Predicting Severe Bacterial Infections in Well-Appearing Febrile Neonates

Laboratory Markers Accuracy and Duration of Fever

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Objectives: To assess the diagnostic accuracy of white blood cell count (WBC), absolute neutrophil count (ANC), and C-reactive protein (CRP) in detecting severe bacterial infections (SBI) in well-appearing neonates with early onset fever without source (FWS) and in relation to fever duration.

Methods: An observational study was conducted on previously healthy neonates 7 to 28 days of age, consecutively hospitalized for FWS from less than 12 hours to a tertiary care Pediatric Emergency Department, over a 4-year period. Laboratory markers were obtained upon admission in all patients and repeated 6 to 12 hours from admission in those with normal values on initial determination. Sensitivity, specificity, positive and negative likelihood ratios, and receiver operating characteristic analysis were carried out for primary and repeated laboratory examinations.

Results: Ninety-nine patients were finally studied. SBI was documented in 25 (25.3%) neonates. Areas under receiver operating characteristic curves were 0.78 (95% CI, 0.69–0.86) for CRP, 0.77 (95% CI, 0.67–0.85) for ANC and 0.59 (95% CI, 0.49–0.69) for WBC. Sixty-two patients presented normal laboratory markers on initial determination. Of these, 58 successfully underwent repeated blood examination at >12 hours from fever onset. Five of them had an SBI. The area under curve calculated for repeated laboratory tests showed better values, respectively of 0.99 (95% CI, 0.92–1) for CRP, 0.85 (95% CI, 0.73–0.93) for ANC and 0.79 (95% CI, 0.66–0.88) for WBC.

Conclusions: In well-appearing neonates with early onset FWS, laboratory markers are more accurate and reliable predictors of SBI when performed after >12 hours of fever duration. ANC and especially CRP resulted better markers than the traditionally recommended WBC.

Key Words: neonate, fever, severe bacterial infection, C-reactive protein, leukocytes

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Fever in the young infant is a common and challenging problem to face for Pediatricians. As well reported in the medical literature, the younger the febrile child, the poorer the ability to manifest specific signs and symptoms of disease and the higher the risk of having a severe bacterial infection (SBI), independently of clinical conditions.

SBI may be the cause of up to 25% of fever in children aged less than 2 months,[1,2] so that many authors focused on the management of the febrile young infant,[1–11] suggesting several different approaches and criteria to detect children unlikely to have a SBI, who could safely be cared with a less aggressive treatment. Nevertheless, few studies[12–18] selectively addressed the management of febrile neonates for whom hospitalization and empiric antibiotic treatment after a full sepsis work-up is still largely recommended.[19–22] Clinical findings provide little help in distinguishing febrile neonates at risk for SBI, considering that the majority of those admitted to the Pediatric Emergency Department (PED) have a short fever evolution, are well-appearing, and present no source of infection on physical examination. Hence, laboratory markers may play an important role as SBI predictors in this group of patients, even though data on their accuracy in the febrile neonate are still lacking.

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OBJECTIVES

To assess the diagnostic accuracy of blood cell count (WBC), absolute neutrophil count (ANC), and C-reactive protein (CRP) in detecting SBI in well-appearing neonates with early onset fever without source (FWS).

To evaluate the diagnostic performance of these tests in relation to duration of fever.

MATERIALS AND METHODS

Patient Characteristics and Inclusion Criteria

An observational study was carried out on previously healthy neonates 7 to 28 days of age consecutively admitted, from January 1, 2003 to June 1, 2007, to the PED of the Children's Hospital of the University of Padova, for fever without source from less than 12 hours and good clinical appearance. Fever was defined as axillary body temperature >37.5°C or rectal temperature >38°C documented at home or in the PED. Duration of fever was timed from the first reported detection at home, independently of the methods of measurement used.

Those children born preterm (<37 weeks gestation), with perinatal complications, underlying diseases or with a history of antibiotic use prior to admission to the hospital were excluded from the study.

Our Children's Hospital provides primary and secondary care for a metropolitan area of 350,000 people (45,000 younger than 15 years) and tertiary care for a regional and extraregional population, with approximately 25,000 PED visits per year.

Clinical and Diagnostic Evaluations

According to the standard of care in use in our PED since 2002, all neonates with FWS were hospitalized and followed the clinical pathway reported below.

