Procalcitonin and C-Reactive Protein as Diagnostic Markers of Severe Bacterial Infections in Febrile Infants and Children in the Emergency Department

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Objective: To assess the value of procalcitonin (PCT) and C-reactive protein (CRP), compared with that of total white-blood cell count (WBC) and absolute neutrophil count (ANC), in predicting severe bacterial infections (SBIs) in febrile children admitted to Emergency Department.

Methods: A prospective study was conducted in 408 children aged 7-days to 36-months, admitted with fever without source, at a tertiary care Pediatric Emergency Department. PCT, CRP, WBC, and ANC were determined upon admission and compared. Specificity, sensitivity, multilevel likelihood ratios, receiver operating characteristic (ROC) analysis, and multivariate stepwise logistic regression were carried out.

Results: SBI was diagnosed in 94 children (23.1%). PCT, CRP, WBC, and ANC were significantly higher in this group than in non-SBI patients. The area under the ROC (AUC) obtained was 0.82 (95% CI: 0.78–0.86) for PCT, 0.85 (95% CI: 0.81–0.88) for CRP ($P = 0.358$), 0.71 (95% CI: 0.66–0.75) for WBC, and 0.74 (95% CI: 0.70–0.78) for ANC. Only PCT (OR: 1.32; 95% CI: 1.11–1.57; $P < 0.001$) and CRP (OR: 1.02; 95% CI: 1.01–1.03; $P < 0.001$) were retained as significant predictors of SBI in a multiple regression model. For infants with fever <8 hours (n = 45), AUC for PCT and CRP were 0.92 (95% CI: 0.80–0.98) and 0.75 (95% CI: 0.60–0.87), respectively ($P = 0.056$).

Conclusion: Both PCT and CRP are valuable markers in predicting SBI in children with fever without source and they perform better than WBC and ANC. PCT appears more accurate at the beginning of infections, but overall CRP may be the most convenient marker for its better sensitivity and feasibility.

Key Words: C-reactive protein, children, fever, leukocytes, procalcitonin

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Fever is one of the most common reasons for visits to the Emergency Department, of children younger than 3 years of age, accounting for approximately 10–35% of admissions.[1,2] Severe bacterial infections (SBIs) represent 10–25% of febrile illnesses in this age group,[3–5] and the diagnosis is often confusing, especially if localizing findings are absent. Because clinical findings (body temperature, Yale Observation Score) often provide inadequate information,[6–9] there is a need for sensitive and specific laboratory markers of infection.

More than a decade ago, Baraff et al[2] published an algorithm that has proven to be useful in practice. In addition to clinical findings, the algorithm incorporates laboratory findings, such as white-blood cell count (WBC) and absolute neutrophil count (ANC), in identifying children at higher risk of severe bacterial illnesses. Subsequent studies have suggested that additional markers such as C-reactive protein (CRP) and, more recently, procalcitonin (PCT) may be useful.[10–15] CRP is an acute-phase reactant synthesized by the liver in response to the elevated levels of the cytokines; it is produced within 4–6 hours after onset of tissue injury or inflammation, it doubles every 8 hours before peaking around 36 hours,[16,17] and it has long been studied as a sensitive marker of bacterial infection. Since the early 1990s, there has been mounting interest in the question of whether PCT, a 14-kDa protein prohormone of calcitonin, is an earlier and more specific marker; PCT levels rise more rapidly than do CRP levels, given the triggers,[18] and it is known to rise slightly in viral infections, but it can increase nearly a 1000-fold in the very invasive bacterial infections. Actually, definitive data are lacking to validate CRP and PCT as screening tools in the Emergency Department.

The aim of this study was to determine the diagnostic performance of PCT and CRP, in comparison to that of WBC and ANC, in detection of SBI in pediatric patients admitted to the Pediatric Emergency Department for fever without a source.

