

ORIGINAL ARTICLE

## FEVER WITHOUT A SOURCE UNDER 3 MONTHS OF AGE: ANY PREDICTIVE FACTORS OF SERIOUS BACTERIAL INFECTION?

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### ABSTRACT

**Introduction:** Fever is one of the main complaints in children admitted to the Emergency Department. It can be a symptom of Serious Bacterial Infection (SBI), being the risk greater in children younger than 3 months.

The aim of this study is to evaluate predictive factors of SBI under 3 months.

**Materials and methods:** We conducted a cohort retrospective study from January 2020 to June 2022 in infants under 3 months who visited the Emergency Department due to fever without a source. Firstly, a bivariate analysis was made to assess the predictive value of clinical and laboratorial parameters. Posteriorly, a backward stepwise model of binary logistic regression was performed, considering the statistical significant variables, with the dependent variable being the presence or absence of SBI.

**Results and discussion:** A total of 292 patients were included, 160 (54.8%) were male. The mean age was 57.8 days (SD 22.3). 73 (25%) patients were diagnosed with SBI: 58 (79.5%) urinary tract infections, 13 (17.8%) occult bacteriemias, 8 (11.0%) meningitis, 3 (4.1%) pneumonias and 6 (8.2%) bacterial gastroenteritis. Classification according to the Rochester criteria, white blood cell and neutrophil count, C-Reactive Protein (CRP) and procalcitonin values were statistically significantly different between the groups ( $p < 0.001$ ). In the multivariate analysis, CRP values ( $p < 0.001$ ; OR 1.045) showed significance (Hosmer-Lemeshow test:  $\chi^2 = 12.043$ ;  $p = 0.149$ ).

**Conclusion:** According to this study, CRP value is the most reliable parameter to predict SBI in this population and should be integrated in the evaluation of these patients to help in the treatment and follow-up decision.

### Introduction

Fever is one of the main complaints in children admitted to the Emergency Department, accounting for 10-20% of visits.<sup>1</sup> Fever without a source stands as an important entity, as the etiology can be a viral infection and have a benign evolution or be a manifestation of a serious illness with potential severe consequences, such as important morbidity and mortality.<sup>2,3,4</sup> According to age, etiologies vary and consequently the diagnostic and treatment approach differ.<sup>2,3,4,5</sup> An important differential diagnosis in a febrile infant under 3 months of age is a Serious Bacterial Infection (SBI), as this group has a higher risk of SBI than older children, affecting up to 10% of patients, particularly newborns.<sup>1,2,3,4,5,6</sup>

The majority of guidelines concerning fever without a source under 3 months of age recommend a thorough

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Fever without a source, Serious Bacterial Infection, Approach.

### Abbreviations:

- CRP – C-Reactive Protein
- CSF – Cerebrospinal fluid
- ESBL - Extended Spectrum Beta-Lactamase
- HPF – High Power Field
- IQR - Interquartile Range
- Mdn – Median
- OR – Odds ratio
- RSV - Respiratory Syncytial Virus
- SBI - Serious Bacterial Infection
- SD – Standart Deviation
- SPSS - Statistical Package for the Social Sciences
- WBC - White blood cell
- YIOS - Young Infant Observation Scale.

anamnesis, complete physical exam and laboratory workup. Recent international guidelines of management of fever without a source <3 months recommend a more invasive approach under 21 days of life or 1 month (depending on the guideline): full blood count, measurement of C-reactive protein (CRP) and procalcitonin, blood culture, urinalysis, urine culture, stool culture if diarrhea, chest radiography if respiratory symptoms and lumbar puncture, followed by beginning of antibiotherapy and hospitalization. Between 21 days or 1 month and 3 months of age: full blood count, measurement of CRP and procalcitonin, blood culture, urinalysis, urine culture, stool culture if diarrhea and chest radiography if respiratory symptoms should be obtained, reserving lumbar puncture for certain cases. Beginning of antibiotherapy and hospitalization should be weighted.<sup>7,8,9</sup>

The aim of this study was to evaluate predictive factors of SBI under 3 months of age, in order to identify infants with fever without a source who have a higher risk of having one of these infections and require a close vigilance and early establishment of antibiotherapy and

also identify the ones that can follow the “watch and wait” approach without prejudice.

