Markers for bacterial infection in children with fever without source

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ABSTRACT

Objectives To compare the diagnostic properties of procalcitonin (PCT), C reactive protein (CRP), total white blood cells count (WBC), absolute neutrophil count (ANC) and clinical evaluation to detect serious bacterial infection (SBI) in children with fever without source.

Design Prospective cohort study.

Setting Paediatric emergency department of a tertiary care hospital.

Participants Children aged 1–36 months with fever and no identified source of infection.

Intervention Complete blood count, blood culture, urine analysis and culture. PCT and CRP were also measured and SBI probability evaluated clinically with a visual analogue scale before disclosing tests results.

Outcome measure Area under the curves (AUC) of the receiver operating characteristic curves.

Results Among the 328 children included in the study, 54 (16%) were diagnosed with an SBI: 48 urinary tract infections, 4 pneumonias, 1 meningitis and 1 bacteraemia. The AUC were similar for PCT (0.82; 95% CI 0.77 to 0.86), CRP (0.88; 95% CI 0.84 to 0.91), WBC (0.81; 95% CI 0.76 to 0.85) and ANC (0.80; 95% CI 0.75 to 0.84). The only statistically significant difference was between CRP and ANC (Δ AUC 0.08; 95% CI 0.01 to 0.16). It is important to note that all the surrogate markers were statistically superior to the clinical evaluation that had an AUC of only 0.59 (95% CI 0.54 to 0.65).

Conclusion The study data demonstrate that CRP, PCT, WBC and ANC had almost similar diagnostic properties and were superior to clinical evaluation in predicting SBI in children aged 1 month to 3 years.

What is already known on this topic

- The pneumococcal vaccine has significantly reduced the prevalence of serious bacterial infection (SBI) in children aged under 3 with fever without source.
- Nevertheless, many clinician decisions depend on patient assessment or interpretation of complementary laboratory tests in such patients.
- The utility of surrogate markers is not well established in the postpneumococcal vaccination era.

What this study adds

- This study compared the diagnostic ability of surrogate markers and clinical evaluation to detect SBI in children vaccinated against *Streptococcus pneumoniae*.
- Based on multilevel likelihood ratios, the study suggests that these markers need to be interpreted depending on the value obtained in each patient.

INTRODUCTION

The introduction of the pneumococcal vaccine has significantly reduced the prevalence of serious bacterial infection (SBI) and, in particular, of occult bacteraemia in children under 3 years of age.[1 2] Despite this, children less than 3 years of age with fever without source remain a clinical challenge as urinary tract infection (UTI), pneumonia or occult bacteraemia cannot be excluded in a well-appearing child.[3] Thus, many decisions made by the clinician depend either on patient assessment or on interpretation of complementary laboratory tests.

As total white blood cells count (WBC) and absolute neutrophil count (ANC) have disappointing diagnostic properties,[4–8] other surrogate markers of SBI have been evaluated and used in recent years. C reactive protein (CRP) and procalcitonin (PCT) were shown to be better predictors of SBI than WBC.[4 6 7 9–11] However, the utility of these surrogate markers is not well established in the postpneumococcal vaccination era since their diagnostic properties depend on the prevalence of the disease. In addition, it is not known whether a clinical evaluation by a physician is good enough to rule out SBI when most of the SBI are now likely to be UTIs.

The objective of the present study is to compare the diagnostic properties of PCT, CRP, WBC, ANC and clinical evaluation to detect SBI in children aged 1–36 months presenting to a paediatric emergency department with fever without source, now that most of these children have been vaccinated against *Streptococcus pneumoniae*.

METHOD

Study design

This prospective cohort study was part of a randomised controlled trial (RCT) assessing the impact of a rapid semiquantitative PCT test on the management of children aged 1–36 months presenting to a paediatric emergency department with fever without source.[12] The institutional review board approved the study and written informed consent was obtained from a parent.

