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Bedside Procalcitonin and C-Reactive Protein Tests in Children With Fever Without Localizing Signs of Infection Seen in a Referral Center

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ABSTRACT. *Objective.* **To assess the value of bedside tests for predicting the occurrence of severe bacterial infections (SBIs) in children with fever without source.**

Methods. **We conducted a prospective study of 99 children, aged 7 days to 36 months, who were seen for fever >38°C and no localizing sign of infection at the emergency department of the University Children's Hospital of Geneva. Blood procalcitonin (PCT), C-reactive protein (CRP), and interleukin-6 (IL-6) values were determined using rapid tests and were compared with the total white blood cell (WBC) count with differential and clinical score. Specificity, sensitivity, predictive values, and multilevel likelihood ratios (LRs) with posttest probabilities of disease were calculated.**

Results. **Twenty-nine (29%) children received a diagnosis of having an SBI. PCT had the best sensitivity (93%) and negative predictive value (96%). Band count had the best specificity (93%), but its positive predictive value was only 38%. Multilevel LRs revealed that a PCT concentration <0.5 ng/mL (LR: 0.093) almost ruled out SBI (posttest probability of disease: 3.7%) in 54 (54%) subjects, whereas a value >2 ng/mL (LR: 5.2) increased the probability of SBI to 68% in 19 (19%) children. For CRP, values <40 mg/L (LR: 0.263) and >100 mg/L (LR: 14.483) generated posttest probabilities for SBI of 9.7% (61 subjects) and 86.5% (14 subjects), respectively. For WBC count, the posttest probabilities of SBI were modestly changed from the pretest prevalence.**

Conclusions. **PCT and CRP performed better than IL-6, WBC, and/or band count in predicting the occurrence of SBI. PCT and CRP bedside tests may be useful tools for emergency and private practice doctors and should be considered in the initial work-up of children with fever without source.** *Pediatrics* **2003;112:1054–1060;** ***interleukin-6, procalcitonin, C-reactive protein, bacterial infection, fever without source, pediatrics, pyelonephritis.***

ABBREVIATIONS. ED, emergency department; SBI, serious bacterial infection; FWS, fever without source; WBC, white blood cell; PCT, procalcitonin; CRP, C-reactive protein; IL-6, interleukin 6; EDTA, ethylenediaminetetraacetic acid; DMSA, 99M-dimercaptosuccinic acid; CSF, cerebrospinal fluid; LR, likelihood ratio; UTI, urinary tract infection.

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Fever is a common cause of childhood visits to emergency departments (EDs) and pediatric offices.[1,2] In the majority of children, a benign infection is diagnosed after a good history and a careful examination that reveal the site of infection. In rare instances, especially in infants, infection is manifested only by fever and vague or nonspecific signs and symptoms, and no focus is evidenced after the clinical examination. Although most of these children also have benign and self-limited illness, a few are at risk of developing a severe bacterial infection (SBI) such as bacteremia, meningitis, or pyelonephritis,[3] the missed diagnosis of which is a common source of malpractice suits.[4] The problem faced by the physician is to find clues that could distinguish the few who have SBI from the vast majority of children who have benign infection. Practical guidelines have been proposed by a panel of experts for the treatment of infants and children with fever without source (FWS).[5] In these recommendations, algorithms based on clinical and laboratory evaluation have been proposed, but in practice, the decision to treat the nontoxic-appearing child is based largely on a white blood cell (WBC) count >15 g/L or band form >1.5 g/L. The diagnostic tests called for in the guidelines are sometimes difficult to obtain for many physicians in private practice, are time-consuming, and require a trained technician. It therefore is not surprising that compliance with these guidelines is low[6] and varies widely between private office settings and hospital EDs.[7] Thus, for many authors, these recommendations are inadequate and favor overhospitalization and overprescription of antibiotics, leading to the selection of resistant bacteria.[8,9] Furthermore, both measures encompass substantial costs.

Blood markers other than WBC count have been investigated in children with suspected bacterial infection.[10–12] Our group and others have demonstrated that procalcitonin (PCT) and C-reactive protein (CRP) performed better than WBC count to differentiate invasive bacterial infection from localized bacterial infection and viral infection.[13,14] However, in previous studies, determination of these blood markers was assessed with tests whose results required several hours and were inappropriate for the treatment of patients in private practice or EDs, where time pressure is important. Actually, PCT, CRP, and interleukin-6 (IL-6) values can be determined with rapid and easy-to-handle assays. The purpose of this study was to compare the value of

different rapid tests and the WBC count for predicting SBIs in children with FWS.