## Methods & Materials

### *Sample and definitions:*

We conducted a cohort retrospective study of 2.5 years duration (January 1, 2020 to June 30, 2022) in infants aged 0 to 3 months who visited the emergency department due to fever without a source.

Fever was defined as rectal temperature  $\geq 38^{\circ}\text{C}$  or axillary temperature  $\geq 37.6^{\circ}\text{C}$  or tympanic temperature  $\geq 37.8^{\circ}\text{C}$ .

Fever without source was considered in patients with fever whose etiology remained unknown after a careful history and physical examination, with a duration of less than 7 days.

We contemplated urinary tract infection, occult bacteriemia, meningitis, bacterial gastroenteritis, pneumonia, septic arthritis, osteomyelitis and soft tissue infection as Serious Bacterial Infections. Current and updated definitions of these infections were considered for the diagnosis.

All patients with fever with an identified source, vaccination in the previous 48 hours and septic appearance were excluded.

### *Data Collection:*

Electronic medical records were consulted. We collected demographic (age and gender), clinical, laboratorial and radiological data from all patients.

The clinical data was described using maximum temperature at admission and two classifications of risk of SBI – Rochester criteria and Young Infant Observation Scale (YIOS).

Rochester criteria was analyzed as patients that fulfilled or not all nine low risk conditions:

- Temperature  $\geq 38^{\circ}\text{C}$
- Born at term
- Without perinatal antibiotherapy
- Without underlying pathology
- Without previous hospitalizations
- Without signs of focal infection
- White blood cell (WBC) count between 5000-15 000/uL
- Neutrophil count  $< 1500/\text{uL}$
- Urinary sediment analysis  $\leq 10$  WBC/hpf

Young Infant Observation Scale was evaluated as low or high risk of SBI: low risk if score  $< 7$  and high risk if score  $\geq 7$ , considering the conditions presented in Table 1.<sup>7</sup>

Laboratorial data included WBC count, neutrophil count, measurement of CRP and procalcitonin, urinary sediment analysis, Cerebrospinal fluid (CSF) cytochemical analysis and microbiological results of blood, urine, respiratory nasopharyngeal secretions, cerebrospinal fluid and stool.

Radiological data included chest radiography.

Management of patients was divided as medical discharged, observation at a short-stay inpatient unit (at least 12 hours of vigilance) or admitted to a pediatric or neonatology ward.

Antibiotherapy was also assessed.

### *Statistical analysis:*

The Statistical Package for the Social Sciences (SPSS®) version 27 was used for statistical analysis.

Categorical variables were presented as frequencies and percentages and continuous variables as means and standard deviations (SD) or medians and interquartile ranges (IQR) for variables without normal distribution. Normal distribution was checked using Shapiro-Wilk test, visualization of histogram or skewness and kurtosis, as appropriate.

To compare a continuous variable with a categorical variable we used the T-test, after checking for equality of variances with the Levene’s test. When normality distribution was not verified, Mann-Whitney test was performed.

To evaluate associations between two categorical variables we used Chi-square/Fisher test.

Posteriorly, the association of the variables that showed statistical significance in the bivariate analysis was assessed by means of binary logistic regression. A backward stepwise model was performed, with the dependent variable being the presence or absence of SBI.

All reported p values were two-tailed, with a p value of  $< 0.05$  indicating statistical significance.

## Results

During the study period a total of 2882 infants under 3 months were observed at our emergency department. 389 (13.5%) because of fever, of which 292 (75.1% of febrile infants) were because of fever without a source.

The sample characterization is described in Table 2.

A total of 292 patients were included in our study, 160 (54.8%) of whom were male and 132 (45.2%) female. The mean age was 57.8 days, with a standard deviation of 22.3. Patients were divided in two groups: 37 (12.7%) newborns and 255 (87.3%) with age  $> 28$  days.

The median maximum temperature at admission was  $38.4^{\circ}\text{C}$  (IQR 0.6).

A total of 263 patients were classified considering the Rochester criteria, 222 (84.4%) didn’t fulfill low risk criteria.