Settings and selection of participants

Patient enrolment took place in the emergency department of a tertiary care urban paediatric centre with 60 000 visits annually. To be included, the patient had to be a child between the ages of 1 and 36 months with a history of a rectal temperature over 38°C (100.4°F) with no identified source of infection after careful history taking and physical examination. All patients with known acquired or congenital immunodeficiency, as well as children already treated with antibiotics, were excluded. It is estimated that among eligible children, over 90% had received at least three doses of the PCV7 vaccine against *S pneumoniae* and over 97% at least two doses.[13 14]

Study protocol

Attending paediatric emergency physicians approached the parents of children meeting the inclusion criteria to participate in the study. After consent was obtained, a blood test for complete blood count (CBC), semiquantitative PCT (for the RCT), CRP, blood culture and a bladder catheterisation or suprapubic aspiration for urine analysis and culture were performed. The attending physicians could perform any other investigations (such as lumbar puncture or chest radiography) as required and the decision to treat with antibiotics or to hospitalise was left to their discretion. A single venipuncture was performed. If this site was lost, or an insufficient amount of blood was drawn, no other attempt was made, as long as a CBC and blood culture were obtained.

The attending physicians, all paediatric emergency physicians, were asked to evaluate the SBI probability with a visual analogue scale (VAS; 0–100%) after the history had been taken and a physical examination had been carried out, but before tests results were available. This comprised the subjective clinical evaluation. Laboratory technicians were blinded to the patients' final diagnosis.

Outcome measures

The primary outcome was to compare PCT, CRP, WBC, ANC and clinical evaluation (using the VAS) to detect an SBI in children aged 1–36 months with fever without source using the receiver operating characteristic (ROC) and the area under the ROC curve (AUC).

The secondary outcomes were to define, for the group studied, (1) the best cut-off values for the selected surrogate markers, and (2) their clinical utility when the urine analysis was normal using sensitivity, specificity, positive and negative likelihood ratios, as well as positive and negative predictive values. We also aimed to evaluate the multilevel likelihood ratios of the surrogate markers and to calculate post-test probabilities of disease using the Fagan nomogram on the basis of the pretest probability of disease.[15] This enabled us to overcome the limit of a single cut-off value.[16]

PCT and CRP measurement

One millilitre of blood was collected by venipuncture in a heparin/lithium Vacutainer (Becton-Dickinson, Franklin Lakes, New Jersey, USA) and centrifuged. Plasma was then frozen at −40°C. At the end of the RCT study, PCT was measured quantitatively with the ultra-sensitive immunoassay using TRACE (time resolved amplified cryptate emission) technology (Kryptor; Brahms, Hennigsdorf, Germany) in Geneva, Switzerland for the purpose of this cohort study. CRP was also measured for the same purpose using a rapid immunometric method (Nycocard CRP; Axis-Shield, Oslo, Norway) according to the instructions of the manufacturer.

Definitions

- Fever without source: Rectal temperature >38°C (100.4°F) without any signs or symptoms identifying an infectious disease
- SBI: Presence of bacteraemia, UTI, pneumonia, bacterial meningitis, osteomyelitis or septic arthritis
- Bacteraemia: Positive blood culture with bacteria not considered a skin contaminant
- UTI: Any bacterial growth on urine obtained by suprapubic aspiration or $\geq 10^4$ colony forming units/ml of a single pathogen on urine obtained by bladder catheterisation
- Pneumonia: Lobar consolidation diagnosed on chest radiography confirmed by a paediatric radiologist
- Bacterial meningitis: Cerebrospinal fluid leucocytes >5 cell/µl and positive bacterial culture
- Osteomyelitis: Positive bone scintigraphy
- Septic arthritis: Positive bacterial culture of synovial fluid
- Normal urine analysis: <5 white blood cells with high magnification and nitrite negative.

Data analysis

The primary investigator, who recorded all important information regarding final diagnosis and laboratory tests results, reviewed the medical chart of each enrolled patient and all collection forms. He also contacted all discharged patients for a 1-week telephone follow-up. All data were entered in an Excel database (Microsoft, Richmond, Washington, USA) and analysed using SPSS (v 15.0; Chicago, Illinois, USA) and MedCalc (v 9.6.0.0; Mariakerke, Belgium).