MATERIALS AND METHODS

Patient Characteristics and Inclusion Criteria. This prospective observational study was conducted in the tertiary care Emergency Department of the Children's Hospital in Padova (Italy) between May 1, 2004 and October 31, 2005. The study included all children younger than 3 years who were consecutively admitted to the Emergency Department with fever of uncertain source, who, after a careful history and physical examination, underwent blood analysis because more likely

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to have a SBI,[2,3] namely: (1) all infants aged 7-days to 3-months-old with fever (rectal temperature) >38°C; (2) children aged 3–36-months old ill/toxic-appearing or with fever (rectal temperature) >39.5°C. Those children with a history of (1) antibiotic use within the 48 hours before admission to the hospital, (2) vaccination during the previous 2 days, (3) known immunodeficiencies, (4) any chronic pathology, or (5) fever lasting longer than 5 days were excluded from the study.

Clinical and Diagnostic Evaluations. Complete history, demographic information, room temperature, degree and duration of fever, physical examination, and clinical evaluation using the Yale Observation Score[7] were recorded at the time of the initial evaluation. According to the guidelines in use at the time of the study in our Department, in all patients the WBC, ANC, and quantitative CRP concentration were, along with urine analysis, obtained; in addition, a serum sample was also collected and stored at −20°C for later determination of PCT level. Toxic-appearing children had a full sepsis workup. Infants from 1-week to 90-days of age and children ill-appearing aged 3–36 months received a blood culture and 2 consecutive urine cultures. Well-appearing children aged 3–36 months received a blood culture when displaying WBC >15,000/mm^3 or ANC >10,000/mm^3, and 2 consecutive urine cultures if urine analysis was positive for leukocyte esterase and/or nitrite test.[2,3]

Urine was collected in sterile bags changed every half an hour or, in older toilet-trained children, by the midstream clean-void technique. In the presence of growth of a single urinary tract pathogen ($\geq 10^5$ colony-forming units/mL) in 2 consecutive urine samples, 99mTc-dimercaptosuccinic acid (DMSA) scintigraphy was performed. Chest radiograph as well as other laboratory and radiographic tests were conducted at the discretion of the child's physician. A spinal tap was performed when meningitis was suspected.

Admission to hospital was mandatory for all neonates. In the case of older infants and children, decisions on therapy and hospitalization were made by the attendant physician. Follow-up of all nonhospitalized patients was performed by telephone contact or clinical assessment by a pediatrician within the next 72 hours. The final diagnosis was registered at the end of the follow up.

On the basis of their final diagnosis, children were classified into 2 groups: patients with (SBI group) or without (non-SBI group) severe bacterial infections. The following were considered as SBI[10,11,13]: (1) bacteremia—recovery of a single bacterial pathogen using standard culture techniques; (2) acute pyelonephritis—growth of a single urinary tract pathogen at $\geq 10^5$ colony-forming units/mL in 2 consecutive urine samples and presence of a renal hypocaptation at DMSA scan performed within the first week after admission; (3) lobar pneumonia—presence of focal infiltrate on chest radiograph observed by the pediatric radiologist in a blinded manner; (4) bacterial meningitis—positive cerebrospinal fluid culture; (5) bone or joint infections—local isolation or isolation in blood culture of a microorganism; and (6) sepsis defined according to Levy et al[19]—signs and symptoms of inflammation plus infection, tachycardia, decreased capillary refill or mottling, and at least one of the following indications of altered organ function as altered mental status, hypoxemia, increased serum lactate level, or bounding pulses, coagulation abnormalities. Remaining children with negative cultures or clinical improvement without antibiotic therapy or with detection of a focal infection at follow-up were classified in the non-SBI group.

Informed consent was obtained from the parents or legal guardians for the additional blood sampling. The study protocol was approved by the Hospital Ethics Committee.

Laboratory Assessments. Erythrocyte, platelet, and WBC 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. Quantitative measurements of PCT concentrations were performed using a sandwich immunoluminometric method (detection limit = 0.04 ng/mL), employing 2 monoclonal antibodies: one against the catacalcin region of procalcitonin and the other against calcitonin (LIAISON BRAHMS PCT; Brahms Diagnostica, Henningdorf BEI, Berlin).

