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C-Reactive Protein in Febrile Children 1 to 36 Months of Age With Clinically Undetectable Serious Bacterial Infection

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ABSTRACT. *Objective.* **To determine the diagnostic properties of quantitative C-reactive protein (CRP) associated with clinically undetectable serious bacterial infection (SBI) in febrile children 1 to 36 months of age.**

Methods. **Febrile children presenting to a pediatric emergency department (ED) with ages ranging from 1 to 36 months, temperatures ≥39°C, and clinically undetectable source of fever were enrolled in this prospective cohort study. Demographic information, ED temperature, duration of fever, and clinical evaluation using the Yale observation scale were recorded at the time of the initial evaluation. The white blood cell count (WBC), band count, absolute neutrophil count (ANC), and CRP concentration were measured at the same time. All patients received blood cultures and either a screening urinalysis or urine culture. A chest radiograph was obtained at the discretion of the ED physician. Patients with history of using antibiotics within 1 week of their presentation to the ED were excluded. The main outcome result was the presence of laboratory or radiographically proven SBI (bacteremia, meningitis, urinary tract infection, pneumonia, septic arthritis, and osteomyelitis).**

Results. **Seventy-seven patients were enrolled in the study. Fourteen (18%) had a SBI (6 urinary tract infection; 4 pneumonia, including 1 patient with *Streptococcus pneumoniae* bacteremia; and 4 occult *S pneumoniae* bacteremia), and 63 had no SBI. The 2 groups were indistinguishable in age, sex, ED temperature, duration of fever, and Yale observation scale. CRP concentration, WBC, and ANC were significantly different between the 2 groups. In a multivariate logistic regression analysis, only CRP remained as a predictor of SBI (Beta = 0.76, 95% confidence interval [CI]: 0.64, 0.89). Receiver-operating characteristic analysis demonstrated CRP (area under curve [AUC] 0.905, standard error [SE] 0.05, 95% CI: 0.808, 1.002) to be superior to ANC (AUC 0.805, SE 0.051, 95% CI: 0.705, 0.905) and to WBC (AUC 0.761, SE 0.068, 95% CI: 0.628, 0.895). A CRP cutoff point of 7 was determined to maximize both sensitivity and specificity (sensitivity 79%, specificity 91%, likelihood ratio 8.3, 95% CI: 3.8, 27.3). Multilevel likelihood ratios and posttest probabilities were calculated for a variety of CRP levels. A CRP concentration of <5 mg/dL effectively ruled out SBI (likelihood ratio 0.087, 95% CI: 0.02, 0.38, posttest probability of SBI 1.9%).**

Conclusions. **Quantitative CRP concentration is a valuable laboratory test in the evaluation of febrile young children who are at risk for occult bacteremia and SBI, with a better predictive value than the WBC or ANC.** *Pediatrics* **2001;108:1275–1279;** ***C-reactive protein, fever, serious bacterial infection, bacteremia, urinary tract infection.***

ABBREVIATIONS. SBI, serious bacterial infection; OB, occult bacteremia; UTI, urinary tract infection; WBC, white blood cell count; ANC, absolute neutrophil count; CRP, C-reactive protein; ED, emergency department; YOS, Yale Observational Score; ROC, receiver operating characteristic; CI, confidence interval; SD, standard deviation; SE, standard error; PPV, positive predictive value; NPV, negative predictive value.

Fever is a common presenting symptom in pediatric outpatient practices and emergency rooms, particularly in children <3 years of age. Approximately 20% of these children will have no identifiable source of fever after history and physical examination.[1,2] Although most of these children will have a benign viral illness, children <3 years of age are at increased risk of clinically undetectable serious bacterial infection (SBI). Approximately 2% to 3% of these children have occult bacteremia (OB),[3–5] while 2% to 8% have urinary tract infection (UTI), depending on the age and gender.[6] Other causes of SBI include occult bacterial pneumonia (3%),[7] meningitis, or less commonly bone and joint infection, deep soft tissue abscess, or bacterial enteritis.