Normally distributed data were reported as mean±SD. Non-normally distributed data were expressed as median and IQR. Categorical variables were reported as percentages. The diagnostic performance of PCT, CRP, WBC, ANC and clinical evaluation (using the VAS) was first evaluated by ROC analysis. The AUC were calculated for each surrogate marker and clinical evaluation. The difference between the AUC of the ROC with standard error was evaluated using MedCalc. Sensitivity, specificity, positive and negative likelihood ratios and positive and negative predictive values were reported with their 95% CI. We calculated post-test probabilities of disease on the basis of the pretest probability of disease (ie, the prevalence) and multilevel likelihood ratios. These multilevel likelihood ratios were based on the optimal cut-off obtained from our ROC analysis and other intuitive cut-offs (including previously published cut-offs).[4 6 7 9–11 17–19] The level of significance was set a priori at $p<0.05$.

RESULTS

Of the 457 infants and children presenting with fever without source who met the inclusion criteria between November 2006 and November 2007, and who were approached by an attending paediatric emergency physician, 328 remained in the study. Reasons for withdrawal are summarised in the study flow chart (figure 1). Table 1 summarises the clinical characteristics of the included patients. During the study, 54 children (16%) were diagnosed with SBI of whom 48 (89%) had UTIs including two with positive blood culture, four (7%) had pneumonia, one (2%) had *Neisseria meningitidis* serogroup b meningitis and one (2%)

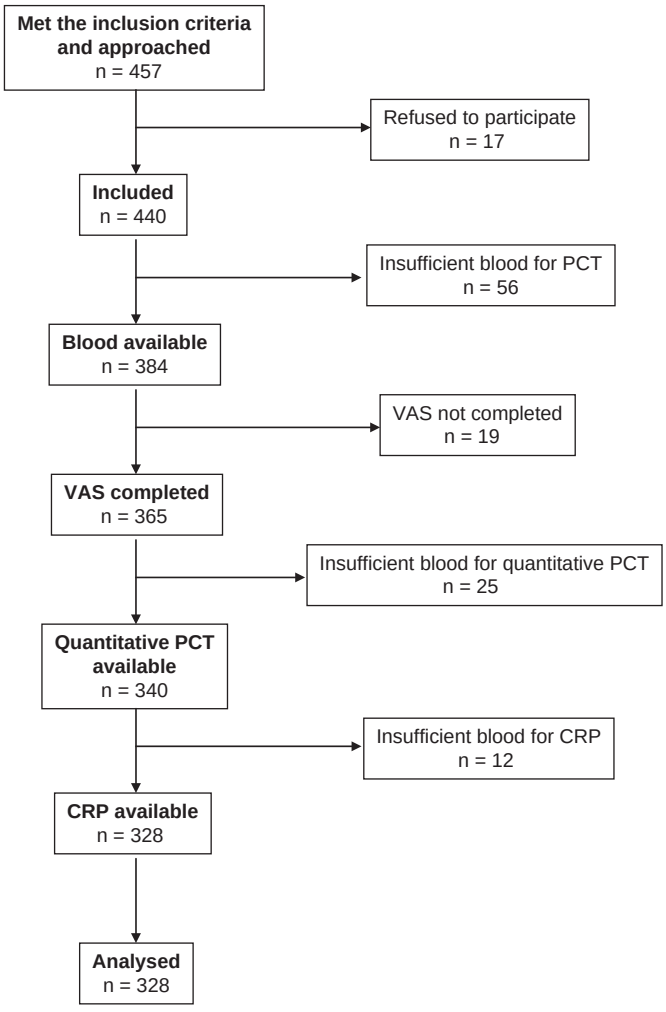

Figure 1 Study flowchart. CRP, C reactive protein; PCT, procalcitonin; VAS, visual analogue scale.

Table 1 Clinical characteristics of the 328 patients included in the cohort study

Characteristic	n
Male (%)	165 (50)
Median age in months (IQR)	11 (6–17)
Children aged 1–6 months (%)	95 (29%)
CTAS* triage level (%)	
1	0 (0)
2	49 (15)
3	131 (40)
4	146 (44)
5	2 (1)
Mean temperature duration in hours (SD)	62 (48)
Mean maximal temperature in °C (SD)	39.6 (0.7)

*CTAS, Canadian Triage Acuity Scale.

had an occult *S pneumoniae* serotype 33 bacteraemia. Among the excluded patients, only eight had an SBI (8/112, 7.1%), all of which were UTIs.

ROC curves for PCT, CRP, WBC, ANC and clinical evaluation are shown in figure 2. The best cut-off values to detect an SBI were determined to be 0.20 ng/ml for PCT, 17.7 mg/l for CRP, 14 100×10^6/l for WBC, 5200×10^6/l for ANC and 14.8% for the VAS.