METHODS

In the ED of the University Children's Hospital of Geneva, we prospectively enrolled children, aged 7 days to 36 months, who had a rectal temperature ≥38°C and no localizing signs of infection in their history or at physical examination. Informed consent was obtained from the parents. Excluded from the study were children with fever lasting longer than 7 days, children who were treated with antibiotics during the 2 previous days, and those with known immunodeficiencies. The study protocol was approved by the Ethics Committee of the Department of Pediatrics, University Hospital of Geneva.

Children were examined by a pediatric resident who took a complete history, performed a physical examination, recorded the degree and duration of fever, and determined a clinical score, according to McCarthy.[15] All children had a WBC count with differential and a determination of CRP, PCT, and IL-6 values. Toxic-appearing children had a full sepsis workup, were admitted to the hospital, and were given parenteral antibiotics. Nontoxic-appearing children, from 1 week to 90 days of age or from 91 days to 36 months of age with fever ≥39°C, had a urine collection by suprapubic aspiration, transurethral bladder catheterization, or midstream catch for analysis and culture. Blood was systematically cultured in children with leukocytes >15 g/L or band counts >1.5 g/L. In children from 91 days to 36 months of age with fever ≥38°C but <39°C, urine and blood culture were not performed unless biological risk factors (leukocytes >15 g/L, band counts >1.5 g/L, or leukocyturia) were present.[5] A spinal tap was performed when meningitis was suspected. Erythrocyte, platelet, and WBC counts were performed in blood samples mixed with ethylenediaminetetraacetic acid (EDTA) using an automated cell counter. Band form was counted manually by trained technicians. CRP value was determined in 50 μL of EDTA-blood with a rapid (15 minutes) immunometric method (Nycocard CRP) according to the instructions of the manufacturer. Procalcitonin was measured by a rapid semiquantitative immunochromatographic test (Brahms PCT-Q; Brahms Diagnostica, Berlin, Germany) in 20 minutes (range of results: <0.5 ng/mL, ≥0.5 ng/mL, ≥2 ng/mL, and ≥10 ng/mL). Briefly, 200 μL of plasma-EDTA was applied onto the test strip. PCT in the sample is bound by mouse anti-catacalcin antibodies conjugated with colloidal gold to form a complex. This complex moves by means of capillarity through an area containing fixed anti-calcitonin antibodies to form a sandwich complex that can be seen as a reddish band. The color intensity of the band is directly proportional to the PCT concentration of the sample. IL-6 was measured using a lateral flow semiquantitative immunoassay (Milenia Quickline Interleukin-6; Milenia Biotec, Bad Nauheim, Germany) in 20 minutes (range of results: <100 ng/L, ≥100 ng/L, ≥300 ng/L, ≥1000 ng/L). Briefly, 100 μL of plasma-EDTA was pipetted onto the test strip. IL-6 present in the sample binds to a monoclonal anti–IL-6 antibody conjugated to gold particles, flows through the test system, and finally overflows a test band coated with a second monoclonal antibody specific for IL-6. The accumulated gold particles are immobilized on the test band and become visible as a red-blue band. Color intensity is directly proportional to the concentration of IL-6 in the sample. Results of both assays were read by 2 investigators (A.L.G., A.G.) in a blinded manner, and the similarity of results was 99%.

Decisions on antibiotic treatment and hospitalization were made by the resident in charge of the patient, based on clinical assessment and the presence of biological risk factors. All children had a clinical follow-up with physical examination by a pediatrician in the following 48 hours or by telephone contact. Antibiotics were discontinued after 48 to 72 hours if the results of the cultures were negative. The diagnosis was registered at the end of the clinical follow-up.

Definition and criteria of SBIs were 1) bacteremia, positive blood culture; 2) pyelonephritis, positive urine culture with $>10^5$ colony-forming units/mL and cortical defect seen at the technetium 99M-dimercaptosuccinic acid (DMSA) renal scintigraphy; 3) lobar pneumonia, lobar consolidation diagnosed on a chest radiograph by a pediatric radiologist unaware of the study; 3) bacterial meningitis, cerebrospinal fluid (CSF) pleocytosis of >5 cells/μL and positive culture of CSF; 4) deep abscess, assessed by computed tomography scan and surgical exploration. Children were classified as having a benign infection for the purpose of this study on the basis of 1) negativity of blood or CSF culture, 2) positive urine culture with a normal DMSA renal scintigraphy, 3) clinical improvement without antibiotics, and 4) the presence of a focal infection at the follow-up visit such as otitis media or gastroenteritis.