Although antibiotic treatment is necessary for children with SBI, it is also important to limit therapy to those children at greatest risk. Because the majority of febrile young children do not have SBI, laboratory tests and expectant antibiotic therapy of these children adds to cost, time, discomfort, and parental anxiety and may contribute to antibiotic resistance. Clinical observations alone lack the necessary sensitivity and specificity in detecting occult SBI.[8] Because it is clinically difficult to identify children with occult SBI, a number of diagnostic and management strategies have been suggested, and the topic remains a source of considerable debate.

Blood culture remains the gold standard in detecting OB; however, the average time to detection of positive cultures is 15 to 16 hours and may be as long as 24 to 48 hours,[4,9] increasing the risk of complications. Total white blood cell (WBC) is the most commonly used screening test for OB, and clinical prac-

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tice guidelines suggest using a total WBC of ≥15 000 as a determining factor between patients who can be observed and those who need antibiotic therapy.[10] However, because of its low predictive value, empiric treatment based on a WBC ≥15 000 results in unnecessary treatment in 85% to 95% of cases.[3,10] Recent data suggest that the absolute neutrophil count (ANC) is a more accurate test in detecting OB[3,5]; however, the overall profile of ANC is similar to that of WBC.[5]

UTI, the most common cause of occult SBI in this age group, can be predicted and confirmed by relatively straightforward methods.[6,11] However, reliable urinary sampling in this age group—catheterization of the bladder—is somewhat traumatic and occasionally difficult in nonpediatric facilities. Furthermore, the risk benefit ratio of universal urine testing in this clinical scenario has been questioned.[12] On the other hand, there is a need for criteria to determine which children need chest radiographs. Occult pneumonia is present in up to 3% of children without tachypnea or other respiratory symptoms,[10] and it is difficult to differentiate viral from bacterial pneumonias based on the chest radiograph alone. Moreover, the true prevalence of occult pneumonia in this setting remains in question because most prospective studies that address this issue include only children in whom a chest radiograph was ordered.[13]

Some studies have suggested that acute phase reactants, including C-reactive protein (CRP) may be helpful in this clinical situation.[14–19] We sought to prospectively study the diagnostic properties of quantitative CRP in comparison with other clinical and laboratory predictors of occult SBI in young children with fever without apparent source of infection.

METHODS

This prospective study was conducted between January 1, 2000, and October 31, 2000. A convenience sample of children ages 1 to 36 months who presented to the duPont Hospital for Children Emergency Department (ED) with temperature ≥39°C were evaluated by residents and pediatric emergency medicine attendings. Those children who, after careful history and physical examination, had clinically undetectable source for the fever were enrolled in the study. Children with acute otitis media, acute pharyngitis, clinical pneumonia, acute respiratory tract infection, acute gastroenteritis, and those with a history of antibiotic use during the past 7 days, a known underlying immunologic disease, or who received vaccination during the previous 2 days were excluded. Informed consent was obtained from parents or guardians. The study protocol was approved by the institutional review board at the duPont Hospital for Children.

Demographic information, ie, age and sex, ED temperature, duration of fever, and clinical evaluation using the Yale Observation Score (YOS)[20] were recorded at the time of initial evaluation. Total WBC, band count, ANC, and quantitative CRP concentration were obtained. All patients received a blood culture and either a screening urinalysis or urine culture. Urine was obtained by urethral catheterization using standard sterile technique. Chest radiographs as well as other laboratory and radiographic tests were obtained at the discretion of the ED physician.

The WBC was quantified by automated laboratory equipment. Laboratory personnel calculated the differential WBC using microscopy. Blood cultures were monitored using the Isolator Blood Culture System (Wampole Laboratories, Cranbury, NJ). Quantitative CRP concentration was obtained using particle enhanced turbidimetric immunoassay technique (reagent by Dade Behering, Deerfield, IL). Laboratory personnel and radiology staff were blinded to clinical information.