The AUC for the surrogate markers and clinical evaluation are listed in increasing order in table 2. PCT was better than clinical evaluation for detecting SBI: difference in AUC 0.22 (95% CI 0.12 to 0.33). There was no difference between PCT and CRP, WBC or ANC. CRP was better than ANC and clinical evaluation for detecting SBI: difference in AUC 0.08 (95% CI 0.01 to 0.16) and 0.28 (95% CI 0.18 to 0.38), respectively. There was no difference between CRP and WBC. WBC was better than clinical evaluation for detecting SBI: difference in AUC 0.21 (95% CI 0.11 to 0.32). There was no difference between WBC and ANC. ANC was better than clinical evaluation for detecting SBI: difference in AUC 0.20 (95% CI 0.10 to 0.31).

The SBI diagnostic accuracy of the various surrogate markers and of the clinical evaluation is presented in table 3. In the case of a normal urine analysis in the emergency department, a situation the clinician often faces, the diagnostic accuracy of the surrogate markers and of the clinical evaluation is likely to change because the relative SBI aetiologies would be different (table 4). Because an SBI was found later in 8/262 (3%) children (four pneumonias, two UTIs, one meningitis and one occult bacteraemia) with normal urine analysis in the emergency department, and confirmed by the telephone follow-up carried out 1 week after the initial visit to the emergency department, the surrogate markers had better negative predictive values.

The multilevel likelihood ratios and post-test SBI probability, assuming a pretest SBI probability of 16% (the SBI prevalence in our population), are presented in table 5. However, when the urine analysis was normal in the emergency department, the multilevel likelihood ratios and post-test SBI probability changed. In that situation, the pretest SBI probability was 3% in our study; the resulting multilevel likelihood ratios and post-test SBI probability are presented in table 6.

DISCUSSION

We report, based on similar AUCs of the different ROC curves, that in a population of children 1 month to 3 years of age presenting to a paediatric emergency department with fever without source, CRP, PCT, WBC and ANC have similar diagnostic properties for detecting an SBI and are superior to clinical evaluation based on VAS. Knowing that all physicians were experienced paediatric emergency specialists in a large tertiary hospital, it is unlikely that this is due to a lack of competence. Actually, the fact that clinical evaluation had such poor accuracy is not surprising as most of the identified SBI in our study were UTIs. Many clinical scores have been developed to detect patients at high or low risk of SBI, but generally these have been disappointing.[4 10 17 20 21] Ancillary testing has always been recommended to help the physician detect SBI in a population such as that studied in the present report.[17 22] Our study shows that in the postpneumococcal vaccination era, ancillary testing is even more important as the prevalence of SBI is lower than in the prevaccination period and that clinical evaluation to ascertain UTI is limited in the 1–36-month-old age group.

In our study, the ROC curves AUC are similar to those previously published. Isaacman *et al*[18] and Pratt *et al*[23] found no statistical difference in AUC between CRP, WBC and ANC. These observations were confirmed by Bilavsky *et al*,[24] who demonstrated that there was no difference between CRP and WBC. However, using either AUC, sensitivity/specificity, positive/negative predictive values or likelihood ratios, other studies obtained better diagnostic properties for PCT and CRP than WBC and ANC.[4 6 7 10 11 19] The difference with our study