Statistical Analysis. Normally distributed data were expressed as mean ± SD; nonnormally distributed data were expressed as median and interquartile range; categorical variables were reported as percentages. For nonnormally distributed data, comparison was performed employing Mann–Whitney *U* or Kruskal Wallis tests when appropriate; 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, PCT, WBC, and ANC) were first investigated by receiver operating characteristic (ROC) analysis.[20] This technique summarizes the validity coefficients of a parameter and provides an overall index of diagnostic accuracy (the area under the ROC curve) from a plot of sensitivity against the false-positive rate (1-specificity) for all possible cutoff scores. Based on ROC analysis, the best statistical cutoff value for each parameter (the point at which the sum of false-positives and false-negatives is less than any other point) was calculated. Sensitivity, specificity, positive and negative likelihood ratios for selected cutoff points were then assessed. A multiple logistic regression model was used to identify variables (body temperature, Yale score, CRP and PCT levels, WBC, ANC) independently associated with the outcome variable, namely the presence of SBI. A stepwise regression procedure was used in obtaining the final model.

The commercial statistical software package used was EpiInfo 2000 (Centers for Disease Control and Prevention, Atlanta), and MedCalc Version 7.3 was the computer program employed for ROC analysis.

RESULTS

Patient Characteristics. During the 18-month period (May 2004 to October 2005), a total of 435 consecutive patients met the inclusion criteria for the study. Sixteen children were

TABLE 1. Final Diagnosis of Patients With Severe Bacterial Infections (n = 94)

	No. of Patients	%
Pyelonephritis	50	53.2
Pneumonia	24	25.5
Meningitis	7	7.5
Occult bacteremia	6	6.4
Sepsis	3	3.2
Osteomyelitis	2	2.1
Septic arthritis	2	2.1

not enrolled for inadvertent omission; 11 were excluded because of insufficient blood samples or lack of follow up. The data of 408 enrolled children were analyzed. Of these, 205 (50.2%) patients were female. The median age was 10 months (2.5–16.5 months); 107 (26.2%) were infants younger than 3 months (median age, 31 days). One hundred forty-three patients (35%) presented fever for less than 24 hours and 45 for less than 8 hours. Two hundred seventeen children (53%) were hospitalized.

Clinical, Microbiological, and Laboratory Data. At the end of the follow-up, SBI was diagnosed in 94 children (23.1%) (Table 1) and non-SBI in 314 children. Among the SBI group, *Escherichia coli* (45), *Pseudomonas aeruginosa* (2), *Enterococcus faecalis* (1), *Klebsiella pneumoniae* (1), *Proteus mirabilis* (1) were isolated in urine cultures; *Streptococcus pneumoniae* (7), *Escherichia coli* (6), *Streptococcus* group B (4), *Staphylococcus aureus* (2) were isolated in blood cultures; *Streptococcus* group B (5), *Escherichia coli* (2) were isolated in cerebrospinal fluid cultures; *Staphylococcus aureus* (2) was isolated in synovial fluid. In the non-SBI children, causative infections were: focal bacterial infection in 64 (15.7%) children (24 lower urinary tract infections, 23 pharingotonsillitis, 7 otitis, 3 adenitis, 3 cellulitis, 2 gastroenteritis, 2 scarlet fevers); proved viral infection in 36 (8.8%) children (positive antigen detection or viral culture, characteristic evolution of disease: ie, exanthema subitum); probable viral infection in 213 (52.2%) children (negative cultures, spontaneous recovery without antibiotics and no signs for focal bacterial infection at clinical follow up). One child had a final diagnosis of Kawasaki disease.

Demographic characteristics and laboratory findings of patients with and without SBI are presented in Table 2. The 2 groups were comparable for sex, median age, and duration of fever before admission, while body temperature and Yale Score were significantly higher in patients with SBI. PCT, CRP, WBC, and ANC were, despite the large intergroup variations, also significantly higher in the group of children with SBI ($P < 0.0001$). Box plots of the distribution of PCT, CRP, WBC, and ANC concentrations are shown in Figure 1 (online only).

Sensitivity and Specificity Measurements for Prediction of Severe Bacterial Infection. Table 3 shows the sensitivity, specificity, and likelihood ratios for the most commonly recommended cutoffs of the diagnostic markers considered. PCT and CRP performed better than the other clinical and laboratory parameters.