The outcome result was the presence of laboratory or radiographically proven SBI (bacteremia, meningitis, UTI, pneumonia, septic arthritis, and osteomyelitis). OB was defined on the basis of recovery of a single bacterial pathogen using standard culture techniques. UTI was defined as growth of a single urinary tract pathogen at $\geq 10^4$ CFU/mL. Pneumonia was defined as the presence of a focal infiltrate on chest radiograph as interpreted by the pediatric radiologist.

Sample size was estimated using a pretest probability for SBI of 10% and a hypothesized sensitivity of 100% for the CRP level. Given these figures; 80 patients needed to be enrolled including 8 patients with outcome of SBI to evaluate the test at a reasonably narrow 95% confidence interval (CI: 0.65, 1.0). Patients with and without SBI were compared using the 2-tailed t test or Mann-Whitney U test for variables expressed as mean values according to their parametric distribution. χ^2 analysis was used to access the association between gender and SBI. Receiver-operating characteristic (ROC) curves for CRP concentration, ANC, and WBC were constructed. Based on the ROC curves, cutoff values for each variable were determined that simultaneously maximized both sensitivity and specificity. For each variable, patients were dichotomized into 2 groups based on the cutoff value and χ^2 analysis was used to assess the association between the dichotomized variable and the presence of SBI. Multilevel likelihood ratios and posttest probabilities for CRP concentration were calculated. All clinically relevant variables (age, sex, ED temperature, duration of fever, YOS, WBC, percent neutrophil count, percent band count, ANC, and CRP) were also analyzed in a logistic regression model using backward elimination to identify predictors for the presence of occult SBI. Statistical analyses were performed using the SPSS statistical software package, version 10.0 for Windows (SPSS, Inc, Chicago, IL).

RESULTS

Seventy-seven children were enrolled in the study ranging in age from 1 to 35 months (mean: 9.7 months; standard deviation [SD]: 8.0). Fourteen patients (18%) had SBI and 63 had no SBI. Causes of SBI included UTI (6), pneumonia (4), 1 of whom also had bacteremia, and OB (4). *Escherichia coli* was the causative organism of all UTI's and *Streptococcus pneumoniae* was the organism recovered from the 5 cases of bacteremia.

Comparison of clinical and laboratory findings between the 2 groups are shown in Table 1. The 2 groups were indistinguishable in age, temperature in the EDS, duration of fever, and clinical YOS. WBC, ANC, and CRP concentration were significantly different ($P < .05$) between the 2 groups. In the multiple logistic regression analysis, CRP was the only predictor for SBI ($P = .001$; Beta = 0.76; 95% CI: 0.64, 0.89).

The diagnostic properties of WBC, ANC, and CRP concentration were analyzed using the receiver operating characteristic curve (Fig 1). The area under the ROC curve was 0.905 (standard error [SE]: 0.05; 95% CI: 0.808, 1.002) for CRP concentration and 0.805 (SE: 0.051; 95% CI: 0.705, 0.905) for ANC. The AUC for WBC was 0.761 (SE: 0.068; 95% CI: 0.628, 0.895).

Based on the ROC analysis, values were identified for each variable that maximized both the sensitivity and specificity. The cutoff value for each variable, along with P value, sensitivity, specificity, likelihood ratio, positive predictive value (PPV), and negative predictive value (NPV) are shown in Table 2.