YIOS (n=292) classified all patients with low risk, except one (99.7% low risk).

73 (25.0%) patients were diagnosed with SBI: 58 (79.5%) urinary tract infections, 13 (17.8%) occult bacteremias, 8 (11.0%) meningitis, 6 (8.2%) bacterial gastroenteritis and 3 (4.1%) pneumonias.

Urine analysis was performed in 279 patients and was altered ( $> 10$  WBC/hpf or nitrituria) in 57 (20.4%). An urine culture was obtained in 242 patients, with

**Table 1.** Young Infant Observation Scale.

<b>Peripheral blood studies</b>			
<b>Observation</b>	<b>Normal (1 point)</b>	<b>Moderate disease (3 points)</b>	<b>Severe disease (5 points)</b>
Appearance	Smiling/Not irritable	Irritable, but consolable	Irritable and inconsolable
Respiratory effort	Without respiratory effort	Mild to moderate respiratory distress (>60 bpm, retractions or grunting)	Respiratory distress with inadequate effort (apnea, respiratory failure)
Peripheral perfusion	Pink Warm extremities	Marbled skin Cold extremities	Pale Shock

Legend: bpm – beats per minute

**Table 2.** Sample characterization.

		<b>All (n=292)</b>	<b>Presence of SBI (n=73)</b>	<b>Absence of SBI (n=219)</b>
Age (days) - mean $\pm$ SD		57.8 + 22.3	57.0 + 24.5	58.0 + 21.6
Age group - n (%)	= 28 days	37 (12.7)	12 (16.4)	25 (11.4)
	> 28 days	255 (87.3)	61 (83.6)	194 (88.6)
Gender - n (%)	Feminine	132 (45.2)	29 (39.7)	103 (47.0)
	Masculine	160 (54.8)	44 (60.3)	116 (53.0)
Max. Temp. – median (IQR)		38.4 (0.6)	38.4 (0.5)	38.5 (0.7)
YIOS – n (%)	Low risk	291 (99.7)	218 (99.5)	73 (100.0)
	High risk	1 (0.3)	1 (0.5)	0 (0.0)
Rochester – n (%)	Low risk	222 (76.0)	70 (95.9)	152 (69.4)
	Not low risk	41 (14.0)	3 (4.1)	38 (17.4)
	Not classifiable	29 (10.0)	0 (0.0)	29 (13.2)
WBC count – median (IQR)		9590.0 (7565)	14234.2 (6981.0)	9619.7 (4595.3)
	Not performed – n (%)	28 (9.6)	0 (0.0)	28 (12.8)
Neutrophil count – median (IQR)		3305.0 (4327.5)	6120.0 (5858.0)	2680.0 (3070.0)
	Not performed – n (%)	28 (9.6)	0 (0.0)	28 (12.8)
PCR – median (IQR)		7 (28.7)	43.6 (60.3)	0 (11.2)
	Not performed – n (%)	25 (8.6)	0 (0.0)	25 (11.4)
PCT – median (IQR)		0.1 (0.3)	0.5 (3.7)	0.1 (0.2)
	Not performed – n (%)	147 (50.3)	41 (56.2)	106 (48.4)
Urinary sediment analysis – n (%)	Altered	57 (19.5)	53 (72.6)	4 (1.8)
	Not altered	222 (76)	20 (27.4)	202 (92.2)
	Not performed	13 (4.5)	0 (0.0)	13 (6.0)
Urine culture – n (%)	With significant bacterial growth	58 (19.9)	58 (79.5)	-
	Without significant bacterial growth	184 (63.0)	15 (20.5)	169 (77.2)
	Not performed	50 (17.1)	0 (0.0)	50 (22.8)
Blood culture – n (%)	With bacterial growth	13 (4.5)	13 (17.8)	-
	Without bacterial growth	202 (69.2)	56 (76.7)	146 (66.7)
	Not performed	77 (26.4)	4 (5.5)	73 (33.3)
CSF cytochemical analysis – n (%)	Altered	8 (2.7)	7 (9.6)	1 (0.5)
	Not altered	22 (7.5)	10 (13.7)	12 (5.4)
	Unsuccessful LP	1 (0.4)	0 (0.0)	1 (0.5)
	Not performed	261 (89.4)	56 (76.7)	205 (93.6)