After a careful history and accurate physical examination by an attending physician, laboratory screening tests were performed in all neonates, including WBC, ANC, quantitative CRP determination, and urine analysis, together with 2 consecutive urine cultures and a blood culture.

Screening tests were considered positive if WBC <5000/mm^3 or >15000/mm^3 and/or ANC >10000/mm^3 and/or CRP >20

mg/L and/or positive urinalysis (ie, 2 consecutive positive samples for leukocyte esterase and/or nitrite test).

Toxic or ill-appearing neonates (not enrolled in the study) received a complete sepsis work-up, including lumbar puncture, and immediate parenteral antibiotics independently of screening tests' results.

Well-appearing neonates with positive screening tests on admission were also given parenteral antibiotic treatment, after completion of a full sepsis work-up. Well-appearing neonates with initial negative screening tests were hospitalized for observation without receiving antibiotics. In these patients laboratory markers were repeated 6 to 12 hours after admission before making a decision to treat.

Clinical appearance was evaluated by the physician in charge of the patient, according to the Yale Observation Score.[23] In case of clinical deterioration (any neonate turning toxic, or ill-appearing) during observation, parenteral antibiotic therapy was contemplated, after completion of the full sepsis work-up.

Urine was collected by sterile bags changed every half an hour. Chest x-rays as well as other laboratory, microbiologic and radiographic tests were conducted at the discretion of the physician in charge of the patient, according to clinical and laboratory evaluation.

SBI was defined by the growth of a known pathogen in cultures from blood, urine, cerebrospinal fluid, stool, or any aspirated fluid from a sterile site. In particular a urinary tract infections (UTI) was defined in the presence of 2 positive urine cultures (2 concordant consecutive tests with growth of only 1 micro-organism $\geq$100,000 colony forming units/mL).[24] A diagnosis such as pneumonia, (presence of focal infiltrate on chest radiograph observed by the pediatric radiologist), abscess, cellulitis, osteomyelitis, or septic arthritis was also considered a SBI.

Data collection and analysis were authorized by the Internal Committee and informed consent was obtained by parents or legal guardians.

Laboratory Assessments

WBC and ANC were performed in blood samples mixed with ethylenediaminetetraacetic acid using an automated cell counter. CRP values were determined employing a nephelometric assay (Dade-Behring, Milan, Italy) according to the instructions of the manufacturer.

Statistical Analysis

Normally distributed data were expressed as mean $\pm$ SD; non-normally distributed data were expressed as median and interquartile range; categorical variables were reported as percentages. For non-normally distributed data, comparison was performed by means of Mann-Whitney *U* test; comparison of normally distributed data were performed using independent-samples *t* test. For categorical data, the χ^2 test with Yates correction for 2×2 tables was used. Parameters displaying $P < 0.05$ were considered statistically significant.

The diagnostic performances of the parameters considered (CRP, WBC, and ANC) were first investigated by receiver operating characteristic (ROC) analysis.[25] Sensitivity, specificity, positive and negative predictive values and likelihood ratios were then assessed for different cut offs.

The commercial statistical software package used was MedCalc Version 7.3.

RESULTS

Patient Characteristics

Overall, 156 neonates were admitted for FWS to our PED during the study period and were hospitalized (Fig. 1).

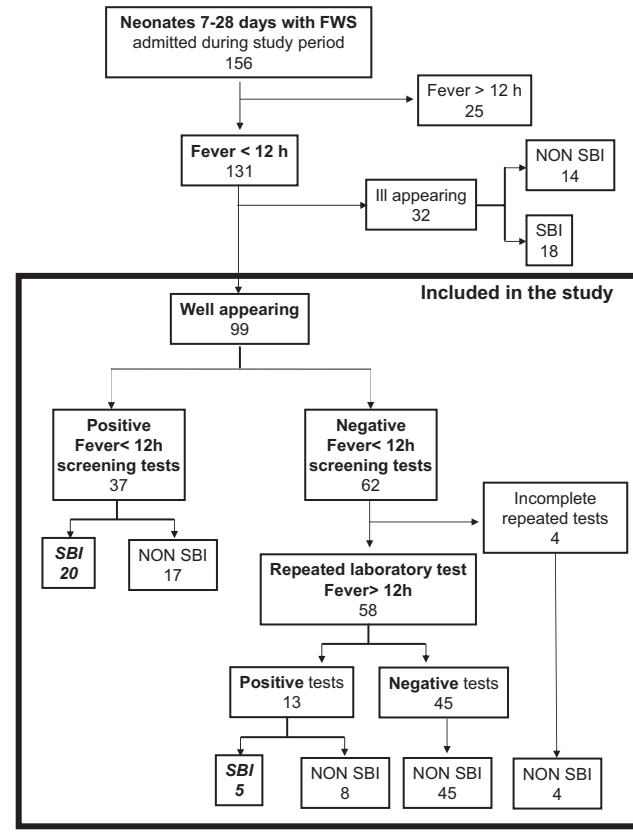

FIGURE 1. Flow diagram for the clinical pathway of neonates with FWS.