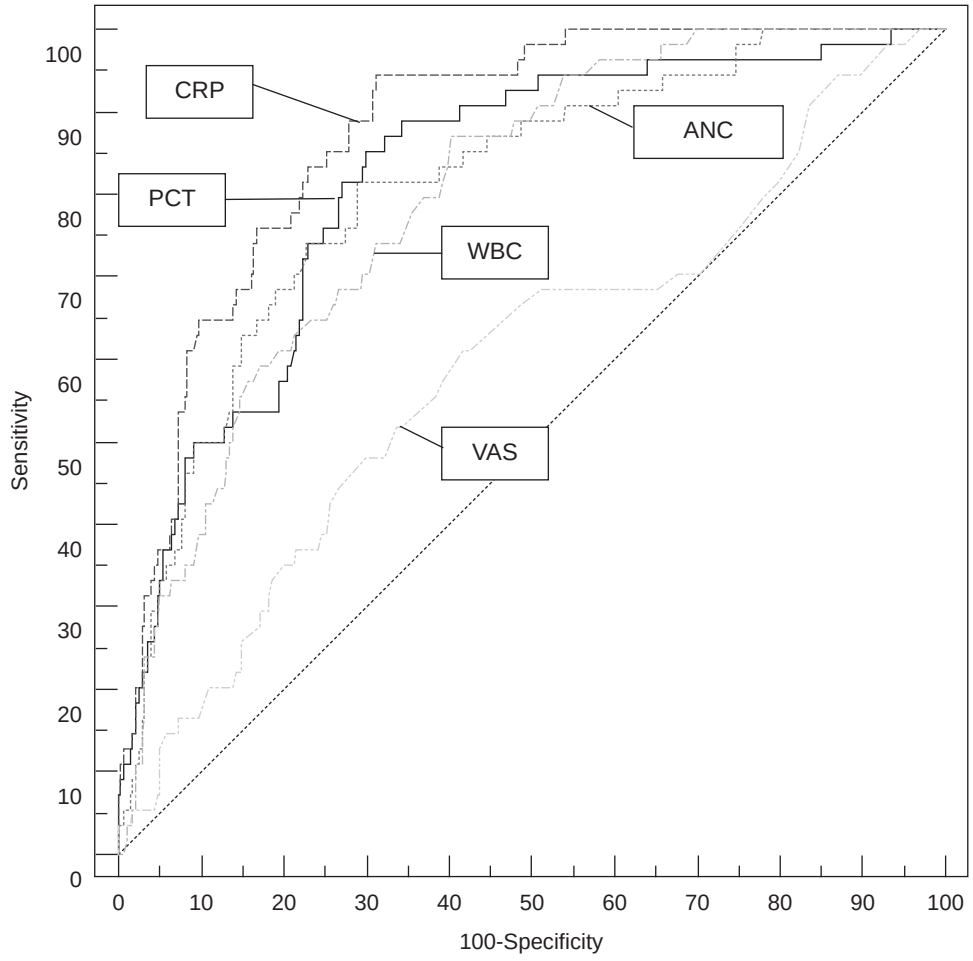

Figure 2 Receiver operating characteristic for procalcitonin (PCT), C reactive protein (CRP), white blood cells count (WBC), absolute neutrophil count (ANC) and clinical evaluation on a visual analogue scale (VAS) to detect a serious bacterial infection in children aged 1–36 months presenting to a paediatric emergency department with fever without source.

Table 2 Area under the curves (AUC) of the receiver operating characteristic for PCT, CRP, WBC, ANC and clinical evaluation on a VAS to detect an SBI in children aged 1–36 months presenting to a paediatric emergency department with fever without source

	AUC (95% CI)
Clinical evaluation (VAS)	0.59 (0.54 to 0.65)
ANC	0.80 (0.75 to 0.84)
WBC	0.81 (0.76 to 0.85)
PCT	0.82 (0.77 to 0.86)
CRP	0.88 (0.84 to 0.91)

See text for statistical differences.
ANC, absolute neutrophil count; CRP, C reactive protein; PCT, procalcitonin; SBI, serious bacterial infection; VAS, visual analogue scale; WBC, white blood cells count.

may be explained by different inclusion criteria. We included every child with fever over 38°C without source presenting to the paediatric emergency department who required a standard work-up because of either their ill appearance or the duration of fever. Andreola *et al*[4] and Galetto-Lacour *et al*[7] included only children who had a temperature of over 39.5°C or who were ill-appearing, while Thayyil *et al*[11] included those with a temperature over 39°C. Fernández Lopez *et al*[6] included children under 36 months of age with fever who were required to undergo blood analysis and found an SBI in 43% of their patients. Galetto-Lacour *et al*[7] found an SBI in 29% of children aged under 36 months with fever (>38°C) without source, which is higher than usually described.[11 18 19 23 25]

We observe optimal cut-offs derived from ROC curves that are lower for all markers than previously published. This is probably because most of our SBI were UTIs. In our study, the optimal cut-off value for CRP is 17.7 mg/l compared to 40 or 70 mg/l for prior studies.[4 7 10 18 19] Similarly, we report an optimal cut-off value of 0.2 ng/ml for PCT, whereas in studies with a similar population, the reported cut-off for PCT ranged from 0.5 ng/ml[6 7 11] to 0.9 ng/ml[4 10] and was as high as 20 ng/ml in critically ill children.[26] The fact that the PCT cut-off apparently depends on the type of population could limit the use of the available semiquantitative test with a 0.5 ng/ml detection limit.

