bacterial infection

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Abstract

Background Fever in children aged 3-36 months is usually caused by viral infection, however, 11-20% of cases may progress into serious bacterial infection (SBI). A good diagnostic tool is required to detect SBI to reduce mortality and avoid unnecessary use of antibiotics.

Objectives To determine procalcitonin (PCT) levels, and etiology of bacteremia in febrile children aged 3-36 months old with suspected SBI.

Methods A cross-sectional descriptive study was conducted in Cipto Mangunkusumo and Tangerang General Hospital during April-May 2010. Complete blood cells count and acute illness observation score (AIOS) were performed on febrile children aged 3-36 months. Subjects meeting the inclusion criteria underwent blood culturing and testing of procalcitonin levels.

Results There were 39 children met the criteria. Boys and girls ratio was 1.6 with median age of 10 months. Mean of AIOS was 20.5 (4.5 SD) and mean of hemoglobin was 10.2 (2.1 SD) g/dl. Median of leukocyte and absolute neutrophyl count were 18,600/ul and 12,300/ul, respectively. Median of procalcitonin 1.8 (0.04-71.60) ng/mL, mean of procalcitonin in bacteremia subgroup 22.60 (27.6 SD) ng/mL and 6.38 in non-bacteremia subgroup (11.0 SB) ng/mL. In children with severely ill appearance, the likelihood of procalcitonin levels $\geq$ 2 ng/ml was 8.67 times higher (95% CI 1.66-50.56) than in moderately or mildly ill-appearing children. In subjects with procalcitonin level of $\geq$2 ng/ml, the risk of bacteremia was 8.1 times (95% CI 2.9-1051.6) higher and the risk of sepsis was 55.47 times higher than in subjects with procalcitonin <2 ng/ml (95% CI 1.22-68.02). We observed bacteriemia in 11 of 39 subjects (28.2%). The pathogens isolated from these 11 subjects were *Klebsiella pneumonia, Staphylococcus aureus, Eschericia coli, Serratia marcesens, Staphylococcus saprophyticus*, and *Serratia liqueafaciens*.

Conclusion The proportion of bacteremia in children aged 3-36 months old with suspected serious bacterial infection was 28.2% with no predominant microorganism. Elevated procalcitonin level of $\geq$2 ng/mL was associated with severe illness apppearance, bacteremia, and sepsis. **[Paediatr Indones. 2010;50:310-5]**.

Keywords: *procalcitonin, serious bacterial infections, bacteremia, children aged 3-36 months, fever without source*

Fever is one of the most common problem in pediatric practice and still a challenging problem to differentiate between acute viral infection and serious bacterial infection (SBI). Children age under 3 years old represent 20% of febrile children and 10-25% of them have risk to develop serious bacterial infection, while 3-11% of them would develop bacteremia. Rapid diagnosis and treatment of SBI is essential in children, since a delay in the treatment may lead to poorer outcome. However, it is important to limit the use of antibiotics to reduce the development of bacterial resistance to antibiotics, to reduce complication and cost, and to prevent unnecessary admission for parenteral administration of antibiotics.[1-3]

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The approach to febrile infant remains a controversial topic and a set of recommendation appeared simultaneously. Previous publications demonstrated that clinical impressions based on examination result alone, as Acute Illness Observation Score (AIOS) that proposed by McCarthy,[5] is inadequate to exclude SBI and bacteremia. Thus the use of biomarker like procalcitonin, has been considered to differentiate infants and children at higher risk for bacterial infection because it has a good performance as a diagnostic marker with sensitivity and specificity of 69-100% and 74-100%, respectively.[2] One objective of this study was to determine procalcitonin levels in febrile children aged 3-36 months at risk of serious bacterial infection. The second objective was to determine the prevalence and etiology of bacteremia in the same patient population.

Methods

Patient characteristics and inclusion criteria

This cross-sectional descriptive study was conducted in Cipto Mangunkusumo and Tangerang Hospital between April to May 2010. We included children aged 3-36 months with fever less than seven days, AIOS score > 10, leukocytes> 15.000/ul, immunocompetence, and availability of informed parental consent. Those children with a history of antibiotic treatment within 48 hours before admission to the hospital, any chronic pathology and malignancy, or suffered from malaria and acute pancreatitis were excluded from the study.