As shown in Figure 2, the area under the ROC curve (AUC) was 0.82 (95% CI: 0.78–0.86) for PCT, 0.85 (95% CI: 0.81–0.88) for CRP, 0.71 (95% CI: 0.66–0.75) for WBC, and 0.74 (95% CI: 0.70–0.78) for ANC. The difference between AUCs for PCT or CRP and AUCs for ANC or leukocyte count was statistically significant. No significant difference was found comparing AUCs of PCT and CRP ($P = 0.748$). In our sample, the optimum statistical cutoff value for detecting SBI was 0.8 ng/mL (sensitivity, 69.1%; specificity, 85.3%) for PCT, 32 mg/L (sensitivity, 84.0%; specificity, 75.5%) for CRP, 10,470/mm^3 (sensitivity, 84.9%; specificity, 47.4%) for WBC, and 6,450/mm^3 (sensitivity, 81.8%; specificity, 62.3%) for ANC.

Multiple Regression Analysis. Body temperature, Yale Observation Score, CRP values, PCT values, WBC, and ANC were introduced in a multiple logistic regression analysis. Only PCT (odds ratio, 1.32; 95% CI: 1.11–1.57; $P < 0.001$) and CRP (odds ratio, 1.02; 95% CI: 1.01–1.03; $P < 0.001$)

TABLE 2. Clinical Characteristics and Laboratory Findings of Patients With SBI and Non-SBI

Variable	SBI (n = 94)	Non-SBI (n = 314)	*P*
Age (mo)	8 (2–20)	9 (2–16)	NS
Sex (F/M)	52/42	153/161	NS
Fever duration (h)			NS
<8	14	31	
8–24	31	67	
>24	49	216	
Max temperature (°C)	39.2 ± 0.8	39.0 ± 0.8	0.004
Yale Score (n)			0.0001
<10	46	225	
10–16	40	82	
>16	8	7	
PCT (ng/mL)	1.9 (0.5–10.7)	0.2 (0.1–0.5)	0.0001
CRP (mg/L)	68.5 (39.0–120.0)	13 (3–31)	0.0001
WBC (mm^3)	15,850 (12,040–20,250)	10,770 (7,050–14,960)	0.0001
ANC (mm^3)	9,522 (6,830–14,154)	5,119 (3,108–8,295)	0.0001

Data are median and interquartile range except for temperature values which are mean ± SD.
NS indicates nonsignificant.

TABLE 3. Sensitivity, Specificity, Positive and Negative Likelihood Ratio Values of PCT, CRP, WBC, ANC, and Yale Observation Score for SBI Prediction

	Sensitivity (% [95% CI])	Specificity (% [95% CI])	Likelihood Ratio+	Likelihood Ratio−
PCT				
>0.5 ng/mL	73.4 (63.3–82.0)	76.4 (71.3–81.0)	3.10	0.35
>1 ng/mL	63.8 (53.3–73.5)	89.8 (85.9–92.9)	6.24	0.40
>2 ng/mL	47.9 (37.5–58.4)	96.5 (93.8–98.2)	13.62	0.54
CRP				
>20 mg/L	88.3 (80.0–94.0)	60.8 (55.2–66.3)	2.25	0.19
>40 mg/L	71.3 (61.0–80.1)	81.2 (76.4–85.4)	3.79	0.35
>80 mg/L	46.0 (36.4–57.4)	94.6 (91.5–96.8)	8.65	0.56
WBC				
>15,000/mm^3	51.6 (41.0–62.1)	75.5 (70.3–80.2)	2.11	0.64
ANC				
>10,000/mm^3	29.9 (20.5–40.6)	78.4 (73.3–82.9)	1.38	0.89
Yale Observation Score				
YOS >10	38.3 (28.5–48.9)	67.8 (62.4–73.0)	1.19	0.91

levels were retained as significant predictors of SBI (outcome variable). The accuracy of the model was 86.5%, signifying that 86.5% of patient outcomes were correctly classified as SBI or non-SBI.

Age Groups. The incidence of SBI in infants <3 months (26.2%) was comparable to that in children 3–36 months (21.9%) ($P = 0.446$). No difference was found in the AUC for both PCT and CRP between infants aged less than 3 months and children aged 3–36 months, respectively.

Severity of Infections. When serum PCT and CRP concentration were analyzed across various SBI categories, only PCT differed significantly in relation to different organ involvement ($P < 0.0001$) with the highest values found in sepsis (36.8 ng/mL [31.0–49.1]) and meningitis (40.5 ng/mL [18.9–70.9]).

