Diagnostic Value of IL-6, CRP, WBC, and Absolute Neutrophil Count to Predict Serious Bacterial Infection in Febrile Infants

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Abstract- Since clinical manifestations of most febrile infants younger than three months old are nonspecific, differentiation of Serious Bacterial Infection (SBI) from self-limiting viral illness is a significant challenge for pediatricians. This study was performed to assess the diagnostic value of white blood cell count (WBC), Absolute Neutrophil Count (ANC), Interleukin -6 (IL-6) and C-reactive protein (CRP) level to predict SBI in febrile infants younger than three months old who were hospitalized. This was a diagnostic test validation study. In this prospective study, 195 febrile infants admitted to 17 Shahrivar Hospital underwent a full sepsis workup including blood, urine, cerebrospinal fluid cultures and chest radiography. WBC count, ANC and CRP and Il-6 level were measured in all patients. Serum IL-6 concentration was measured by Enzyme-linked Immunosorbent Assay test. Then diagnostic, values of these tests for predicting SBI was compared with each other. Of total cases, 112 (57.4%) infants were male. SBI was diagnosed in 29 (14.9%) patients. The most common type of SBI was Urinary Tract Infection (UTI). Serum IL-6 (≥20pg/dl) had sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of 79/1%, 91.6%, 75.4%, 60.3%, respectively and for CRP (≥ 10mg/l) values were 81.6%, 89.8%, 78.2%, and 52%, respectively. The predictive values of CRP and IL-6 were higher than WBC and ANC. IL-6 and CRP are more valid and better diagnostic markers for predicting SBI than WBC count and ANC. CRP level seems to be an accessible and cost-effective marker for early diagnosis of SBI. Since by no marker we can totally rule out SBI in febrile infants < three months of age, it is recommended to administer systemic antibiotics until culture results become available.

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Introduction

Fever is the most common chief complaint in less than three months infants visiting emergency departments or outpatient clinics (1). The management of these patients is challenging because of the relatively high prevalence of serious bacterial infection (SBI) and inability to easy discriminate those with SBI from those with simple viral illness. Definitive diagnosis of SBI requires a positive culture of the cerebrospinal fluid (CSF), blood, urine or an identifiable bacterial focus by physical examination or radiography (2). Between 7 to 18% of febrile infants, <3 months old are reported to have SBI (1). However because most of these infants have a unrevealing physical examination and the results of cultures are not immediately available, clinicians must decide on appropriate patient management based on history, physical examination and laboratory tests (2). Much work has been performed to identify potential screening markers by means of them physicians can reliably discriminate febrile children with higher risk of SBI from those with lower risk. One of these markers is C-reactive protein (CRP), an acute phase reactant that quickly rises during infection, inflammation and trauma (3). Another marker is IL-6, which is one the pre-inflammatory cytokines and can be detected in serum during early stages of infection. IL-6 also has a role in the production of CRP and fibrinogen by the liver, particularly during bacterial infection. Its level may be higher than CRP in early Stages of disease, so it is

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helpful for early diagnosis (4). WBC count and its differential have been evaluated as predictive markers in nearly all studies of febrile infants (5).

Since there is not any certain opinion about accuracy of predicted value of these markers in literature, this study was designed to: 1-determine serum concentration of IL-6, CRP levels, WBC count and absolute neutrophil count (ANC) in febrile infants < three months old with no obvious site of fever on admission 2- evaluate the usefulness of these markers for predicting SBI in study participants.

Materials and Methods

This prospective diagnostic test validation study was performed between June 2012 and March 2013 in 17 Shahrivar children hospital in Rasht-Iran and was approved by the school of medicine Ethics committee, Guilan University of Medical Science. A total of 195 febrile infants < 3 months of age admitted to the hospital with no clear source of the fever and anorectal temperature ≥38oc were studied. Exclusion criteria were: prematurity, positive history of receiving antibiotics during 48h before admission, duration of fever less than 6 h before hospitalization and apparent source of infection on physical examination other than acute otitis media (AOM). According to previous studies, AOM was not considered as an SBI (6,7). All participants underwent the same sepsis evaluation including blood, urine and cerebrospinal fluid (CSF) cultures, complete blood cell count with differentiation, CRP and serum IL-6 level, chest X-Ray(CXR) and stool examination and culture (only for infants with diarrhea). Urine culture was obtained by suprapubic aspiration or by transient bladder catheterization. Isolation of any bacteria from a bladder aspirate or count of ≥103 colony-forming units per milliliter of catheterized urine was considered as urinary tract infection (UTI) (6). All infants were treated by systemic antibiotics after obtaining cultures. A questionnaire was designed for each case. SBI was defined by 1- Growth of any bacterial pathogen in one or more of CSF, blood, urine or stool cultures. 2- Any disease commonly associated with bacterial pathogens including pneumonia or soft tissue infection (cellulitis) (6,8). Pneumonia was diagnosed according to clinical and radiological findings in CXR (6). No specimen was processed for viral pathogens. CRP was measured with commercially available immunonephelometry; serum IL-6 concentration was measured with the enzyme-linked immune sorbent assay (ELISA) by using Bender-med kit. Cut-off levels for IL-6 and CRP assay, WBC and ANC were considered: 20pg/ml (9), 10mg/l) (3), 15.000/mm3 (5) and 10.000/mm3 (5) respectively. Statistical analysis was performed using SPSS statistical package (Versionm15). Categorical variables were analyzed by chi-square test. Comparisons of means were examined using a t-test, where the data fit a normal distribution, and the Mann-Whitney U test, where the data was non-normal. *P* value of < 0.05 was considered significant.

