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Original Article

Fever and laboratory profiles as predictors of serious bacterial infection in children

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Abstract

Background There is a debate on the use of high fever with other morbidities to predict serious bacterial infection (SBI). Bacterial infection occurs in 3-15% of children with fever of ≥ 39°C. Various laboratory parameters including increased C-reactive protein (CRP) levels, leukocyte counts, and absolute neutrophil counts (ANC) have been studied for their usefulness in predicting the occurrence of SBI, but with varied results. The ability to discriminate whether a patient has a SBI can lead to improved patient management.

Objective To evaluate fever of ≥ 39°C, leukocyte counts of ≥15,000/mm^3, ANC of ≥10,000/mm^3 and CRP of ≥10 mg/L as predictors of SBI in children aged 1 month-18 years.

Methods A case-controlled study was conducted by collecting data from medical records at Sanglah Hospital, Denpasar. Subjects in the case group were diagnosed with SBIs (bacterial meningitis, bacterial pneumonia, bacteremia or sepsis, urinary tract infections, or bacterial gastroenteritis), and subjects in the control group non serious bacterial infections (non-SBI). Data was analyzed using bivariate and multivariate methods with 95% confidence intervals and a statistical significance value of P <0.05.

Results Sixty subjects were studied, with 30 subjects in the case group and 30 in the control group. Baseline characteristics of subjects were similar between the two groups. Fever and CRP were predictors of SBI [OR 8.71 (95% CI 1.61 to 46.98), P = 0.009; and OR 6.20 (95% CI 1.58 to 24.24), P = 0.012, respectively].

Conclusion Fever ≥ 39°C and CRP ≥ 10 mg/L were significant predictors of serious bacterial infections in children. **[Paediatr Indones. 2012;52:313-6]**.

Keywords: *serious bacterial infection, fever, leukocytes, neutrophil, C-reactive protein, children*

Fever in children is one of the most common complaints in pediatric emergency rooms. Although the majority of these children have a benign cause for their fever, distinguishing the child with a serious bacterial infection (SBI), such as bacteremia, urinary tract infection (UTI), meningitis, bacterial gastroenteritis, and pneumonia is important and may be difficult to perform.[1] Bacterial infection occurs in 3-15% of children with fever of ≥39°C.[1,2]

If a patient's fever has lasted for more than 12 hours (with a temperature of ≥ 39°C), the following bacterial markers have been reported to be predictive of SBI: leukocyte cut-off value of 10,000/mm^3, ANC cut-off value of 10,000/mm^3, and C-reactive protein (CRP) cut-off level of 7 mg/L.[1] Similar study of predictors for SBI in children aged 3-36 months with fever showed that patients with leukocytes of ≥ 16,000/mm^3 had a five times greater risk of SBI.[3] In contrast, other studies reported that age and high fever were not significant predictors of SBI, while leukocyte counts and CRP were associated with increased SBI.[2,4] However, none of these studies were done in children aged 1

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month-18 years. Therefore, we evaluated fever of ≥ 39°C, leukocyte count of ≥ 15,000/mm^3, ANC of ≥ 10,000/mm^3, and CRP of ≥ 10 mg/L as predictors for SBI in children aged 1 month-18 years.

Methods

A case-control study was conducted in children aged 1 month-18 years admitted to the Department of Child Health, Udayana University Medical School /Sanglah Hospital, Denpasar from January 2010 to January 2011.

Subjects in the case group were children with SBI, including bacteriemia or sepsis, bacterial meningitis, bacterial pneumonia, urinary tract infections, or bacterial gastroenteritis, according to the standard diagnostic tests at Sanglah Hospital. As the control group, we included all children without SBI, which included any diagnosis beyond the diagnosis of SBI. Patients with malignancies, trauma, immune disorders or incomplete data were excluded. Data was collected from medical records. We first identified SBI and non-SBI subjects, then retrospectively collected the data of fever, leukocyte counts, ANCs, and CRP levels at the time of hospital admission. This study was approved by the Research Ethics Committee of Udayana Medical School/Sanglah Hospital.

Required sample size was calculated using the unpaired case control method, with an assumed odds ratio (OR) for each variable (fever, leukocytes, ANC, and CRP). We calculated the largest OR for fever, with a type I error of 5% and power of 80%, resulting in 30 subjects in each group without matching. Data was analyzed for each factor separately with bivariate analysis (Chi square test). Multivariate analysis was performed using logistic regression with backward stepwise elimination. Results were presented in OR, 95% confidence intervals, and a statistical significance value of $P < 0.05$.

Table 1. Baseline characteristics of subjects

Characteristics	SBI n=30	non-SBI n=30
Age, n		
1 – <3 months	4	4
3 – 36 months	17	22
≥36 months	9	4
Male gender, n	19	24
Duration of fever, n		
<72 hours	17	22
≥72 hours	13	8
Nutritional status		
Undernourished	16	9
Well-nourished	14	19
Overweight	0	1
Obese	0	1
Hydration status		
No dehydration	30	29
Mild-moderate dehydration	0	1
Medication history		
Antibiotics, n	11	10
Antipyretics, n	23	26
Diagnoses, n		
Pneumonia	15	-
Bacterial meningitis	7	-
Sepsis	6	-
UTI	2	-
Bronchiolitis	-	14
Rhinotonsilopharingitis	-	7
Febrile seizure	-	4
Others	-	5*

*Others: encephalitis (1), acute otitis media (1), acute diarrhea (1), hydrocephalus (1), epilepsy (1)

Table 2. Bivariate analysis of prediction of SBI

Variables	SBI	non-SBI	OR	95%CI	P value
Fever, n					
≥39°C	14	2	12.25	2.46 to 60.9	0.001
<39°C	16	28			
Leukocytes count, n					
≥15,000/mm^3	19	8	4.75	1.58 to 14.24	0.004
<15,000/mm^3	11	22			
CRP level, n					
≥10 mg/L	17	4	8.51	2.37 to 30.46	0.001
<10 mg/L	13	26			
ANC, n					
≥10,000/ mm^3	18	6	6.00	1.89 to 19.04	0.002
<10,000/ mm^3	12	24			

Results

There were 30 subjects in the case group (SBI) and 30 subjects in the control group (non-SBI). Subjects' ages ranged from 1 month to 13 years. No subjects had severe dehydration. Baseline characteristics of subjects are shown in **Table 1**.