Statistics

Demographic characteristics and laboratory values of children with benign infection and SBI were compared using the Fisher exact test for frequencies, the *t* test for normally distributed continuous variables, and the Mann-Whitney *U* test otherwise. The sensitivity, specificity, and negative and positive predictive values for the detection of an SBI were determined for the McCarthy score and the different laboratory parameters using the cutoff points listed in Table 1. For additional insight into the interpretation of diagnostic test data, likelihood ratios (LR) were also determined for PCT, CRP, and leukocytes. The LR for a positive test expresses the odds that a positive test result would be expected in a patient with (as opposed to one without) an SBI and is calculated as sensitivity/(1 − specificity).[16] The LR indicates the value of the test for increasing certainty about a positive diagnosis. Starting from a pretest probability of disease that is equal to the prevalence, the LR will generate a posttest probability of disease. Three ranges of values were used to generate LR for PCT (<0.5, 0.5–2, >2 ng/mL), CRP (<40, 40–100, >100 mg/L), and leukocytes (<15, 15–20, >20 G/L). To calculate 95% confidence intervals for the LR, we used a Taylor series expansion to determine the variance of this ratio.[17]

RESULTS

This study included 110 children. Eleven children were excluded (4 were older than 3 years, 2 received antibiotics, 1 had a temperature <38°C, 2 had focal symptoms already at the inclusion, and 2 had insufficient blood samples), so the data of 99 children were analyzed. A blood culture was performed in 88

TABLE 1. Sensitivity, Specificity, and Predictive Values of Markers of SBI

	Sensitivity (% [95% CI])	Specificity (% [95% CI])	NPV (%)	PPV (%)
PCT (*0.5 ng/mL)	93 (77–99)	74 (62–84)	96	60
CRP (*40 mg/L)	79 (60–92)	79 (67–88)	90	61
Leukocytes ≥15 G/L	52 (33–71)	74 (62–84)	78	45
Band ≥1.5 G/L	11 (2–28)	93 (84–98)	72	38
Leukocytes ≥15 G/L or band ≥1.5 G/L	55 (36–74)	72 (61–83)	80	46
IL-6 (*100 pg/L)	36 (13–65)	80 (64–91)	77	38
YOS score >10	23 (5–54)	82 (67–92)	76	30

NPV indicates negative predictive value; PPV, positive predictive value; YOS, Yale observation scale; CI, confidence interval.
* Cutoff.

(89%) children, a urine culture in 89 (90%), and a CSF culture in 17 (17%). Of 40 (40%) children who were hospitalized, 35 (88%) were treated with antibiotics, only by intravenous route, and among those sent home, antibiotics were prescribed for 36 (61%; 10 oral, 1 intramuscularly, and 25 intravenously). SBIs were diagnosed in 29 (29%) children and included 4 occult bacteremia, 21 pyelonephritis, 2 lobar pneumonia, 1 mastoiditis, and 1 retropharyngeal abscess. *Streptococcus pneumoniae* and *Streptococcus agalactiae* were the causative organisms of 3 and 1 occult bacteremia, respectively. *Escherichia coli* was the organism recovered from 90% of all urinary tract infections (UTIs). Benign infection was diagnosed in 70 (71%) children. Eleven subjects had lower UTI, 4 developed acute otitis media diagnosed at the follow-up visit, and 3 had aseptic meningitis. Fifty-two (52%) children were considered as having a probable viral infection based on negative bacterial cultures and no sign of a focal infection (except nonbloody diarrhea) at the clinical follow-up visit. Demographic characteristics and laboratory parameters of patients with and without serious bacterial infections are compared in Table 2. The duration of fever before consultation was significantly longer for patients with SBI ($P = .026$; Table 2). Leukocytes, band form, CRP, and PCT were also significantly increased in children with SBI compared with children with benign infection.