Clinical and diagnostic evaluations

Complete history, demographic information, degree and duration of fever, physical examination and clinical evaluation using acute illness observation score (AIOS) were recorded at the time of initial evaluation. We performed a complete blood count on children with AIOS > 10. For those meeting the inclusion criteria, we obtained an additional 5 ml blood sample for blood culture and procalcitonin testing. Our study protocol was approved by the Ethics Committee of Medical Faculty of University of Indonesia, Cipto Mangunkusumo Hospital.

Laboratory assessment

Complete blood cells count were performed on blood sample mixed with ethylenediaminetetraacetic acid (EDTA) using an automated cell counter. Blood culture were drawn in BacT/Alert pediatric tube and incubate in BacT/Alert incubation. Procalcitonin measurement was performed using Brahms PCT-Kryptor Compact sensitive (Brahms Diagnostica, Henningdorf BEI, Berlin).

Statistical analysis

Statistical analysis was performed by using SPSS 17.0 (SPSS, Chicago, IL). Demographic characteristics of laboratory values for subjects with and without SBI and bacteremia were compared. Normally distributed data were expressed as mean (SD); non-normally distributed data were expressed as median; categorical variables were reported as percentages. Parameters displaying $P < 0.05$ were considered statistically significant.

Results

The value of the variable clinical and laboratory values of subjects are listed in **Table 2.**

Table 1. The characteristics of study subjects (n = 39)

Characteristics		n
Sex	Boys	24
	Girls	15
Age	3-12 months	25
	13-24 months	11
	25-36 months	3
Nutritional status	Well-nourished	20
	Under-nourished	19
Immunization Status	Completing basic immunization	17
	Incomplete immunization	22
General appearance of illness	Mild	1
	Moderate	21
	Severe	17
Level of consciousness	Alert	25
	Altered consciousness	14
State of recovery	Recovered	29
	Dead	9
	Rejected to continue the treatment	1
Blood culture	Positive	11
	Negative	28

Table 2. The central tendency of clinical and laboratory values (n = 39)

Variable	*Mean (SD) #Median (min-max)	CI 95% PI
Age (months) #	10 (3 to 36)	10.1 to 15.5
Length of fever (days) #	2.0 (1 to 7)	2.1 to 3.1
Length of hospitalized (days) #	6.0 (1 to 30)	6.1 to 10.5
AIOS *	20.5 (4.5)	19.1 to 21.9
GCS #	13 (4 to 15)	10.2 to 12.6
Heart rates (times / minute) *	138.7 (20.5)	132.2 to 145.1
Respiratory rate (times / minute) *	41.5 (13.0)	37.4 to 45.6
Temperature (ºC) #	38.6 (38,1 to 40,4)	38.7 to 39.1
Hemoglobin (g / dL) *	10.2 (2.1)	6.9 to 10.9
Hematocrit (%) *	30.7 (5.8)	28.9 to 32.5
Leukocytes (x 1000/uL) #	18.6 (15.1 to 78.5)	18.4 to 25.5
Thrombocyte (x1000/uL) #	384.0 (16.0 to 1040)	310.1 to 542.7
ANC (x 1000 / uL) #	12.3 (5.12 to 62.015)	11.6 to 17.6
Procalcitonin #	1.8 (0.04 to 71.90)	5.1 to 16.7

The mean AIOS was 20.5 (4.5 SD) with a median body temperature of 38.6 °C (38.1 to 40.4 °C). Twenty-six subjects had anemia with a mean hemoglobin level of 10.2 g/dl (SD 2.1) and a median leukocyte count of 18,600/ul (range 15,100-78,500/ul). Of these subjects, 71.8% had an ANC count > 10,000/ul.