		<b>All (n=292)</b>	<b>Presence of SBI (n=73)</b>	<b>Absence of SBI (n=219)</b>
Chest radiograph – n (%)	Altered	12 (4.1)	3 (4.1)	0 (0.0)
	Not altered	3 (1.0)	4 (5.5)	8 (3.7)
	Not performed	277 (94.9)	66 (90.4)	211 (96.3)
Stool culture – n (%)	With significant bacterial isolation	6 (2.1)	6 (8.2)	-
	Without significant bacterial isolation	15 (5.1)	3 (4.1)	12 (5.5)
	Not performed	271 (92.8)	64 (87.7)	207 (94.5)
Respiratory nasopharyngeal secretions – n (%)	Not identified	148 (50.7)	55 (75.3)	93 (42.5)
	SARS-CoV-2	75 (25.7)	4 (5.5)	71 (32.4)
	Influenza A	8 (2.7)	2 (2.7)	6 (2.7)
	RSV	4 (1.4)	0 (0.0)	4 (1.8)
	Not performed	57 (19.5)	12 (16.4)	45 (20.5)

**Table 3.** Cultural exams.

<b>Serious Bacterial Infection – n (%)</b>	<b>73 (25.0)</b>
Urinary tract infection – n (%)	58 (19.8) (79.5% of SBI)
E.coli	50 (86.2)
Proteus mirabilis	3 (5.2)
Klebsiela oxytoca	3 (5.2)
Klebsiela pneumoniae ESBL +	1 (1.7)
E. coli ESBL +	1 (1.7)
Occult bacteriemia – n (%)	13 (4.5) (17.8% of SBI)
Staphylococcus aureus	3 (23.1)
Staphylococcus epidermidis	3 (23.1)
E. coli	3 (23.1)
Neisseria meningitidis	1 (7.7)
Streptococcus pneumoniae	1 (7.7)
Staphylococcus saprophyticus	1 (7.7)
Staphylococcus hominis	1 (7.7)
Meningitis – n (%)	8 (2.7) (11.0 of SBI)
Without identification of agent	4 (50.0)
Neisseria meningitidis	1 (12.5)
E. coli	1 (12.5)
E. coli ESBL+	1 (12.5)
Streptococcus pneumoniae	1 (12.5)
Pneumoniae – n (%)	3 (1.0) (4.1 of SBI)
Bacterial gastroenteritis – n (%)	6 (2.1) (8.2% of SBI)
Campylobacter jejuni	6 (100)

Chest radiography was taken in 15 patients and 3 (20.0%) were diagnosed with pneumonia.

**Table 4.** Bivariate analysis

	Presence of SBI	Absence of SBI	p-value	
Gender – n (%)	Female	29(39.7)	103(47.0)	0.277
	Male	44(60.3)	116(53.0)	
Age (days) – Median (IQR)	56(42)	61(34.0)	0.881	0.264
Age group – n (%)	= 28 days	12(16.4)	25(11.4)	
	> 28 days	61(83.6)	194(88.6)	
Maximum temperature (°C) – Median (IQR)	38.5(0.7)	38.4(0.5)	0.053	
YIOS – n (%)	Low risk	73(100.0)	218(99.5)	-
	High risk	0(0.0)	1(0.5)	
Rochester criteria – n (%)	Low risk	3(4.1)	38(20.0)	0.001
	Not low risk	70(95.9)	152(80.0)	
WBC count – Median (IQR)	12720(9305)	8670(5910)	<0.001	
Neutrophil count – Median (IQR)	6120(5858)	2680(3070)	<0.001	
CRP value – Median (IQR)	43.6(60.3)	0.0(11.2)	<0.001	
Procalcitonin value – Median (IQR)	0.5(3.7)	0.1(0.2)	<0.001	

**Table 5.** Multivariate analysis - final model.

Nagelkerke R2	X2	df	p-value
0.540	12.043	8	0.149
	p-value	OR	Confidence interval 95%
WBC count	0.082	1.000	1.000-1.000
CRP value	<0.01	1.045	1.020-1.069
Procalcitonin value	0.05	1.336	1.000-1.785

significant bacterial growth in 58 (24.0%). The most frequent pathogen was *E. coli* (n=50, 86.2%).