In Table 1, the sensitivity, the specificity, and the predictive values of parameters routinely recommended in the treatment of children with FWS are compared with those of PCT, CRP, and IL-6 rapid tests for the diagnosis of SBI. PCT and band form showed the best sensitivity and specificity, respectively, with values >90%. PCT and CRP had comparable positive predictive values for SBI of 61% and 60%, respectively, and performed better than the other clinical or biological parameters. PCT showed an excellent negative predictive value of 96%. Combination of PCT (>0.5 ng/mL) and CRP (>40 mg/L) increased the sensitivity to 97% but decreased the specificity to 61% (data not shown). Among the 29 children with SBI, 2 had a PCT concentration below the limit of detection of the test (<0.5 ng/mL). One had occult pneumococcal bacteremia and came to the ED with a fever lasting <10 hours. The second case had pyelonephritis with minimal but positive changes at the DMSA renal scintigraphy. Six (6%) and 14 (14%) children with SBI had a CRP value <40 mg/L and a leukocyte count <15 G/L, respectively (Fig 1).

LRs and the generated posttest probabilities of diseases for PCT, CRP, and leukocytes are presented in Table 3. For a better visual understanding, the pretest probability, the LR for specified range of values, and the probability of having an SBI after measuring PCT, CRP, and the leukocyte count were plotted on a nomogram (Fig 2).[16] For PCT, >70% of the population was distributed in clinically useful ranges, either narrowing the probability of SBI to 3% in 54 subjects with PCT <0.5 ng/mL or increasing the probability to 68% in 19 children with PCT >2 ng/mL. These figures were similar for CRP, but for leukocytes, the posttest generated probabilities were modestly changed from the pretest prevalence in the specified ranges (Table 3, Fig 2).

DISCUSSION

Our study demonstrates that determination of blood PCT and CRP using rapid tests is superior to WBC and band counts for predicting an SBI in children aged <3 years with FWS. The ease of use and the rapidity of the tests assayed in this study are other key considerations for the office practitioner and the emergency doctor.

The treatment of children younger than 3 years with fever without localizing signs of infection remains a debated question.[8,18–21] Although wide-scale *Haemophilus influenzae* type b vaccination has dramatically decreased the incidence of occult bacteremia and meningitis in young children, *S pneumoniae* is still a leading cause of severe sepsis and death in this population, especially in countries where conjugated vaccines against pneumococci are not yet routinely recommended.[22] Although the heptavalent conjugate pneumococcal vaccine is licensed for use in young children, pneumococcal disease caused by a serotype not in the vaccine, as a result of vaccine failure, or occurring in children who were not immunized or partially immunized will continue to be the most frequent cause of occult bacteremia. As emphasized recently by Klein,[21] the treatment of febrile infants with FWS aged 3 months to 3 years should not be changed on the basis of vaccine status until more extensive experience with heptavalent conjugate pneumococcal vaccine is available. UTI is also a major bacterial cause of fever in young chil-

TABLE 2. Demographic Characteristics and Laboratory Parameters of Children With Benign and Serious Bacterial Infection

	Benign Infection (Median [Range])	SBI (Median [Range])	*P*
Age (mo)	7.2 (0.4–31.1)	9.7 (0.7–34)	NS
Sex (M/F)	39/31	14/15	NS
Fever duration (h)	24 (1–140)	48 (6–140)	.026
Fever (°C)	39.5 (38–40.8)	39.4 (38.3–41)	NS
PCT (</≥0.5 ng/mL)	52/18	2/27	<.01
CRP (mg/L)	16 (10–200)	100 (10–200)	<.01
IL-6 (</≥100 ng/L)	31/9	8/5	NS
Leukocytes (G/L)	10.2 (3–29.3)	15.1 (3.8–46.4)	<.01
Band (G/L)	0.2 (0–2.7)	0.7 (0–13)	<.01

NS indicates nonsignificant.