The median PCT was 1.8 ng/mL with a mean of 10.9 (SD 18.5) ng/ml. This study used two cut off points for PCT: PCT > 0.5 ng/ml for the likelihood of SBI and PCT ≥ 2ng/ml for the likelihood of bacteremia. There were 27 (69%) subjects with PCT > 0.5 ng/ml with a mean of 15.67 ng/ml (SD 20.55) and 19 (48%) subjects with PCT ≥ 2 ng/ml ranging from 0.04 to 71.90 ng/ml. The mean value of PCT in the bacteremic sub-group was 22.61 ng/ml (SD 27.6), while that of the non-bacteremic sub-group was 6.38 ng/ml (SD 11.0) (p = 0.054). All subjects with sepsis had PCT >2 ng/ml with a mean of PCT 29.79 ng/ml (SD 25.19). The possibility of sepsis was found to be 55.47 times higher at PCT level of ≥ 2 ng/ml (95% CI 2.9 to 1051.6) than at < 2 ng/ml.

Sepsis was the most common diagnosis in this study (n=11), followed by diarrhea (9), pneumonia (8) and bacterial meningitis (7). The proportion of bacteremia in this study was 11 cases out of 39 subjects. The pathogens isolated in this study are stated in **Table 3.** There were two *BacT / Alert* media that were grown fungi; no further analysis was done to the species of fungi.

Table 3. Types of microorganisms causing bacteremia

Types of microorganisms	Amount
Klebsiella pneumonia	2
Staphylococcus aureus	2
Eschericia coli	2
Serratia marcesens	2
Staphylococcus saprophyticus	1
Pseudomonas sp	1
Serratia liqueafaciens	1
Total	11

Table 4 shows the correlation of clinical variables with PCT and bacteremia. Febrile children aged ≤1 year had a higher risk of bacteremia 23 times than those aged more than 1 year.

Discussion

Previous studies reported that AIOS may be used to predict bacteremia in febrile children. Separate studies suggest that procalcitonin levels of febrile children may also have predictive value, although neither of these has been used convincingly in making diagnoses. In this study, AIOS and procalcitonin were used together to diagnose bacteremia. Bang et al[4] reported that AIOS >10 alone had a sensitivity of 87.93% and specificity of 83.78% for diagnosing bacteremia. These results were similar to those of

Table 4. The correlation of clinical variables with PCT and bacteremia

Clinical variables	PCT		P	OR (CI 95%)	Blood culture		P	OR (CI 95%)
	Pos	Neg			Pos	Neg		
Age*#)								
<1 years	14	11	0.378	2.29	11	14	0.003	23.00
>1 years	5	9		(0.49 to 11.04)	0	14		(2.82 to 187.5)
General appearance*								
Severe illness	13	4	0.006	8.67	7	10	0.158	3.15
Mild/moderate	6	16		(1.66 to 50.56)	4	18		(0.61to 17.38)
Blood culture								
Positive	9	2	0.025	8.10				
Sterile	10	18		(1.22 to 68.02)				

*) Absolute Fisher Test (performed on blood culture)

#) Formula Corrected OR (for blood culture test based on age)

McCarthy et al[5] (sensitivity 77%, specificity 88%), while Pratiwi[6] reported lower accuracy (58.06% sensitivity, specificity 94.33%, positive predictive value 76.6% and negative predictive value 87.56%) by using the same AIOS score. Several studies have used procalcitonin levels to diagnose bacteremia with good sensitivity and specificity.

The median age of subjects in our study was 10 months, with a boy to girl ratio of 1.6:1, a ratio close to that of Bang et al[4] who observed a ratio of 1.46:1. Only 44% of our subjects had complete basic immunizations, but none of our subjects had received boosters, pneumococcal or *Haemophilus influenza type b* immunizations.

Anemia was observed in 67% of subjects in this study. Wahidiyat suggested that the most common cause of anemia in children under 5 years is lack of nutrients, especially iron. Based on household surveys in 2001, Wahidiyat reported a 48.1% prevalence of iron deficiency anemia.[7] Hadinegoro[8] reported that acute infections can cause severe anemia due to disturbance of hematopoiesis in bone marrow caused by excessive systemic inflammatory response. High median value of leukocytes (18,600/ul) in this study does not imply high leukocyte value in SBI patients in the population, because this study excluded SBI patients with leukocytes < 15,000/ul. Earlier studies reported that leukocyte count is not a good predictor for SBI and bacteremia in children, thus, it should not be used solely to screen for risk of SBI. Mintegi et al[9] reported that a leukocyte count of > 15.000/ul was observed in only 34.4% of 1586 subjects aged 3-36 months with bacteremia.