Blood culture was obtained in 215 patients, 13 (6.0%) had bacterial growth and 202 (94.0%) were sterile. Considering the positive cultures, were identified 3 (23.1%) *Staphylococcus aureus*, *Staphylococcus epidermidis* and *E. coli*; 1 (7.7%) *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Staphylococcus saprophyticus* and *Staphylococcus hominis*.

Lumbar puncture was performed in 31 patients, CSF cytochemical analysis was normal in 23 (74.2%) and 8 (25.8%) had meningitis. Of the later patients, in one patient (12.5%) was identified *Neisseria meningitidis*, *E. coli*, *E. coli* with extended spectrum beta-lactamase (ESBL+) and *Streptococcus pneumoniae* and no agent was identified in 4 (50.0%).

Stool samples were collected in 21 patients, 6 (28.6%) had isolation of *Campylobacter jejuni* and 15 (71.4%) had no bacterial identification.

Cultural exams are described in Table 3.

Respiratory nasopharyngeal secretions were collected in 235 patients for the detection of respiratory viruses (panel of *Influenza A virus*, *Influenza B virus*, *Respiratory Syncytial Virus* and *SARS-CoV-2 virus*). In 75 (31.9%) SARS-CoV-2 was identified, in 8 (3.4%) *Influenza A virus*, in 4 (1.7%) *Respiratory Syncytial Virus (RSV)* and

in 148 (63.0%) no virus was identified. Considering the patients with SBI, 6 (8.2%) had co-infection with one of the mentioned virus.

Admission to a Pediatric or Neonatology ward was needed in 94 (32.2%) cases, observation at a short-stay inpatient unit in 86 (29.5%) and 112 (38.4%) were discharged.

85 (29.1%) patients of all infants observed were treated with antibiotics.

We found a statistical significant difference of classification according to the Rochester criteria, WBC count, neutrophil count, measurement of C-Reactive Protein and procalcitonin between the groups. The classification according to the Rochester criteria demonstrated that there was a significant statistical association between not fulfilling the low risk criteria and having SBI, p=0.001. The median value of WBC count was significantly superior in the presence of SBI (Mdn=12720.0; IQR=9305.0) when compared to the group without SBI (Mdn=8670.0; IQR=3070.0), p <0.001. The median value of neutrophil count was significantly superior in the presence of SBI (Mdn=6120.0; IQR=5858.0) when compared to the group without SBI (Mdn=2680.0; IQR=3070.0), p <0.001. The median value of CRP was significantly superior in the presence of SBI (Mdn= 43.6; IQR=60.3) when compared to the group without SBI (Mdn 0.0;

IQR 11.2),  $p < 0.001$ . The median value of procalcitonin was significantly superior in the presence of SBI (Mdn = 0.5; IQR = 3.7) when compared to the group without SBI (Mdn 0.1; IQR 0.2),  $p < 0.001$ .

Age, gender and maximum temperature didn't present statistical significant results. It was not possible to calculate an association between YIOS classification and the presence or absence of SBI.

In a multivariate analysis for evaluating predictive factors to have SBI, CRP values ( $p < 0.001$ ; OR 1.045) showed statistical significance (Hosmer-Lemeshow test:  $\chi^2 = 12.043$ ;  $p = 0.149$ ). This result means that an elevation of one unit (mg/L) in CRP values, elevates the risk of SBI in 1.045.

Bivariate analysis is described in Table 4 and multivariate analysis is described in Table 5.