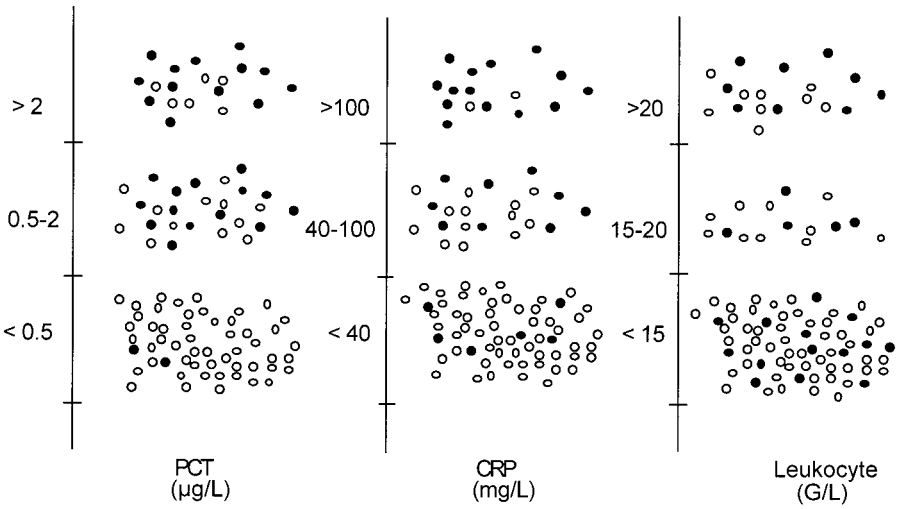

Fig 1. Distribution of children with SBI ● and benign infection ○ in regard to PCT, CRP, and leukocyte values.

TABLE 3. LRs for Selected Range of Values of PCT, CRP, and Leukocyte Counts and Posttest Probability of SBI in Children With FWS

	n	LR (95% CI)	Posttest Probability (%)
PCT			
<0.5 ng/mL	54	0.09 (0.02–0.36)	3
0.5–2	26	2.8 (1.49–5.33)	54
>2	19	5.2 (2.20–12.42)	68
CRP			
<40 mg/L	61	0.26 (0.13–0.54)	10
40–100	22	2.0 (1.04–4.01)	45
>100	16	14.5 (3.46–60.70)	86
Leukocyte			
<15 G/L	66	0.65 (0.44–0.97)	21
15–20	15	1.6 (0.63–4.11)	40
>20	18	2.4 (1.07–5.46)	49

Pretest probability: 29%.

dren with a prevalence of 5% to 20%.[13,23,24] If cystitis is not associated with long-term sequelae, then delay in the initiation of antibiotics in children with pyelonephritis can lead to permanent, serious renal damage such as chronic hypertension and renal insufficiency.[25,26] Several experts state that careful daily observation of a nontoxic-appearing child should suffice to correctly treat children with FWS, pending the results of urine and blood culture.[8,27] Despite these statements, antibiotics are still largely prescribed in private office and in EDs. Factors that urge physicians to give antibiotics include the absence of an adequate diagnostic marker of bacterial infections, the concern about lack of patient follow-up,[28] and the time pressure. Furthermore, the results of a survey of pediatricians found that parental pressure, rather than concerns about legal liability or the need to be efficient in practice, was the major reason that antimicrobials are prescribed inappropriately.[29] For example, in this study, the decision to give an antibiotic treatment was taken by the resident in charge of the patient. Of 40 nontoxic-appearing children without biological risk factors, 20 (50%) were given antibiotics. In those children, the only measurable significant parameter associated with antibiotic prescription was a younger age (6.8 months ± 7.0 vs 12.3 months ± 8.2; $P = .03$). As a consequence, the widespread use of antibiotics favors the selection of resistant bacteria and increases the risk of drug-related adverse events and the cost of care.

If algorithms are used to select patients who are the most likely to benefit from an antibiotic treatment, then they must be accurate and applicable in all medical settings where time pressure is important. In previously published guidelines,[5] total WBC and differential counts were the most common laboratory tests recommended in children with FWS. They can be obtained in <30 minutes in most EDs but are seldom obtained in this time frame by office practitioners, who do not have a laboratory and a skilled technician.[30] Although these tests are rapidly obtained, our results showed that the sensitivity of the total leukocyte and band count or the combination of both was between 11% and 55%, with negative predictive values ranging from 72% to 79%. These results are in accordance with those published recently by Pulliam et al.[12] By contrast, serum PCT showed better sensitivity (93%) and negative predictive value (96%). Regarding the LR, the rapid PCT test performed much better than leukocyte count. A WBC count superior to 20 G/L increased only the probability of SBI from 29% to 49%. The probability of SBI with a WBC count <15 G/L was barely unchanged, decreasing from 29% to 21%. By contrast, in children with a PCT value <0.5 ng/mL, which represented half of the study population, the risk of SBI