Duration of Fever Before Admission. In children with evolution of fever earlier than 8 hours before admission (n = 45), PCT, CRP, and ANC were significantly higher in the group with SBI, whereas WBC was not (data not shown). In this population, PCT presented a better diagnostic performance than did CRP: the AUC for SBI detection was 0.92 (95% CI: 0.80–0.98) for PCT versus 0.75 (95% CI: 0.60–0.87) for CRP ($P = 0.056$) (Fig. 3 [online only]). AUC for ANC was 0.69 (95% CI: 0.54–0.82). The optimum cutoff value for PCT in this group of patients was 1 ng/mL (sensitivity, 85.7%; specificity, 100%).

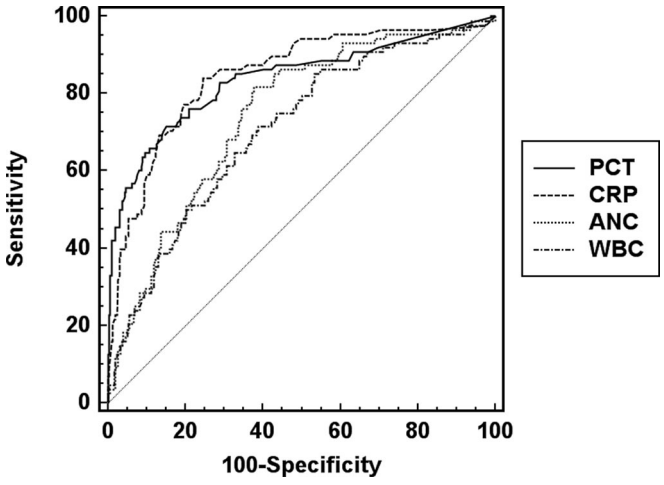

FIGURE 2. ROC for PCT, CRP, WBC count, and ANC for prediction of SBI.

DISCUSSION

Our results demonstrate that both CRP and PCT have superior discriminatory power to total and differential WBC in detecting SBI in children with fever without a source. These indices, when compared with WBC and ANC at their traditional cut off values (WBC >15,000/mm^3; ANC >10,000/mm^3), were more sensitive and specific, with multilevel likelihood ratios higher for all the considered cut-offs. On ROC analyses, PCT and CRP had the greatest AUC and no overlap was found in the 95% CIs between either CRP or PCT and WBC or ANC, suggesting a significantly better diagnostic performance. In addition, in a multivariate model controlling for potentially confounding factors, PCT and CRP remained the only significant predictors of SBI.

To the best of our knowledge, this prospective study represents one of the largest single center clinical experiences in assessment of the diagnostic efficiency of CRP and PCT, compared with other most commonly used laboratory tests, such as WBC and ANC, in predicting SBI in children less than 3 years of age admitted to Emergency Department for fever without source. The study was conducted in a Pediatrics Emergency Department of a tertiary care Children's Hospital, which serves a large referral area where greater than 95% of children younger than 3 years have their primary care pediatrician and approximately 90% are vaccinated for *Haemophilus influenzae* B and 20% for *Streptococcus pneumoniae*. All febrile infants and children commonly considered more likely to have a SBI were consecutively included.[2,3]

In this population, the prevalence of SBI was approximately 20%, higher than that found in some previous studies carried out in an emergency setting,[21] but closer to others with

similar patient selection.[22,23] Moreover, in our clinical setting, pyelonephritis is the most common SBI, whereas very invasive infections, such as sepsis and meningitis, are uncommon.