Results

Of 195 febrile infants, < 3 months of age who met inclusion criteria, 112 (57.4%) were male. In 29 (14.9%) patients, SBI was diagnosed according to mentioned criteria. We found no difference between male and female with regards to the prevalence of SBI (18 and 11 cases respectively, *P*= 0.686). UTI was diagnosed in 19 (65.5%) pneumonia in 4 (13.8%) and bacteraemia in 6 (20.7%) cases, with SBI. Meningitis was diagnosed in 2 infants according to CSF analysis, but they were excluded from the study because of receiving antibiotics before admission. Levels of CRP and IL-6 and WBC count and ANC are shown in table 1. Sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) of measured indicators are listed in Table 2.

Table 1. WBC count, ANC, CRP and IL-6 levels in study participants

	Group	Number	Mean	Standard deviation	Z. value	*P*-value
WBC count	SBI +	29	13624.1	7689	2.67	0.006
	SBI -	166	9251.8	4175		
ANC	SBI +	29	8213.5	6085.6	2.18	0.029
	SBI -	166	4872.2	2796.8		
CRP mg/l	SBI +	29	47.7	18.4	8.45	0.0001
	SBI -	166	6.2	3.7		
IL-6 Pg/ml	SBI +	29	34.7	16.3	7.94	0.0001
	SBI -	166	7.7	7.3		

Table 2. Predictive values of measured indicators

	IL-6	CRP	ANC	WBC count
Sensitivity	79.1	81.6	34.5	41.4
Specificity	91.6	89.8	76.2	80.2
PPV	75.4	78.2	52.6	60
NPV	60.3	52	44.5	41.1

Discussion

According to current findings, the incidence of SBI was 14.9% in febrile cases. The incidence in febrile infants < 3 months of age has been reported from 7% to 18%. Enteroviral infections may be the major causes of febrile episodes in infants younger than three months (1). As mentioned we had not access to facilities necessary for viral culture. In the current study WBC count, ANC, CRP level, and serum IL-6 were significantly higher in patients with SBI. Abdollahi *et al.,* reported that neonates with early onset sepsis had a significantly higher WBC count, the serum level of IL-6 and high sensitive CRP level than neonates without sepsis. This remained significant even after 12-24 hours of admission (10).

In the present study, serum IL-6 and CRP level were better predictors for SBI than WBC count and ANC. In a report by Galette- Lacour *et al*., WBC count with a cutoff level of 15.000/mm3 had a poor sensitivity of 52% and specificity of 74% in detecting SBI in febrile children (11).

Although sensitivity and specificity of WBC count was not present in Bachur *et al.,* study, they concluded that WBC count by itself was neither a dependable nor accurate predictor of SBI in febrile infants < 3 months of age (2). Current findings confirm theirs.

In kuppermann study ANC of ≥ 10.000/mm3 was a predictor of SBI as a WBC count of more than 15.000/mm3, with a sensitivity of 69% and specificity of 70% in febrile children between 3 to 36 months of age (12). In another study, Bakes and Bressan *et al.,* found that CRP and ANC were better predictors of SBI in febrile neonates than WBC count (13,14). The discrepancy maybe due to difference in group's ages. In the study by Gajdos *et al.,* NPV of CRP > 20mg/l was 93.1% in predicting SBI in febrile infants < 3 months of age (15). In another study in Rasht- Iran, CRP was more sensitive than WBC count and ANC to predict SBI in febrile neonates (6).

Shahkar *et al.,* in a meta-analysis on 13 publications reported that IL-6 is a valid marker for predicting neonatal sepsis. The pooled sensitivity and specificity of IL-6 was 0.79 and 0.84 respectively. Cut-off levels of IL-6 ranged from 10 to 160 pg/ml (16). In a study by Huang *et al*., IL-6 with cut-off value of 20pg/ml had a sensitivity of 68%, specificity of 88%, PPV of 91% and NPV of 58% for predicting sepsis in children(8). Celik *et al*., reported that sensitivity, specificity, PPV and NPV of Il-6 to predict neonatal sepsis was 72%, 84%, 95% and 42% respective and for CRP was 67%, 97%, 99% and 39% respectively (4).

The differences in predictive values of IL-6 and CRP could be due to various factors like methods and cut- off levels, the low sample size in some studies and case characters (age).

According to present findings, IL-6 and CRP are better markers in predicting SBI in young febrile infants. In comparison, CRP is more accessible and cost effective than IL-6. Since none if these markers have 100% accuracy for detecting SBI, it is recommended that these infants become hospitalized and receive broad spectrum antibiotics until results of their cultures become available.

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