To further explore the diagnostic utility of CRP concentration, multilevel likelihood ratios were calculated for a range of CRP concentrations and are

TABLE 1. Characteristics of Children With and Without SBI

Characteristic*	Patients With SBI (n = 14)	Patients Without SBI (n = 63)	P Value
Age (mo)	10.6 (9.3)	9.5 (7.8)	.64
Sex (% female)	71.4	52.4	.19
Temperature in ED (°C)	39.5 (0.74)	39.5 (0.73)	.99
Duration of fever, median (range), h	24 (3, 168)	24 (1, 168)	.24
Total YOS	8.9 (3.8)	8.6 (3.8)	.77
WBC (thousand/mm^3)	22.3 (9.8)	12.5 (7.0)	.003
Polymorphonuclear cells (%)	56.3 (7.6)	52.5 (15.3)	.19
Band count (%)	5.7 (5.8)	3.6 (4.2)	.11
ANC (thousand/mm^3)	13.9 (6.1)	7.3 (5.4)	<.0001
CRP concentration, median (range) mg/dL	9.7 (0.2, 37.2)	1.0 (0.2, 20.7)	.002

* Values shown are means ±SD unless otherwise noted.

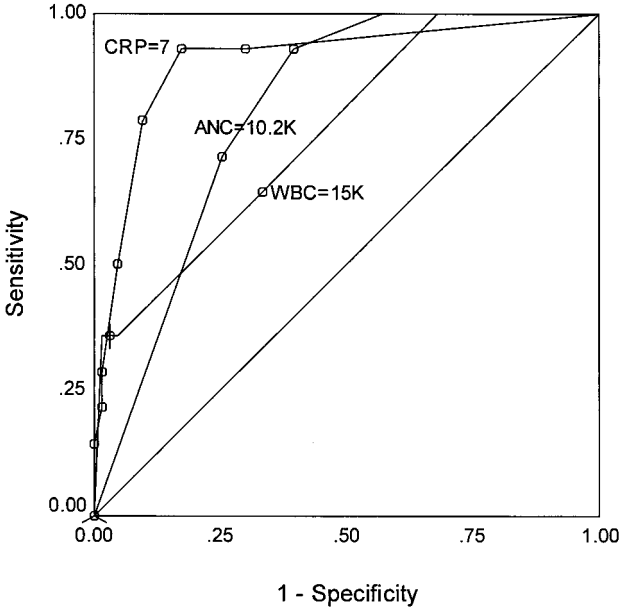

Fig 1. ROC for variables associated with SBI. Area under the curve for CRP 0.905 (95% CI: 0.808, 1.00); for ANC 0.805 (95% CI: 0.705, 0.905); and for WBC 0.761 (95% CI: 0.628, 0.895)

shown in Table 3. A CRP concentration of <5 mg/dL had a likelihood ratio of SBI of 0.087, corresponding to a NPV of 98%. A CRP concentration of >9 mg/dL had a likelihood ratio of SBI of 9, corresponding to a PPV of 67%.

Three patients with SBI had CRP concentrations <7 mg/dL, 1 with UTI (age 1 month, CRP 6.8 mg/dL, duration of fever 6 hours), 1 with pneumonia (4 months old, CRP 5.4 mg/dL, duration of fever 8 hours), and 1 with OB (4 months old, CRP 0.2 mg/dL, duration of fever 3 hours).

DISCUSSION

Our study demonstrates that CRP concentration is superior to other tests in predicting which febrile young children have occult SBI requiring antibiotic therapy. CRP concentration was both more sensitive and more specific than either the WBC or the ANC. In a multivariate model controlling for potentially confounding factors, CRP remained the only significant predictor of occult SBI.

The management of febrile young children without apparent source of infection remains controversial, because there has been no test available with adequate sensitivity and specificity required to distinguish which children are at risk for bacterial infection. Total WBC is the most commonly used laboratory test used in this clinical situation. As a screening test for OB, a total WBC ≥15 000/mm^3 has a sensitivity of 80% and a specificity of 69%.[5] Although the total WBC is relatively sensitive and somewhat specific, because of the low incidence of OB, the test has a NPV of 99% and a PPV of only 6%. Therefore, although 80% of children with OB will have a WBC ≥15 000, 94% of children with a WBC >15 000 will not have OB. In our study, the mean total WBC was significantly different between those with and without SBI; however, using a level of ≥15 000 did not significantly distinguish between the 2 groups. Recent studies investigating the utility of WBC indices conclude that ANC is a better test for detecting pneumococcal bacteremia than WBC, with an approximate cutoff value of 10 × 10^9 cells/L.[3,5] We found that ANC has a similar profile as a screening test for occult SBI.

