

Usefulness of C-Reactive Protein and Clinical Characteristics in Identifying Severe Bacterial Infection in Children with Fever without Source

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What is already known on this topic?

- There is disagreement in the diagnosis and treatment of patients with fever without source. It frequently uses invasive tests which lead to discomfort to the patients and higher costs to the health system.

What this study adds on this topic?

- Among all the clinical and biochemical variables assessed, serum C-reactive protein greater than 80 mg/L and the number of previous days with fever were variables associated with the presence of serious bacterial infections.

ABSTRACT

Objective: Fever continues to be the most frequent cause of care in the pediatric population. The uses of invasive and unnecessary tests result in discomfort to the patients. Local epidemiological data could help to refine screening strategies, especially in low resources settings. The present study aims to describe the prevalence of serious bacterial infections in infants with fever without source and to evaluate the usefulness of clinical and laboratory parameters in the identification of serious bacterial infections.

Materials and Methods: We included all children aged 0–36 months presenting with fever without source between January 2015 and December 2017. Demographic and clinical characteristics, investigations, and management procedures were recorded at the time of inclusion. Potential predictors of serious bacterial infections were compared between patients with and without serious bacterial infections.

Results: In total, 137 patients were included. Serious bacterial infections were diagnosed in 41 patients (29.9%; 95% CI, 22%–38%). The most frequent diagnosis in serious bacterial infection patients was urinary tract infection (78%). Serum C-reactive protein levels greater than 80 mg/L (odds ratio, 2.79 [1.14,6.86]) and total days with fever (odds ratio, 2.56 [1.81,3.62]) showed a significant association to predict serious bacterial infections.

Conclusion: Most infants with fever without source presented self-limited febrile syndromes without evidence of severe bacterial infection. C-reactive protein levels greater than 80 mg/L and the number of previous days with fever were variables associated with the presence of serious bacterial infections. Our results need to be validated in other tropical countries.

Keywords: Fever, children, serum C-reactive protein (CRP)

INTRODUCTION

Fever without source (FWS) is the one of most common diagnoses in pediatric patients less than 2 years.¹ In 30% of infants, this diagnosis could be the principal manifestation of potentially serious infections.^{2–4} After introducing, at the beginning of this century, specific vaccination against *Haemophilus influenzae* type b and *Streptococcus pneumoniae*, the rates of serious bacterial infection (SBI) decreased significantly worldwide.^{4–9} However, this syndrome continues to generate concerns, especially among parents and doctors. There is no consensus on the diagnosis and treatment of patients with FWS. It is usually the use of invasive and (cerebrospinal fluid [CSF] or Blood culture, etc) which fallouts in discomfort to the patients.^{10,11} Additionally, in tropical countries, where diseases such as malaria or dengue fever or parasitic diseases are still prevalent, even the epidemiological characterization of

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fever in children is incomplete.¹² Local epidemiological data could help to refine screening strategies, especially in low-resource settings where the lack of information does not allow the design of health policies. The present study aims to describe the prevalence of SBI in infants with FWS and to evaluate the usefulness of clinical and laboratory parameters in the identification of SBI.

MATERIALS AND METHODS

Study Design

This single-center retrospective study was carried out in the pediatric emergency department (ED) of a tertiary hospital that has nearly 190 000 visits per year. Due to the retrospective nature of our study, informed consent was not obtained, according to local regulations. All research was performed following relevant guidelines/regulations approved by the Institutional Review Board of Uniremington University (Acta No 4 de 2014).

Study Population

All patients aged 0–36 months with FWS in emergency room between January 2015 to December 2017 in a tertiary care hospital in Rionegro, Colombia, were eligible for inclusion in the study. We define FWS as a patient with a temperature of $\geq 38.0^{\circ}\text{C}$ (less than 10 days of duration) with no other infectious source such as respiratory symptoms, diarrhea, acute otitis media, etc. Patients with major chronic condition, ongoing antibiotic treatment, or difficulty in communicating were excluded. Serious bacterial infection was defined as “patients diagnosed with bacteremia or urinary tract infection (UTI) or bacterial meningitis, or pneumonia.” Our hospital adapts the clinical guideline of manage feverish illness in children aged under 5 years from the National Institute for Health and Clinical Excellence to define diagnosis and treatment of all patients with FWS.¹³ The decision for inpatient versus outpatient management and antibiotic treatment was at the discretion of the treating physician on a patient-by-patient basis.