One hundred thirty-one (83.9%) presented fever <12 hours. Thirty-two were ill appearing and received antibiotic therapy immediately after cultures were performed, independently of screening tests results. Of these, 18 had a final diagnosis of SBI: 10 UTI (1 with associated bacteremia), 3 bacteremia, 1 meningitis and bacteremia and UTI, 2 meningitis, 1 pneumonia, and 1 septic arthritis.

The remaining 99 well-appearing neonates with FWS <12 hours were eventually included in the study. Of these 43 were female. The mean age at admission was 19.6 $\pm$ 7 days. The mean maximum body temperature resulted 38.4°C $\pm$ 0.6°C. Twenty-five (25.3%) finally had an SBI. The diagnoses, case numbers, and causative organisms for the patients with SBI are listed in Table 1.

In the non-SBI children, causative affections were: viral syndrome in 65 (87.8%) neonates, non bacterial gastroenteritis in

TABLE 1. Final Diagnosis of Patients With Severe Bacterial Infections (n = 25)

	No. Patients	%	Causative Organisms
Urinary tract infections (UTI)	15	60%	13 *Escherichia coli* 2 Enterococco 1 *Klebsiella pneumoniae*
Bacteremia	3	12%	3 group B Streptococcus
Bacteremia and UTI	2	8%	2 *Escherichia coli*
Meningitis	3	12%	3 group B Streptococcus
Pneumonia	1	4%	Not determined
Osteomyelitis	1	4%	Not determined

8 (10.8%) neonates and bronchiolitis, due to respiratory syncytial virus, in 1 patient (1.4%).

As for demographic characteristics patients with and without SBI were comparable for age (19 ± 7 days vs. 20 ± 7 days, $P = 0.39$), sex distribution (female to male ratio of 8/17 vs. 35/39, $P = 0.27$),and maximal body temperature (38.5°C ± 0.8°C vs. 38.4°C ± 0.5°C, $P = 0.58$).

Thirty-seven of 99 showed positive screening tests (blood markers and/or urinalysis) at admission and were given antibiotics immediately after completion of a full sepsis evaluation. Of these 20 (54%) were finally diagnosed with an SBI (Fig. 1).

The 62 neonates with negative screening tests at admission were hospitalized for observation without receiving antibiotic therapy. None showed significant clinical deterioration prior to laboratory markers determination at >12 hours from fever onset. The repeated blood examination was successfully obtained in 58 neonates. Four patients had undetermined tests at this time point, because of clotted samples or difficult blood sampling, and were therefore excluded from the subsequent analysis. None of them had a final diagnosis of SBI: 3 became permanently afebrile within 24 hours from fever onset and 1 developed a mild rotavirus gastroenteritis.

Laboratory markers determined at >12 hours from fever onset turned positive in 13 of 58 patients. All of them received immediate antibiotic treatment after completing a full sepsis work-up. Of these 5 were finally diagnosed with an SBI (3 bacteremia and 2 meningitis) and all recovered well after appropriate therapy. Forty-five neonates showed persistent negative markers values on repeated determination. None of them had an SBI. They were not given antibiotics and all did well (Fig. 1).

Blood Markers Accuracy for the Prediction of Severe Bacterial Infection at Admission (Fever <12 Hours)

Of the blood markers tested on admission only CRP and ANC resulted significantly higher in the group of children with SBI compared with those without ($P < 0.0001$) (Table 2).

Table 3 shows the sensitivity, specificity, predictive values, and likelihood ratios for the most commonly recommended cut offs.

As shown in Figure 2, the area under the ROC curve (AUC) was 0.78 (95% CI, 0.69–0.86) for CRP, 0.77 (95% CI, 0.67–0.85) for ANC and 0.59 (95% CI, 0.49–0.69) for WBC. The AUCs of both CRP and ANC resulted significantly larger than leukocyte count ($P < 0.03$).