The WBC optimal cut-off of 14 100×10^6/l is similar to the traditional and preferred 15 000×10^6/l limit described by others and official guidelines.[4 7 10 11 19] Finally, the ANC cut-off found in our study (5200×10^6/l) was also lower than the 10 000–10 600×10^6/l usually described.[4 18 19 23] These results are probably related again to our inclusion criteria compared with those of other studies as we previously noted.[4 6 7 10 11 18 19]

These differences in cut-offs highlight what is in our opinion the main error in using markers. A surrogate marker has to be interpreted depending on the value obtained in each patient: the higher the result, the higher the probability of

Table 3 Diagnostic accuracy of PCT, CRP, WBC, ANC and clinical evaluation on a VAS to detect an SBI in children aged 1–36 months presenting to a paediatric emergency department with fever without source

Variable best cut-off	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
PCT >0.20 ng/ml	85.2 (74.4 to 92.1)	69.7 (67.6 to 71.1)	35.7 (31.2 to 38.6)	96.0 (93.1 to 97.9)
CRP >17.7 mg/l	94.4 (85.5 to 98.1)	68.6 (66.9 to 69.3)	37.2 (33.7 to 38.7)	98.4 (95.9 to 99.5)
WBC >14 100×10^6/l	81.5 (70.3 to 89.3)	70.8 (68.6 to 72.4)	35.5 (30.6 to 38.9)	95.1 (92.1 to 97.2)
ANC >5200×10^6/l	87.0 (76.5 to 93.5)	59.9 (57.8 to 61.1)	29.9 (26.3 to 32.1)	95.9 (92.6 to 97.9)
VAS >14.8%	68.5 (56.5 to 78.8)	38.7 (36.3 to 40.7)	18.0 (14.9 to 20.7)	86.2 (80.9 to 90.7)

ANC, absolute neutrophil count; CRP, C reactive protein; PCT, procalcitonin; SBI, serious bacterial infection; VAS, visual analogue scale; WBC, white blood cells count.

Table 4 Diagnostic accuracy of PCT, CRP, WBC, ANC and clinical evaluation on a VAS to detect an SBI if urine analysis was normal in the emergency department

Variable best cut-off	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
PCT >0.20 ng/ml	87.5 (53.6 to 97.8)	70.5 (69.4 to 70.8)	8.5 (5.2 to 9.5)	99.4 (97.9 to 99.9)
CRP >17.7 mg/l	87.5 (53.6 to 97.8)	69.7 (68.6 to 70.0)	8.3 (5.1 to 9.3)	99.4 (97.9 to 99.9)
WBC >14 100×10^6/l	75.0 (41.5 to 92.8)	71.7 (70.6 to 72.2)	7.7 (4.3 to 9.5)	98.9 (97.5 to 99.7)
ANC >5200×10^6/l	75.0 (41.4 to 92.8)	59.8 (41.5 to 92.8)	5.6 (3.1 to 6.9)	98.7 (97.0 to 99.6)
VAS >14.8%	75.0 (41.4 to 92.8)	39.4 (38.3 to 39.9)	3.8 (2.1 to 4.6)	98.0 (95.4 to 99.4)

ANC, absolute neutrophil count; CRP, C reactive protein; PCT, procalcitonin; SBI, serious bacterial infection; VAS, visual analogue scale; WBC, white blood cells count.