Both the erythrocyte sedimentation rate and CRP have been evaluated as predictors of bacterial illness in febrile children, with mixed results and applicability to today's clinical setting. Early studies used qualitative or semiquantitative CRP,[14] and most studies were conducted in the era in which *Haemophilus influenzae* type b was a common cause of bacterial illness.[15–17,21] Furthermore, many studies were conducted on both inpatients and outpatients.[15,16] With the exception of 1 study,[20] CRP was found to have good sensitivity and specificity,[16,17] and when compared with WBC, CRP was found to be a better test.[14,15] Recent prospective studies of febrile young children have found CRP to be a more sensitive and specific predictor of SBI compared with WBC.[18,19] CRP has also been found to be valuable in the diagnosis of bacterial meningitis.[22,23]

Although there is yet no test available that is 100% reliable, this study demonstrates that CRP is both more sensitive and more specific in distinguishing children with occult SBI from those without bacterial illness. Although a CRP concentration of 7 mg/dL is the value that simultaneously maximizes both sensitivity and specificity, it may not necessarily be the clinically most useful value. Both the ROC and the

TABLE 2. Predictors of SBI

Variable	Cutoff Point	Sensitivity (95% CI)	Specificity (95% CI)	Likelihood Ratio (95% CI)	PPV (95% CI)	NPV (95% CI)
WBC (thousand/mm^3)	15.0	64 (35.8, 85.9)	67 (53.6, 77.7)	1.9 (1.1, 3.1)	30 (14.7, 49.4)	89 (76.9, 96.5)
ANC (thousand/mm^3)	10.2	71 (42.2, 90.3)	76 (63.6, 85.6)	3.0 (1.7, 5.1)	40 (21.1, 61.3)	92 (81.5, 97.9)
CRP concentration (mg/dL)	7.0	79 (49.0, 94.2)	91 (79.8, 96.0)	8.3 (3.8, 27.3)	65 (38.3, 85.8)	95 (86.1, 99.0)

TABLE 3. Multilevel Likelihood Ratios for CRP Concentration

CRP Concentration (mg/dL)	Likelihood Ratio (95% CI)	Posttest Probability of SBI
>9	9.0 (3.2, 25)	67%
7–9	6.8 (1.4, 31)	60%
5–7	1.8 (0.42, 7.0)	29%
<5	0.087 (0.02, 0.38)	1.9%

table of multilevel likelihood ratios allow clinicians to choose a cutoff point for CRP suited to particular clinical situations, depending on whether it is more important to avoid overtreatment or undertreatment. A CRP concentration of <5 mg/dL "rules-out" SBI, with a likelihood ratio of 0.087 and a posttest probability of <1.9%. A CRP concentration of greater than 9 mg/dL is helpful and has a much higher likelihood ratio (9.0) than that of total WBC of ≥15 000 (1.9); however, it is not high enough to be diagnostic. Clinicians can use the likelihood ratios to calculate posttest probabilities for different clinical scenarios.

Other studies have demonstrated that CRP concentration is dependent on the duration of the fever, suggesting that CRP is more reliable as an indicator of bacterial infection if fever has been present for >12 hours.[16,17] Although our study size was insufficient to evaluate the effect of duration of fever on CRP concentration, it is interesting to note that the 3 patients with SBI who had CRP values <7 mg/dL all had a fever duration of <9 hours. A larger study would allow the utility of CRP to be evaluated at differing durations of illness, ie, fever.