Blood Markers Accuracy for the Prediction of Severe Bacterial Infection at >12 Hours From Fever Onset

After >12 hours from fever onset all the blood tests were significantly higher in the group of children with SBI compared with those without (Table 2).

Sensitivity, specificity, predictive values, and likelihood ratios for the most commonly recommended cut offs, showed better results than for initial determination (Table 3). After >12 hours of fever duration CRP presented a better diagnostic performance than did ANC and WBC: the AUC for SBI detection was 0.99 (95% CI, 0.92–1) for CRP, 0.85 (95% CI, 0.73–0.93) for ANC and 0.79 (95% CI, 0.66–0.89) for WBC (Fig. 3). The improvement in AUC values, compared with initial determination, resulted significant only for CRP ($P = 0.002$). Of note, laboratory markers determined at >12 hours of fever duration turned abnormal for all the 5 patients with an SBI who presented normal blood tests at admission.

DISCUSSION

The management of the febrile neonate is still a matter of debate. Whether to empirically treat these patients with antibiotics after a full sepsis investigation or to consider a close follow-up as in- or outpatients without immediate antibiotic therapy is a dilemma not yet solved.

The present study is the first that evaluates the accuracy of laboratory markers in relation to fever duration for predicting SBI in neonates with early onset fever, unremarkable history, and physical examination. These patients, for whom diagnostic and therapeutic decisions are the most discussed in the medical literature, constitute the largest part of the febrile neonates admitted to hospital.[1–5,8,12–18]

According to our results almost 84% of neonates with FWS were admitted with fever duration of less than 12 hours and of these 75.6% presented in good clinical conditions. Nevertheless a negative history and a normal physical examination do not exclude the presence of an SBI, that is why many authors routinely recommend for all these patients a full sepsis work up and immediate antibiotic therapy.

Unnecessary antibiotic treatment, however, is related to increased iatrogenic risks, bacterial resistance, financial burden, and family and patients' discomfort. For these reasons many authors tested different subset of low risk criteria (including both clinical and laboratory parameters) to identify febrile neonates and young infants unlikely to have SBI who could be spared antibiot-

TABLE 2. Laboratory Markers of Patients With and Without SBI for Initial (<12 h From Fever Onset), and Repeated Determination (>12 h From Fever Onset)

	SBI (n = 25)	Non SBI (n = 74)	*P*
<12 h from fever onset (99 patients)			
WBC (mm^3)	11130 (8600–13950)	9960 (7560–12500)	NS
ANC (mm^3)	6700 (4300–8040)	3670 (2600–5100)	<0.0001
CRP (mg/L)	16.1 (3.7–49.6)	1.8 (1.0–6.3)	<0.0001
	SBI (n = 5)	Non SBI (n = 53)	*P*
>12 h from fever onset (58 patients)			
WBC (mm^3)	21520 (10400–23220)	9980 (7150–11575)	0.0341
ANC (mm^3)	11580 (8600–15030)	3040 (2050–3870)	0.0104
CRP (mg/L)	55.3 (44.3–62.5)	3.5 (1.3–10.1)	0.0003

Data are expressed as median and interquartile range.
NS indicates non significant.

TABLE 3. Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value, and Likelihood Ratio Values for the Most Commonly Recommended Cutoffs of WBC, ANC, and CRP for SBI Prediction in Relation to Fever Duration

	Sensitivity (% [95% CI])	Specificity (% [95% CI])	PPV (% [95% CI])	NPV (% [95% CI])	LR+ (% [95% CI])	LR− (% [95% CI])
Initial determination: fever <12 h (all patients)						
WBC <5000/mm^3	28 (14.3–47.6)	87.7 (78.2–93.4)	43.75 (23.1–66.8)	78.1 (68.0–85.6)	2.3 (0.9–5.8)	0.8 (0.7–0.9)
OR >15,000/mm^3						
ANC >10,000/mm^3	20.0 (8.9–39.1)	97.3 (90.6–99.3)	71.4 (35.9–91.8)	78.0 (68.5–85.3)	7.3 (0.6–93.3)	0.8 (0.7–0.9)
CRP >20 mg/L	48.0 (30.3–66.5)	93.2 (85.1–97.1)	70.6 (46.9–86.7)	84.2 (74.7–90.5)	7.1 (4.0–12.5)	0.6 (0.5–0.7)
Repeated determination: fever >12 h (58 patients)						
WBC <5000/mm^3	80.0 (37.6–96.4)	90.6 (79.7–95.9)	44.4 (18.9–73.3)	98.0 (89.3–99.6)	8.5 (5.1–14.2)	0.2 (0.0–1.6)
OR >15,000/mm^3						
ANC >10,000/mm^3	80.0 (37.6–96.4)	100 (93.2–100)	100 (51.0–100)	98.2 (90.2–99.7)	Undefined	0.2 (0.0–1.4)
CRP >20 mg/L	100 (56.6–100)	96.2 (87.2–99.0)	71.4 (35.9–91.8)	100 (93–100)	26.5 (9.9–79.6)	0.0