Predictive factors for SBI in children are shown in **Table 2**. Bivariate analysis revealed that fever of > 39°C, leukocyte count of > 15,000/mm^3, CRP of > 10mg/mL, and ANC of ≥ 10,000/mm^3, were all significant predictive factors for SBI. Multivariate analysis revealed that fever of ≥39°C and CRP of ≥10 mg/L were significant predictive factors for SBI [OR 8.71 (95% CI 1.61 to 46.98), P = 0.009 and OR 6.20, (95% CI 1.58 to 24.24), P = 0.012, respectively] (**Table 3**).

Table 3. Multivariate analysis with backward stepwise elimination of predictive factors of SBI

Step	Variable	OR	95%CI	P value
1	Fever of ≥ 39°C	8.25	1.40 to 48.54	0.02
	Leukocytes of ≥ 15,000/mm^3	2.27	0.40 to 121.73	0.349
	CRP of ≥ 10 mg/L	4.63	1.02 to 20.85	0.046
	ANC of ≥ 10,000/mm^3	1.03	0.15 to 6.91	0.972
2	Fever of ≥ 39°C	8.31	1.49 to 46.19	0.015
	Leukocytes of ≥15,000/mm^3	2.32	0.63 to 8.55	0.20
	CRP of ≥ 10 mg/L	4.66	1.11 to 19.67	0.036
3	Fever of ≥ 39°C	8.71	1.61 to 46.98	0.009
	CRP of ≥ 10 mg/L	6.20	1.58 to 24.24	0.012

Discussion

Body temperature measurements in children may flucuate depending on the thermometer type and the use of antipyretics. In our study, the use of antipyretics was similar between groups. Logistic regression analysis showed that high fever and CRP levels were significant markers of SBI occurrence.

During acute fever, higher temperatures are related to the degree of bacterial invasion and systemic host response against bacterial infection.[5] A previous study showed that the risk of SBI increased with higher body temperature with a cutoff point of 39°C.[6] An average temperature of 40.2 (SD 0.5) °C in children with bacteremia and 38.9 (SD 0.5) °C in children without bacteremia was also reported.[7]

A prior study in Sanglah Hospital showed that children with bacteremia had higher temperatures than children without bacteremia [OR 11.4 (95% CI 11.23 to 11.7)].[8]

We found that fever of ≥ 39°C was significantly associated with increased of SBI occurrence. Similarly, temperature of ≥ 39°C had previously been associated with bacteremia with RR 8.4 (P <0.001) compared to leukocyte counts of ≥15,000/uL with RR 1.2 (P = 0.7).[9] Listen Also, Bonadio *et al*. reported that temperature of ≥ 39°C had a greater proportion of SBI occurrence compared to temperature of ≥ 39°C (3.2% vs. 6.8%, respectively).[10] The best cutoff point to assess the occurrence of SBI was reported to be 39.6°C.[11] Despite this data, the validity of higher temperature as a predictor of serious disease remains unclear.[12] Hsiao *et al*. found that infants aged 57-180 days divided into subject with SBI and without SBI groups had similar mean temperatures of 38.5 (SD 1.0) °C vs. 38.4 (SD 1.0) °C, respectively.[4] Our results may differ because our subjects were in a different age range. Since infants have immature immune systems, lower temperatures do not eliminate the probability of SBI.

The results of our study were comparable to a previous study where CRP of ≥ 10 mg/L was found to significantly increase the probability of SBI. CRP levels have been shown to have high sensitivity and specificity in detecting SBI.[13] Hsiao *et al*. reported that the mean CRP was significantly higher in the SBI group than in the non-SBI group [2.7 (SD 3.7) mg/dL vs. 0.9 (SD 1.4) mg/dL, P <0.001].[4] Past studies have also found that the bacterial markers studied were more predictive of SBI if the duration of fever was > 12 hours. CRP performed better than leukocytes count and ANC for predicting SBI.[1,4]

Kofteridis *et al*. reported a correlation between CRP and body temperature, where higher body temperature correlates with higher CRP level.[14] CRP is the best marker for SBI detection because it has higher sensitivity and the tests are relatively affordable.[15] Quantitative CRP concentration is a valuable laboratory test in the evaluation of febrile young children who are at risk for occult bacteremia and SBI, with a better predictive value than leukocyte count or ANC. [16]

CRP is an acute phase reactant synthesized by the liver due to increased levels of cytokines, especially IL-6, released during infection or inflammation. IL-6 binds to polysaccharides of pathogens and activates the classical complement pathway. It is produced 4-6 hours after the onset of tissue damage or inflammation, increases two-fold every 8 hours and peaks at 36 hours. IL-6 is also a sensitive marker of bacterial infections.[17]

A limitation in this study was not analyzing the type and duration of antibiotic and antipyretic used. Also, retrieving data retrospectively may give biased information, especially for the previous number of febrile days. In addition, the use of different thermometers and complete blood count equipment may have lead to data errors.

We conclude that fever of ≥39°C and CRP of ≥10 mg/L were significant predictive factors for SBIs in children.

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