Several studies examining the diagnostic use of CRP and PCT have been published,[24–30] but a few have been conducted to predict SBI in febrile children in an emergency setting.[10,11,21–23,31–34] Moreover, most studies in EDs have shown that CRP has a better performance than WBC and ANC in predicting SBI,[10,31,32] whereas Isaacman et al[21] found that WBC, ANC, and CRP (better cutoff 44 mg/L) performed quite similarly with little discernible difference in distinguishing febrile infants aged 3–36 months with viral illnesses from those with occult bacteremia. Although these different results may, at least in part, be accounted for by differences in study and analytic designs as well as in the inclusion criteria, the few studies conducted evaluating the diagnostic performance of PCT in emergency settings have provided evidences that PCT may be superior to WBC or CRP in detecting invasive infections. Gendrel et al,[11] in a selected group of children 1-month to 15-year-old hospitalized after admission to Emergency Department, found that PCT, at the cutoff of 2 ng/mL, had a very high sensitivity (96%) and specificity (87%) in detecting invasive bacterial infection and performed better than CRP at different cutoff levels (AUCs of 0.94 [0.90–0.96] versus 0.89 [0.85–0.92]; $P < 0.0001$). Similar results were reported by Fernandez Lopez et al[33,34] in 2 studies, both of which included febrile children admitted to Pediatric Emergency Department and subsequently hospitalized. In these studies, both PCT and CRP were found to perform better when used alone than do WBC and ANC in detecting invasive infections; in addition, PCT displayed higher diagnostic accuracy than did CRP, with an AUC of 0.95 for PCT and 0.81 for CRP ($P < 0.01$). Of note, however, is that the better performance of PCT found in these studies may be related to the considerable number of severe bacterial infections and, among these, the high rate of invasive infections, such as meningitis and sepsis, reported.

By contrast, our study subjects were a heterogeneous Emergency Department pediatric population, mostly comprised of noncritically ill patients, approximately 50% of whom were discharged to home. In this population, PCT and CRP displayed similar diagnostic accuracy, a finding in accord with that reported by Galetto-Lacour[22,23] in 2 consecutive studies considering smaller unselected populations of children 7-days to 36-months old, admitted to a Pediatric Emergency Department for fever without localizing signs. Moreover, in our study, PCT was slightly more specific and CRP fairly more sensitive, when considered at their best statistical cut-off values (respectively of 0.8 ng/L and 32 mg/L based on the ROC analysis), in detecting SBI. When PCT and CRP were combined using their best cut-offs, a slightly better screening profile for ruling out SBI was provided (sensitivity of 92.6%), yet at the expense of a decrease in specificity (69.8%). These results are of utmost relevance in the context of clinical practice, where the scientific and the clinical value of a false-positive result is not the same as that of a false-negative.

Also, in our study, we found that PCT, but not CRP, concentrations were significantly higher in the group of children with more invasive bacterial infections, ie, sepsis-meningitis group, suggesting that PCT is not just a marker of infection but, more importantly, an appropriate marker of the severity of infection. This may explain why the better performance of PCT with respect to CRP is principally reported in those papers including a very high rate of invasive infections, such as sepsis or meningitis.[30,33,34] Moreover, in patients with fever evolution <8 hours, we observed that PCT may perform better than does CRP ($P = 0.05$), with a difference at limit for significance likely as a result of the small number of patients in this group (n = 45). This is in accordance with results obtained in other clinical studies[22,23,34] as well as with findings showing PCT levels rise more rapidly than CRP levels after endotoxin injection in the bloodstream.[18]

The major limitation of our study is that blood culture was not routinely performed in all children older than 3 months of age. Although this may have led to missing of some occult bacteremia, the risk is, in our experience, minimal and does not likely affect the validity of our results. In fact, the prevalence of occult bacteremia in nontoxic-appearing children between 3 and 36 months of age with temperatures higher than 39°C has declined to about 2% after the introduction of conjugate vaccines against *Haemophilus influenzae* type B,[35,36] whereas the licensure of conjugate pneumococcal vaccine has been shown to further reduce the rate of invasive pneumococcal disease in immunized children.[37,38] Moreover, the strict follow-up of our nonhospitalized patients and the contact with their primary care pediatrician have minimized this risk. In addition, using a preapplied screening based on ANC and WBC thresholds to decide which children older than 3 months received a blood culture, might have biased CRP and PCT performance. However, considering only infants younger than 3 months (all receiving a blood culture and a urine culture independently on the results of the screening tests), we found that both PCT and CRP performed exactly the same as in older children, suggesting that PCT and CRP might perform well if applied to all the pediatric population.

We believe that CRP and PCT are both valuable markers for prediction of SBI in children admitted to an Emergency Department with fever without a source. PCT seems to be a more accurate predictor at the beginning of an infection, whereas CRP, if correctly employed by taking into account the time needed for its rise in the bloodstream, may be a better screening test in emergency settings, because of its overall better sensitivity and feasibility, ie, lower cost, better availability, and better historical practice.

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