## Discussion

In our study we found a prevalence of observations due to fever under 3 months of age in the emergency department of 13.5%, which is coherent with the literature.<sup>1</sup> Furthermore, in this group in particular, there is a preponderance of fever without a source as a first diagnostic impression for febrile infants (75.1% of febrile infants), which is also consistent with descriptions from other populations.<sup>2</sup>

In our study, 25.0% of infants under 3 months of age with fever without a source turned out to have a SBI, which is a value superior to that described in some published studies<sup>5</sup>, although some recent investigations have reported similar values.<sup>1</sup> Urinary Tract Infection was the most frequent SBI, with *E. coli* being the most common causative pathogen, which is similar to that described in the great majority of articles concerning this theme.<sup>1,2,3,4,5,6</sup> The other Serious Bacterial Infections diagnosed - occult bacteremias, meningitis, pneumonias and bacterial gastroenteritis - are described as the other infections more frequently found in comparable populations.<sup>6</sup>

In 6 cases there was a SBI and a viral co-infection, that means the diagnosis of a viral infection didn't reject the hypothesis of a SBI.

Risk classifications such as Rochester criteria and YIOS used in this study have been widely used, in order to try to establish a stratification of risk that allows clinicians to optimize their approach. The main objective is to balance a less invasive approach with the intention and necessity to detect all cases of SBI and initiate proper treatment in due course.<sup>6</sup> Rochester criteria showed that there was an association between not fulfilling the low risk criteria and having SBI in the bivariate analysis, but not after including it in the final model. In order to increase the accuracy of this classification, to assess if it would improve our model, a study with more patients categorized with this criteria should be performed. In our study it was not possible to evaluate the existence of an association between YIOS and the presence or absence of SBI, which limits the ability to rely on this scale and requires further studies of application of YIOS.

The laboratory evaluation of WBC count, neutrophil count, CRP and procalcitonin showed a statistically

significant difference between groups in the bivariate analysis, which is consistent with the literature, that indicates that inflammatory markers give an important diagnostic information in this patients.<sup>2,4,6,10</sup> However, in the multivariate analysis, WBC and neutrophil count didn't present a statistically significant difference between the group with SBI and the group without SBI, which is consistent with the fact that their diagnostic value is limited, as other studies have proved.<sup>10</sup> On the other hand, CRP maintains its statistical value and procalcitonin has a  $p$  value that is near statistical significance ( $p = 0.05$ ). CRP and procalcitonin measurements have a much higher diagnostic value than WBC and neutrophil count.<sup>2,4,6,10</sup> Some investigations suggest that procalcitonin is a better predictor of SBI<sup>4</sup> and others advocate that none of these variables is better than the other<sup>10</sup>, but in our study CRP values have a better result in predicting SBI. Procalcitonin diagnostic value might be underestimated in our population due to lack of data in an important proportion of patients.

An association between high fever (particularly  $> 40^\circ\text{C}$ ) and an increased risk of SBI has been reported in some studies<sup>11</sup>, but in this one there was no relevant association between maximum temperature and the presence or absence of SBI. This is a data provided by the infant's caregiver, which can be a possible cause to this discrepancy, as a superior temperature might not be objectified and antipyretic might be administered in an early phase. A superior temperature might also be noticed in a posterior time to the first observation at the emergency room, which can underestimate the importance of this parameter.

Although SBI is more prevalent in the group with  $< 28$  days than the older patients<sup>1,2,3,4,5,6</sup>, in our study there was no statistically significant difference considering the age of the patients. The asymmetric sample size of the two groups, with a much higher number of patients with more than 28 days (87.3%), can influence this result.

Gender is usually not a criteria to consider as a risk factor according to recent guidelines and studies<sup>7,8,9</sup>, which is consistent with the results found in this investigation.

## Conclusion

To conclude, the evaluation of these parameters has a great potential to integrate a model to predict SBI in infants under 3 months of age with fever without a source. This prediction intends to promptly treat the ones with high risk of SBI and to not expose the ones with low risk to more invasive investigations and exposure to antibiotics. According to this investigation, CRP values should be assessed in each patient's context and should help in the treatment and follow-up decision.

### Limitations:

Our study has some limitations that should be evaluated, in order to enhance them and possibly replicate this study with more accurate data. Firstly, the approach to the febrile infants was not guided by a protocol, which leads to a variable methodology according to each clinician that consults the patient and a lack of some data needed in this study. Secondly,

it was a retrospective analysis, with all limitations associated with this type of report. Finally, this study was conducted using medical records from a single hospital, this population might not be representative of others.

**Compliance with Ethical Standards****Funding** : None**Conflict of Interest** : None**References:**

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