The following variables were recollected: age, sex, comorbidities, previous vaccination for *Haemophilus influenzae type b* (3 doses at 2, 4, and 6 months of age) and *Streptococcus pneumoniae* (2 doses at 4 and 12 months of age of PCV13), symptoms and signs in emergency room. White blood cell counts, absolute neutrophil count, serum C-reactive protein (CRP), and urine dipstick were obtained in all patients. Tests such as blood culture, chest radiograph, and cerebrospinal fluid examination were taken at the discretion of the physician.

Statistical Analysis

Continuous variables were described using mean with standard deviation and medians are reported with interquartile ranges (IQRs); while for categorical variables, relative frequencies with their 95% CI were used. According to its parametric or non-parametric distribution, Student’s t-tests or Kruskal–Wallis tests for continuous variables and chi-square test or Fisher’s exact tests for categorical variables were used to compare clinical and sociodemographic variables between patients with and without SBI. Odds ratios (OR) were calculated for each of the possible predictor variables of SBI using logistic regression models, adjusting for potential confounders. All tests were 2-tailed, and a value of $P \leq .05$ was considered statistically significant. All analyses were made using STATA 17.0.

RESULTS

Characteristics of the Study Population

Totally 137 patients were included and 57% were females. The median age was 14 months with an IQR between 8 and 24 months. Ninety-nine percent of the study population had complete vaccination. Most of the infants were qualified as “good general appearance” at admission ($n = 102$, 74.5%), had pink skin coloration ($n = 127$, 92.7%), and were hydrated ($n = 123$, 89.8%). Two-thirds of the children had a CRP value greater than 20 mg/L ($n = 87$, 63.5%). Sixty-nine infants (50.4%) had a white blood cell count $\geq 15\ 000\ 10^3/\mu\text{L}$ and 39% had neutrophils $\geq 10\ 000\ 10^3/\mu\text{L}$. No patients died, and 6 children (4.4%) required an intensive care unit.

Frequency of Serious Bacterial Infections

Serious bacterial infection was diagnosed in 41 children (29.9%; 95% C.I. 22%–38%). The most frequent cause of SBI was UTI ($n = 32$, 78%) followed by pneumonia ($n = 3$, 7%), bacteremia ($n = 4$, 9%) and meningitis ($n = 2$, 4%). Among the non-SBI patients, their final diagnosis was upper respiratory infection ($n = 16$), gastroenteritis ($n = 11$), viral rashes ($n = 6$), and 63 have FWS without a recognized etiology. Except for age and adequate hydration status, there were no differences in the baseline characteristics of patients with and without SBI (Table 1). The pathogens isolated in urine cultures were *Escherichia coli* ($n = 22$), *Klebsiella pneumoniae* ($n = 2$), *Proteus mirabilis* ($n=3$), while in the blood culture were *Streptococcus pneumoniae* ($n = 2$), *Pseudomonas aureginosa* ($n = 1$), *Staphylococcus epidermidis* ($n = 1$). *Staphylococcus aureus* was isolated from the blood culture of the infant diagnosed with meningitis.

Risk Factors Associated with Serious Bacterial Infection

A higher proportion of infants with CRP levels greater than 80 mg/L (cut-off point used) was present in the SBI group compared to the non-SBI group (33% vs. 15%, $P = .02$). There were no significant differences at admission regarding abnormal leukocyte levels and toxic aspects, when comparing the groups with and without SBI ($P > .05$) except in weight ($P = .046$), Table 2.

To evaluate the predictive value of the laboratory and clinical parameters under study, we created logistic regression models with raw data (using only one of the predictor variables of interest) and models adjusted by sex, age, and weight. Also, we created a model that included all the variables of interest jointly and assessed the predictive value of these variables in a raw and adjusted form. In this analysis, the total number of days with fever and CRP levels greater than 80 mg/L showed a significant OR to predict the SBI (Table 3). The combination of clinical and laboratory parameters for the diagnosis of SBI showed an area under ROC curve of 0.913.