Table 5 Multilevel likelihood ratios and post-test SBI probability for each surrogate marker and clinical evaluation at different cut-off values

Marker and cut-off	Pretest probability (%)	LR+ (95% CI)	Post-test probability if test positive (%)	LR− (95% CI)	Post-test probability if test negative (%)
PCT >0.2 ng/ml	16	2.8 (2.3 to 3.2)	35	0.2 (0.1 to 0.4)	4
PCT >0.5 ng/ml	16	3.9 (2.6 to 5.5)	42	0.5 (0.4 to 0.7)	9
PCT >2 ng/ml	16	7.1 (3.4 to 14.9)	58	0.8 (0.7 to 0.9)	13
PCT >10 ng/ml	16	∞ (4.0 to ∞)	100	0.9 (0.9 to 1.0)	15
CRP >10 mg/l	16	2.1 (1.9 to 2.3)	29	0.1 (0.03 to 0.3)	2
CRP >17.7 mg/l	16	3.0 (2.6 to 3.2)	36	0.1 (0.03 to 0.2)	2
CRP >40 mg/l	16	4.4 (3.3 to 5.5)	46	0.3 (0.2 to 0.4)	5
CRP >80 mg/l	16	5.9 (3.5 to 9.9)	53	0.6 (0.5 to 0.8)	11
WBC >10 000×10^6/l	16	1.7 (1.5 to 1.9)	25	0.2 (0.1 to 0.5)	4
WBC >14 100×10^6/l	16	2.8 (2.2 to 3.2)	35	0.3 (0.1 to 0.4)	5
WBC >20 000×10^6/l	16	5.1 (3.2 to 7.9)	49	0.6 (0.5 to 0.7)	10
ANC >5200×10^6/l	16	2.2 (1.8 to 2.4)	30	0.2 (0.1 to 0.4)	4
ANC >10 000×10^6/l	16	3.6 (2.4 to 5.2)	41	0.6 (0.4 to 0.7)	10
ANC >15 000×10^6/l	16	5.6 (2.5 to 12.9)	52	0.8 (0.8 to 0.9)	14
VAS >14.8%	16	1.1 (0.9 to 1.3)	17	0.8 (0.5 to 1.2)	14
VAS >25%	16	1.5 (1.1 to 2.0)	22	0.7 (0.6 to 1.0)	13
VAS >50%	16	2.2 (1.1 to 4.4)	30	0.9 (0.8 to 1.0)	15

A pretest SBI probability of 16% (the SBI prevalence) was assumed. LR+, positive likelihood ratio; LR−, negative likelihood ratio.
ANC, absolute neutrophil count; CRP, C reactive protein; PCT, procalcitonin; SBI, serious bacterial infection; VAS, visual analogue scale; WBC, white blood cells count.

having an SBI. It should not only be positive or negative. This is illustrated by multilevel likelihood ratios. For example, a PCT concentration >2 ng/ml or a CRP concentration >80 mg/l raises the SBI probability from 3% to 20% if urine analysis is normal, and a PCT >10 ng/ml is diagnostic of SBI in these children (table 6). Conversely, a CRP <10 mg/l in that situation lowers SBI probability to less than 1%. This has also been reported by other authors.[7 19 24] Thus, regardless of their respective AUC, these markers can play an important role in the decision making process when multilevel likelihood ratios are used, even when the urine analysis is normal.

In our study, UTIs were the most frequent SBI in patients, accounting for nearly 90% of all SBI. In contrast, occult bacteraemia was unusual, with only one (0.3%) occurrence. This is consistent with other postpneumococcal vaccine studies that showed a drop in the rate of occult bacteraemia from 2–4% to less than 1%.[2 5 8 25 27 28] The utility of blood culture in children with fever without source is more and more challenged as a result.[2 17 25 29 30] Our study confirms that blood cultures are generally not helpful. Indeed, assuming that only 5–20% of the untreated pneumococcal occult bacteraemias will result in an SBI such as pneumonia or cellulitis and less than 2% in meningitis or sepsis, this represents only 0.05–0.2% of the well-appearing children aged 1 month to 3 years with fever without source with a 1% occult bacteraemia prevalence.[22 31] If the prevalence is less, as in our study, this number is even lower, reaching 0.0015–0.06%. Nevertheless, as the very young infant, not fully protected by the streptococcal vaccine, has a higher risk of bacteraemia, care must be taken in this population.[32]

Table 6 Multilevel likelihood ratios and post-test SBI probability for each surrogate marker and clinical evaluation at different cut-off values if urine analysis was normal in the emergency department