In severely ill-appearing children, procalcitonin levels of ≥2 ng/ml occurred 8.67 times more often (95% CI 1.66 to 50.56) than in mild or moderately ill-appearing children. There have been no studies to explain the association of general appearance with PCT levels, probably due to the difficulty in standardizing clinician judgement of clinical appearance. We observed 27 subjects with procalcitonin levels >0.5 ng/ml and SBI (69%) with a mean PCT 15.67 ng/ml (SD 20.55) and a median of 5.97 (0.5 to 71.90) ng/ml. These figures are higher than reported by Andreola et al,[1] who observed 23.1% of subjects had SBI and PCT levels > 0.5 ng/ml, with a median PCT of 1.8 (0.5 to 10.5) ng/ml. All subjects diagnosed with sepsis had PCT >2 ng/ml, with a mean of 29.79 (SD 25.19) ng/ml, with odds ratio of 55.47 (95% CI 2.9 to 1051.6). Only 6 cases of sepsis had proven bacteremia with the odds ratio of 5.52. The risk of bacteremia in sepsis cases was 5.52 times higher than with other diagnoses (95% CI 1.19 to 25.5). Our results suggest that PCT levels may be used as a biomarker to diagnose sepsis.

The mean PCT in 11 subjects with proven bacteremia was 22.60 (SD 27.6) ng/ml, while that in the non-bacteremic subgroup was 6.3 ng/ml (SD 11.0). The risk of bacteremia in subjects with PCT ≥ 2 ng/ml was 8.1 times higher compared to subjects with PCT <2 ng/ml. In this study, we found two cases of bacteremia who had procalcitonin levels <2 ng/ml suspected of the low sensitivity of blood cultures (30-50%). Phetsouvanh et al[10] recommended performing serial blood cultures within 24 hours to increase the sensitivity of blood culture as a diagnostic tool.

We observed bacteremia in 28.2% of our subjects (11 of 39 cases). This figure is similar to that reported by Bang et al,[4] who found bacteremia in 28.16% of subjects in the same age group. However, different results were reported by others, namely Wilkinson et

al[11] 0.25%, from Hsiao et al[12] 0.9%, Mintegi et al[9] 0.9%, and Lee et al[13] 1.6%. This is a discrepancy may be explained by the fact that these studies were done in developed countries that have had mandatory immunization programs since the 1990s to regulate pneumococcal and *Haemophilus influenza* type b vaccinations. After the era of pneumococcal and *Haemophilus influenza* type b immunization programs, other studies reported the lower prevalence of bacteremia less than 1%. REF

We found no single, predominant pathogenic microorganism to be the cause of infections. This might be due to our small sample size, making it difficult to draw conclusions on trends of commonly-infecting microorganisms in children aged 3-36 months. Yilmaz *et al*[14] reported that the dominant pathogen in their study was *Steptococcus pneumoniae*. Similarly, Laupland *et al*[15] recorded *Streptococcus pneumoniae, Staphylococcus aureus* and *Eschericia coli* as the common microorganisms causing bacteremia in children. On the other hand, Shwe *et al*[16] reported a variety of pathogens: *Salmonella typhi* (43.1%), followed by *Eschericia coli* (12.3%), *Staphylococcus aureus* (7.7%) and *Pseudomonas aeruginosa* (7.7%) during their one year observation of febrile children aged 1 month to 12 years at the Myanmar Yangon Children's Hospital. The case fatality rate from bacteremia in our study is quite high (9 children), a 23% mortality rate.

Based on our findings, we conclude that elevated procalcitonin level $\geq$2 ng/ml is associated with severe illness, bacteremia, and sepsis, suggesting its use as a diagnostic tool to predict bacteremia in febrile infants.

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