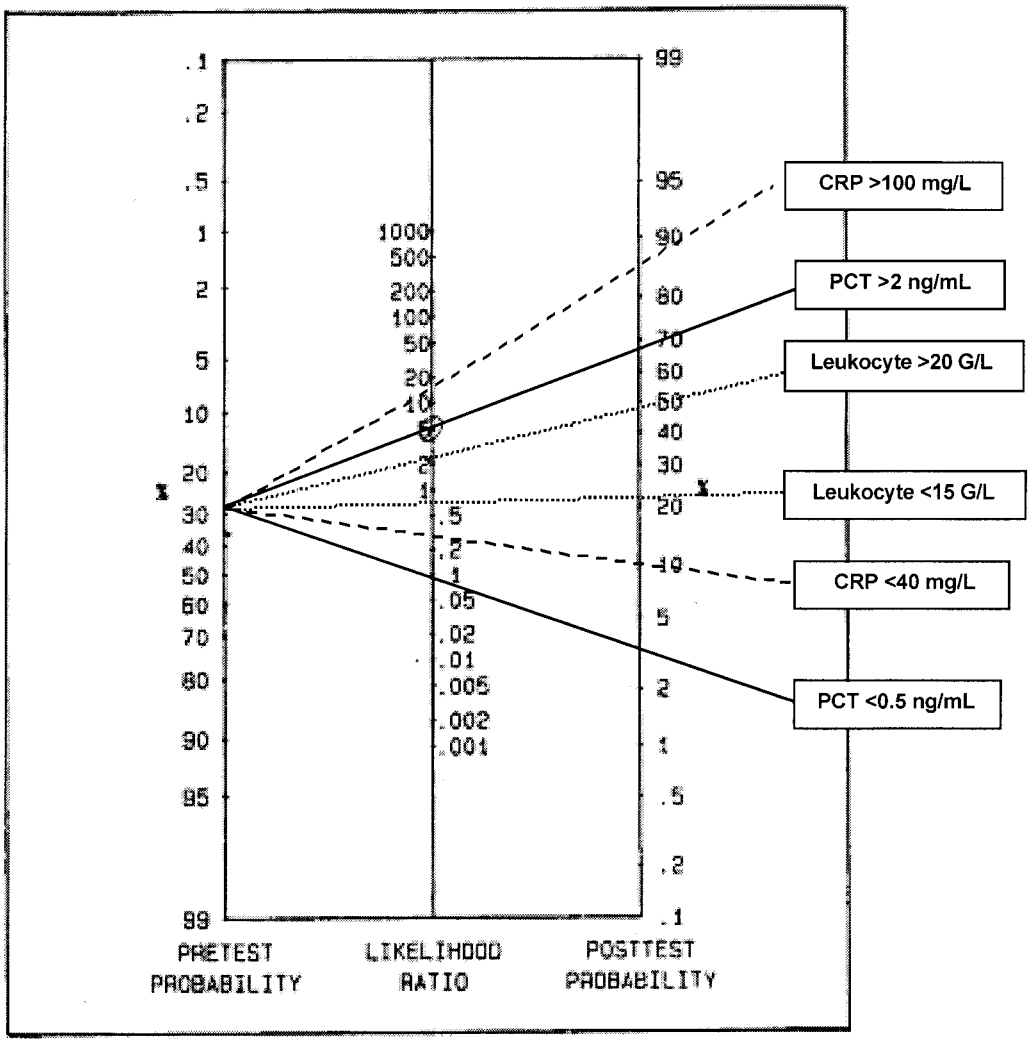

Fig 2. A nomogram for applying LRs calculated for selected ranges of values of PCT, CRP, and leukocyte counts (adapted from Sackett et al[16]). Pretest probability was 29%.

was considerably decreased from 29% (pretest probability) to 3%, supporting the absence of antibiotic treatment in such children. Children with a PCT value >2 ng/mL had a posttest probability of SBI of 68%, which in our opinion justifies antibiotic treatment pending the results of cultures. In the quarter of the study population with PCT values between 0.5 and 2 ng/mL, the uncertainty remained with a posttest risk of SBI of 54%. However, 11 of the 25 children with a PCT value in this range also had a pathologic urinalysis, and a pyelonephritis was confirmed in 10. In a previous study, we showed that a PCT value >0.5 ng/mL and a positive urinalysis predicted a pyelonephritis in 87% of cases.[31] Similar advantage of PCT over leukocyte count and other blood markers has also been reported in febrile neutropenic children[32] and in critically ill children.[33]

The rapid CRP test also gave more useful information than the WBC count. Its sensitivity and negative predictive value were 79% and 90%, respectively, for a cutoff value of 40 mg/L. The LRs that we calculated were comparable to those obtained in the same settings in a recently published study.[12] Below 40 mg/L, the risk of SBI was decreased from 29% to 10%.