PPV indicates positive predictive value; NPV, negative predictive value; and LR, likelihood ratio.

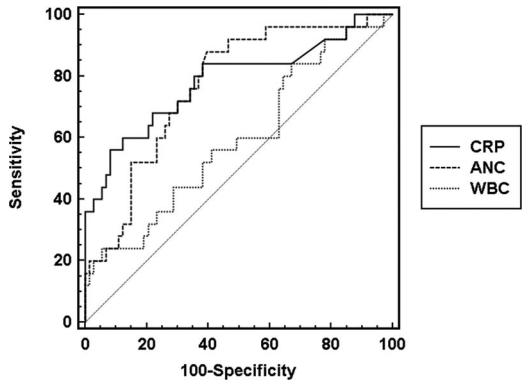

FIGURE 2. ROC for CRP, ANC and WBC count for prediction of SBI at <12 from fever onset.

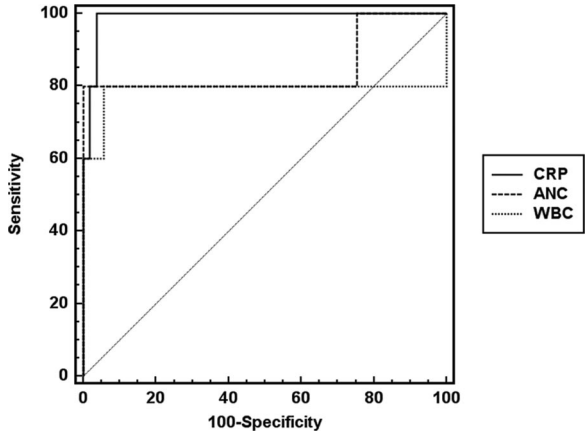

FIGURE 3. ROC for CRP, ANC, and WBC count for prediction of SBI at >12 from fever onset.

ics.[1–3,5,7–9,11–18] Most of these studies demonstrated that febrile neonates with good clinical conditions, unremarkable history and physical examination, and negative laboratory screening tests have a very low probability to develop an SBI[1–3,8,11–14,16–17]; consequently, some authors even suggested an outpatient management, being a meticulous follow-up provided.[1,26] Other investigators, in favor of a close inpatient observation without antibiotics for low-risk neonates, reported good outcomes for those who received treatment as soon as pending cultures turned positive or clinical deterioration was noticed, emphasizing that death and serious morbidity, and not positive blood or CSF cultures results, are the real and final outcomes physicians should be concerned about.[13,26,27] Based on these considerations, and taking into account laboratory markers kinetics,[28] the policy in use in our PED for the management of well-appearing neonates with early onset FWS and negative screening tests on admission, is close inpatient observation, delaying decision on antibiotic therapy until laboratory markers >12 hours of fever are available or clinical conditions worsen.

In our study an SBI was found in 25.3% of the well-appearing neonates with early onset FWS, quite similar to the prevalence reported in 2 recent studies[17–18] on unselected febrile neonates. Lower rates were reported in other previous works addressing the issue of fever in neonates.[12,13,15–18] Differences in the rate of circumcision in males, in the local epidemiology of pathogens, in the management by pediatric office practice, and in the quality of perinatal care may have contributed to our SBI prevalence result.

According to our data, laboratory markers did not result reliable predictors of SBI when performed at <12 hours of fever duration. In particular the traditionally recommended WBC proved to be the less accurate test. Both CRP and ANC showed a significant better performance than WBC. Nevertheless their low sensitivity in the first hours of fever did not allow for the early identification of all cases of SBI. As a matter of fact 3 patients with bacteremia and 2 with meningitis had normal blood tests values on initial determination. However, laboratory markers performance greatly improved, with a significant AUC increase for CRP, when

determined after more than 12 hours from fever onset. On repeated evaluation their rise above normal values allowed for the detection of all the previously missed 5 patients with SBI. These neonates received immediate antibiotic therapy after completing a full sepsis work-up and all recovered well, without any reported damage on follow-up.