Marker and cut-off	Pretest probability (%)	LR+ (95% CI)	Post-test probability if test positive (%)	LR− (95% CI)	Post-test probability if test negative (%)
PCT >0.2 ng/ml	3	3.0 (1.8 to 3.3)	8	0.2 (0.03 to 0.7)	0.6
PCT >0.5 ng/ml	3	5.6 (2.9 to 7.2)	15	0.3 (0.1 to 0.7)	0.9
PCT >2 ng/ml	3	7.9 (2.0 to 24.6)	20	0.8 (0.5 to 1.0)	2
PCT >10 ng/ml	3	∞ (8.4 to ∞)	100	0.9 (0.9 to 1.0)	3
CRP >10 mg/l	3	2.0 (1.2 to 2.6)	6	0.2 (0.04 to 0.8)	0.7
CRP >17.7 mg/l	3	2.9 (1.7 to 3.3)	8	0.2 (0.03 to 0.7)	0.6
CRP >40 mg/l	3	4.8 (2.5 to 6.1)	13	0.3 (0.1 to 0.7)	0.9
CRP >80 mg/l	3	8.5 (3.3 to 15.4)	21	0.5 (0.2 to 0.8)	2
WBC >10 000×10^6/l	3	1.7 (1.0 to 1.9)	5	0.3 (0.1 to 1.0)	0.8
WBC >14 100×10^6/l	3	2.6 (1.4 to 3.3)	7	0.3 (0.1 to 0.8)	0.9
WBC >20 000×10^6/l	3	4.3 (1.5 to 8.9)	12	0.7 (0.3 to 0.9)	2
ANC >5200×10^6/l	3	1.9 (1.0 to 2.3)	6	0.4 (0.1 to 1.0)	1
ANC >10 000×10^6/l	3	3.7 (1.5 to 6.2)	10	0.6 (0.3 to 0.9)	2
ANC >15 000×10^6/l	3	4.0 (0.7 to 18.8)	11	0.9 (0.6 to 1.0)	3
VAS >14.8%	3	1.2 (0.7 to 1.5)	4	0.6 (0.2 to 1.5)	2
VAS >25%	3	1.5 (0.6 to 2.5)	5	0.7 (0.3 to 1.2)	2
VAS >50%	3	7.5 (2.9 to 13.3)	19	0.5 (0.2 to 0.8)	2

A pretest SBI probability of 3% with normal urine analysis was assumed.
ANC, absolute neutrophil count; CRP, C reactive protein; PCT, procalcitonin; SBI, serious bacterial infection; VAS, visual analogue scale; WBC, white blood cells count.

Since urine infection is the most frequent SBI in children aged 1–36 months with fever without source, a urine analysis is considered necessary in such patients. However, the risk of SBI when the urine analysis obtained by an appropriate method (catheterisation or suprapubic aspiration) is normal in the emergency department is not well known. In this situation, surrogate markers may become useful for the clinician for detecting SBI because, as we show in this study, clinical evaluation is inferior to those markers. Because of the rarity of other SBI, surrogate markers have an excellent negative predictive value (98–99.4%) but poor positive predictive value with the optimal cut-offs when the urine analysis is normal in the emergency department.

Limitations

We considered the usual clinical diagnosis for UTI and pneumonia (positive urine culture and lobar consolidation on chest radiography). Nevertheless, studies that assessed UTI by renal 99mTc-dimercaptosuccinic acid scintigraphy show that as many as 30% of febrile UTIs are cystitis and not pyelonephritis.[33–35] Also, viral or bacterial pneumonias can be indistinguishable.[36–38] This could have influenced the real diagnostic properties of the markers used in our study. The study took place in a paediatric emergency department of a large tertiary hospital. As results could be different in smaller community hospitals or other settings, it is not known if the results are generalisable. Another potential limitation is that not all markers were available in every patient as some were missing in 15% (56/384) of the children included in the RCT. Finally, although the AUC is a strong descriptor to explore the diagnostic properties of a marker, it does not weigh its clinical consequence.

Conclusion

In our population of children 1 month to 3 years of age with fever without source, CRP, PCT, WBC and ANC had similar diagnostic properties to detect an SBI. Clinical evaluation was inferior to all of these markers. Although we report lower best cut-off values than previously described, a marker has to be interpreted depending on the value obtained in each patient: the higher the result, the higher the probability of having an SBI. By reporting multilevel likelihood ratios, we showed that these markers can play an important role in the decision making process.

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