In the present study, we chose to examine the utility of rapid tests in predicting the occurrence of SBI, not limited to occult bacteremia. We believed that this would be more representative of typical clinical scenarios in which clinicians must decide in all children with FWS what work-up is necessary and whether antibiotic therapy is indicated. However, the rate of SBI (29%) used as the pretest probability was higher than previously reported. There are 2 reasons for this difference: 1) our ED is a referral center for sicker children and, 2) children with a positive urine culture ($n = 32$) underwent a DMSA renal scintigraphy that was positive in 63% of cases. This high rate of renal involvement in children with UTI has been reported in several studies from different countries where such sensitive methods were used and accounted for 50% to 67% of all UTIs.[31,34,35] We can assume that in previous studies, where a distinction between lower and upper UTI was not performed accurately, most of the children were classified in the non-SBI group. However, this distinction is important because the oral or parenteral administration of antibiotics is still debated for the treatment of pyelonephritis.[24] Although the overall prevalence of SBI was high in this study per-

formed in a referral center, the rate of occult bacteremia (4%) was similar to previously published data.[20] Nevertheless, as LRs are independent of disease prevalence, we can extrapolate our figures using an SBI rate of 10%, as reported in the general population of children with FWS. In this scenario, PCT <0.5 ng/mL or CRP <40 mg/L almost rules out SBI with a posttest probability <1% and <3%, respectively, whereas using a leukocyte count <15 G/L, the posttest probability stays at approximately 6%.

In several studies, IL-6 was shown to be a good marker of bacterial infection and superior to intercellular adhesion molecule 1 and CRP in predicting neonatal sepsis.[11,36] However, in our study, IL-6 did not allow an accurate determination of children with SBI. The poor sensitivity of this marker is probably attributable to its rapid kinetics. Indeed, blood IL-6 increases in the first few hours after bacterial endotoxinemia and starts already to decrease after 12 hours.[37] This can explain why, in our study, the higher IL-6 concentrations were found in children with SBI and a short duration of fever before consultation. Compared with IL-6, PCT increases in blood 6 hours after a stimulus, reaches a plateau between 12 and 48 hours, and then decreases if the stimulus stops.[37] Finally, CRP increases later than PCT, explaining why, for several authors, it is important to be cautious with the interpretation of CRP values in children with fever lasting <12 hours.[12,13] Comparing the 3 rapid tests, PCT seems to have a slight advantage over CRP because of its earlier increase after stimulation and a better negative predictive value. Nonetheless, although this test seems promising, it has been investigated less than CRP in children and needs additional investigation. Both CRP and PCT performed better than IL-6 in this study.

Although these rapid tests look promising, this study has been performed in a specific ED setting, on a relatively small number of children, and with the specific aim to compare their values with the ones of WBC and band counts to detect SBI. Therefore, larger studies in private offices are needed and should also be undertaken to assess the reliability of these tests in physicians who do them occasionally and to evaluate their cost-effectiveness.

CONCLUSIONS

The algorithms published >10 years ago by Baraff et al[5] and still largely cited in recent literature takes into account clinical scores and biological parameters, especially WBC and band counts. However, the difficulty in obtaining timely results in addition to the low predictive values of leukocytes make them difficult to use in practice. CRP and PCT rapid tests can be performed at the bedside, have good predictive values, and deserve additional investigations in the initial treatment of children with fever without localizing signs of infection.

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THE TOBACCO SCOURGE

"Of the more than 1.1 billion smokers worldwide, 82 percent live in low- or middle-income countries. Between high population growth and aggressive tobacco marketing campaigns in these regions, most of the growth in smoking is expected to occur in these nations—a development that will increasingly burden public health systems already straining from a lack of resources and from diseases like AIDS. . . . Currently, smoking kills 4.9 million people a year–one in 10 adult deaths—from a range of illnesses that includes heart disease, various forms of cancer, and stroke. By 2030, experts foresee smoking becoming the leading cause of death, responsible for 10 million deaths a year—of which 7 of every 10 would occur in low- or middle-income countries."

World Watch Institute. *Vital Signs 2003*. New York: Norton; 2003

Submitted by Student

Bedside Procalcitonin and C-Reactive Protein Tests in Children With Fever Without Localizing Signs of Infection Seen in a Referral Center

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