Our results advise physicians not to rely on negative laboratory tests values to decide to manage without antibiotics well-appearing neonates with only few hours of fever duration. For these patients repeated laboratory tests evaluation, at least 12 hours from fever onset, as well as close inpatient observation should be warranted if initial management without antibiotic therapy is chosen.

In 1990s, Chiu et al[12,13] suggested that a substantial number of febrile neonates at low risk for SBI, could have safely be managed as inpatients without antibiotics. However, laboratory markers performance and time from fever onset were not evaluated. Of interest theirs were the only studies including CRP determination (with a cut-off of value of 20 mg/L) as part of low risk criteria, whereas WBC was a common parameter to many studies, with defined normal values between 5000/mm^3 and 15,000/mm^3.[1–5,8,12–18]

Overall, our work demonstrates that CRP and ANC performed better than WBC as SBI predictors, in both initial and repeated determination. In particular the sensitivity and negative predictive value of CRP were superior to ANC. These results are consistent with the ones of a previous study we conducted in our PED in children aged 7 days 36 months[28] and with other authors' works in older children.[29–34] Recently, even the NICE guidelines on feverish illness in children[21] expected pediatric specialists to use the CRP result as part of the assessment of the febrile neonate, but the guideline development group was unable to recommend a specific cut-off level and no recommendation was made on the time-related determination from fever onset.

Only few studies evaluated the diagnostic accuracy of laboratory markers in relation to duration of fever and none was selectively conducted on a population of febrile neonates. Recently, Pratt and Attia[35] reported a better diagnostic accuracy of CRP, ANC, and WBC in children aged 1 to 36 months with fever duration >12 hours compared with those with fever evolution <12 hours and, in accordance with our results, they also found a better performance of CRP than ANC and WBC, in both cases.

Additional studies conducted in children of the same age group[28,32] and, more recently, in infants younger than 3 months,[34] with early onset fever demonstrated a better diagnostic accuracy of Procalcitonin (PCT) compared with CRP. These findings reflect the different kinetics of the 2 molecules, with a more rapid rising of PCT level in the bloodstream after the infectious insult. Considering that the great majority of neonates is brought to visit to the PED after a very short fever evolution, PCT could be a valuable tool for the early identification of those children at risk for SBI, but further prospective studies are needed to validate PCT benefit in the management of the febrile neonate.

The present study has some limitations as the use of sterile bags for urine collection. This technique is less specific than suprapubic aspiration or bladder catheterization for the diagnosis of urinary tract infections, but it highly reduces the discomfort for the patients and their family. That is why sterile bags are widely used in the day to day practice both in primary care and in emergency department settings.[24,36–41] As already stated by Leroy et al[39] the range of specificity related to bag urine collection varies widely across the studies, and the low specificity reported by some authors is supported by a questionable level of evidence. In our experience changing the bag every half an hour and obtaining 2 samples for urinalysis and urine culture minimize the risk of false positive results.[24]

Another limitation of this study is that not all patients received a cerebrospinal fluid analysis and culture as part of the diagnostic work-up. As a matter of fact according to the guidelines in use in our PED, lumbar puncture is not routinely performed in all febrile neonates, but reserved to the ones suspected to have bacteremia or meningitis, ie, in the presence of poor general conditions, clinical deterioration, or significant elevation of laboratory markers at admission or at follow-up determination. This attitude is also shared by other authors[1,12,13,42] who believe that a spinal tap and antibiotic therapy may safely be spared if a close clinical observation is warranted.

Finally, the number of patients included in the study is quite small, due to the selected population considered and does not allow for definitive conclusion. However, this was intended as a preliminary study and further larger studies are needed to better define the accuracy of laboratory markers as predictors of SBI in the febrile neonate.

We conclude that physicians should not rely on negative laboratory markers values determined at <12 hours of fever duration, to consider a well-appearing febrile neonate at low risk of SBI. ANC and especially CRP proved to be more accurate predictors of SBI than the traditionally recommended WBC.

Well-appearing neonates with early onset FWS and negative screening tests on admission should be hospitalized for close inpatient observation and laboratory markers repetition after >12 hours of fever, if management of these patients without antibiotic therapy is chosen.

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