DISCUSSION

We illustrate the prevalence of SBI in a population of highly vaccinated infants with FWS. In our study, 41 of 137 infants (29%) had SBI. This prevalence was similar to previous studies in Latin America and slightly higher than that reported in developed countries.^{5,14–16} As has been published in other studies, most of the infants with FWS were children with a good

Table 1. Baseline Characteristics and Clinical Evolution of SBI and Non-SBI Patients

Variable		Non-SBI (n = 97)	SBI (n = 40)	P
Age, (%)	<3 months	2 (2)	7 (17)	.002
	3-6 months	13 (13)	8 (20)	
	>6 months	82 (85)	25 (63)	
Age, months, median (IQR), (%)		16.0 (9.0, 24.0)	10.0 (3.5, 23.5)	.005
Sex, (%)	Male	40 (41)	18 (45%)	.69
	Female	57 (59)	22 (55)	
Weight (kg)		10.0 (7.9, 12.0)	9.0 (6.0, 11.5)	.046
Complete vaccination for <i>Haemophilus influenzae</i> type b and <i>Streptococcus pneumoniae</i> , (%)	Yes	97 (100)	39 (97)	.12
	No	0 (0)	1 (3)	
Underlying pathology, (%)	No	57 (59)	25 (63)	.68
	Yes	40 (41)	15 (37)	
Recurrent urinary tract infections, (%)	No	86 (89)	33 (83)	.33
	Yes	11 (11)	7 (17)	
Recurrent wheezing, (%)	No	95 (98)	37 (93)	.12
	Yes	2 (2)	3 (7)	
Good general appearance at admission, (%)	Yes	76 (78)	26 (65)	.10
	No	21 (22)	14 (35)	
Adequate hydration status, (%)	Yes	83 (86)	40 (100)	.01
	No	14 (14)	0 (0)	
Color, (%)	Normal color	89 (92)	38 (95)	.51
	Pale/mottled/blue	8 (8)	2 (5)	
Temperature, median (IQR)		38.0 (37.7, 38.7)	38.5 (37.8, 39.0)	.12
Temperature, °C, (%)	<39	48 (49)	13 (33)	.06
	≥39	49 (51)	27 (67)	
Clinical evolution				
Hospitalization days, median (IQR)		4.0 (3.0, 5.0)	7.0 (5.0, 7.0)	<.001
Antimicrobials, n (%)		77 (79)	40 (100)	.002
Antimicrobials days, median (IQR)		3.0 (3.0, 5.0)	7.0 (5.5, 7.0)	<.001
Admission to ICU, n (%)		1 (1)	5 (13)	.008

P-values correspond to Mann-Whitney test or Fisher exact test or chi-square test. IQR, interquartile range; ICU, intensive care unit; SBI, serious bacterial infection.

general appearance and good general condition. Moreover, 45% of the infants had no clear etiology of fever during hospitalization and 25% had non-severe infections. This is consistent with what is already known about the etiology and prognosis of FWS; most of the cases are febrile illnesses with possible viral etiology, self-limited, and without complications, even in tropical countries such as ours.¹⁷ The most frequent cause of SBI, and also in agreement with previous studies, was UTI; *E. coli* was the most frequent etiologic agent in 68% of the cases.^{18,19} This finding highlights the necessity to screen all patients with

FWS for the presence or absence of UTI regardless of their clinical status or medical history.

Among the biochemical and clinical markers studied, the presence of CRP levels greater than 80 mg/L and the number of days with fevers were the best predictors of the presence of SBI in our population. While 33% of patients with SBI had CRP levels greater than 80 mg/L, only 15% of non-SBI patients had such levels. In the adjusted logistic model, patients with CRP levels greater than 80 mg/L were twice as likely to have SBI.

Table 2. Clinical and Laboratory Parameters

Variable		Non-SBI (n = 97)	SBI (n = 40)	P
CRP (mg/L)	<80	82 (85%)	27 (68%)	.02
	>80	15 (15%)	13 (33%)	
White blood cell count ($15 \times 10^3/\mu\text{L}$)	<15 000	49 (51%)	19 (48%)	.75
	>15 000	48 (49%)	21 (53%)	
Total days with fever, median (IQR)		3.0 (2.5, 5.0)	7.0 (5.0, 7.0)	.00
Traffic light system for identifying risk of serious illness (NICE)	Low risk	51 (53%)	19 (48%)	.61
	Intermediate risk	37 (38%)	15 (38%)	
	High risk	9 (9%)	6 (15%)	

P-values correspond to Mann-Whitney test or Fisher exact test or chi-square test. SBI, serious bacterial infection; IQR, interquartile range; CRP, C-reactive protein; WBC, white blood cells.

Table 3. SBI Predictive Value of Clinical and Laboratory Parameters

Model		Crude OR	Adjusted OR
Total days with fever		2.45 [1.78,3.37]	2.56 [1.81,3.62]
Traffic light system for identifying the risk of serious illness (NICE)	Low risk	1	1
	Intermediate risk	1.08 [0.48,2.41]	1.01 [0.43,2.36]
	High risk	1.78 [0.56,5.70]	1.03 [0.28,3.76]
CRP (mg/L)	>80	2.63 [1.11,6.22]	2.79 [1.14,6.86]
White blood cell count (15 × 10 ³ /μL)	>15 000	1.12 [0.53,2.35]	1.18 [0.55,2.53]
Combined			
Total days with fever		2.52 [1.81,3.51]	2.67 [1.85,3.86]
Traffic light system for identifying risk of serious illness (NICE)	Low risk	1	1
	Intermediate risk	1.01 [0.35,2.88]	0.89 [0.30,2.64]
	High risk	0.98 [0.16,5.75]	0.61 [0.07,4.88]
CRP (mg/L)	>80	3.20 [0.95,10]	3.89 [1.10,14.33]
White blood cell count (10 ³ /mL)	>15000	0.63 [0.22,1.80]	0.67 [0.22,2.01]
Odds ratio is obtained by logistic regression models considering only the indicated variable (crude model) or adjusted variable (by sex, age, and weight). The model considers all the above variables in a single model (hours of fever, toxic aspect, alteration of CRP, and leukocytes). CRP, C-reactive protein; WBC, white blood cells; OR, odds ratio.			

This finding correlates with previous studies that have shown that in infants with FWS, CRP levels are one of the independent markers most frequently associated with SBI.²⁰⁻²⁴ Likewise, on each day of fever before admission to the emergency department, the risk of SBI increased twice. Patients with SBI were admitted with a median number of days with a fever of 7 days, while in non-SBI patients, it was 3 days. Previous studies have found that the AUC in the prediction models was greater in patients who presented with fever >12 hours than those with fever <12 hours.^{20,25}

As has been previously documented and occurred in our study, no single symptom, sign, or biomarker has a high capacity to discriminate against infants with or without SBI.^{16,17,26} It is the combination of clinical and laboratory findings (as in our case, days of fever, CRP levels, age, urinalysis) that can guide the physician regarding the presence or absence of SBI and the need for invasive studies or antibiotic treatment. This information is very important in developing countries where a thorough clinical history, CRP levels, and urinalysis can be used to make better decisions. In our study, the prevalence of meningitis was low but slightly higher than that reported by recent clinical practice guidelines. However, in patients with good clinical appearance do not support routinely obtaining cerebrospinal fluid in all patients, among other reasons due to the high frequency of UTI over meningitis in this population, as was also the case in our study.²⁷ Our study has certain limitations. Although this is a study carried out in a single tertiary center, which may limit its external validity, it includes most of the consultations in the region, which has an epidemiological profile not very different from that of the population of the country.^{25,26} Additionally, we cannot exclude information biases due to retrospective nature of the secondary source information; however, all the information from the patients was available at least to guarantee the completeness of the information presented here.

In conclusion, most infants with FWS presented self-limited febrile syndromes without evidence of SBI. C-reactive protein levels greater than 80 mg/L and the number of previous days with fever were variables associated with the presence of SBI. Our results need to be validated in other tropical countries.

Ethics Committee Approval: This study was approved by Ethics committee of University Uniremington, (Approval No: 26).

Informed Consent: Informed consent was not obtained, according to local regulations.

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