S pneumoniae is now the predominant cause of OB.[1,4] The use of the conjugate pneumococcal vaccine decreases the risk of OB; widespread use may change the management of febrile young children at risk of OB. Some experts have speculated that the current strategy of obtaining WBC, blood cultures, and starting empiric antibiotic therapy will become obsolete in vaccinated children.[13] However, the vaccine is only 90% effective at preventing invasive disease, therefore, even vaccinated children will be at some risk of invasive pneumococcal disease.[24] In the clinical setting of a febrile young child with no apparent source of fever, the child is at risk of other SBIs in addition to invasive pneumococcal disease. There will remain a need for a rapid screening test for SBI even after widespread use of the conjugate pneumococcal vaccine, particularly given the time, costs, and discomfort associated with evaluation for occult SBI.

There are several limitations to our study. The study was conducted in a pediatric ED and may not be generalizable to other settings. However, the similarity between febrile young children in the outpatient setting and the pediatric ED has been well documented. In addition, there were a small number of patients with each type of SBI, limiting the ability to determine the utility of CRP in each type of infection. A larger study would allow CRP concentration to be evaluated as a predictor for specific types of bacterial infection and at different durations of illness. Furthermore, it would allow CRP to be evaluated along with other predictors in a multivariate predictive tool for occult SBI.

The prevalence of occult SBI, including that of OB and UTI, in our study was higher than in other reports.[4–6] Because we chose a convenience sample of children presenting to the ED with fever without source, sampling bias may have occurred. There may be a tendency to discharge certain well-appearing febrile children from the ED without performing any laboratory studies. Children who were more ill-appearing (and therefore presumably more likely to have SBI) may have been more likely to be enrolled in the study. Also, our ED serves a large referral base of suburban pediatric practices. Children who were more ill-appearing may have been more likely to be referred to our ED. In addition, the mean age of children in our sample population was lower than that of children in other studies of OB.[3–5] Because younger children are at higher risk of occult SBI,[5] this may have also affected our prevalence rate.

Both the PPV and the NPV of a diagnostic test are affected by the prevalence, or pretest probability, of the disorder; a higher prevalence of occult SBI improves the PPV of a screening test. However, the likelihood ratios are not affected by prevalence and are therefore a more powerful method for evaluating the utility of a diagnostic test compared with positive and NPVs; moreover, multilevel likelihood ratios are more stable than sensitivity and specificity to changes in prevalence.[25] Likelihood ratios are a powerful clinical tool because a clinician may estimate the pretest probability of the presence of disease in a particular patient and use the likelihood ratio to calculate the posttest probability (PPV) of disease for that particular patient.

In this study, we chose to examine the utility of CRP in predicting which children had occult SBI, including but not limited to OB. We believed that this would be more representative of typical clinical scenarios. When presented with a febrile young child with no identifiable source of fever, the clinician is presented with the dilemma of deciding how rigorous a workup is necessary and if antibiotic therapy is indicated. The most helpful screening test would predict which children are at a higher risk of bacterial infection and, therefore, in need of additional workup and possible antibiotic therapy. UTI remains

the most common occult SBI in this clinical setting. Although screening children for UTI is relatively straightforward, it is also uncomfortable for patients and parents and time consuming for staff. Moreover, opinion varies on the optimal testing strategy for diagnosing UTI,[6,26,27] and clinical practice varies.[28] Additionally, the results of the urine culture are delayed by 24 to 48 hours. Similarly, the diagnosis of OB by blood culture is delayed by a mean of 15 to 16 hours and for up to 48 hours.[4,9] Occult pneumonias do occur, but which children need chest radiography remains unclear. Blood cultures are positive in only 3% to 5% of febrile young children with pneumonia, and studies evaluating the risk include only the subset of children who received a chest radiograph, so the true prevalence and therefore the risk remains unclear.[13] Moreover, it is difficult to differentiate viral from bacterial pneumonias based on the chest radiograph alone.

On the other hand, CRP concentration can be measured from blood obtained from a capillary specimen, the results are rapidly available, and the test is inexpensive. With the recent availability of rapid CRP tests for use in outpatient and ED settings,[29,30] CRP may become a valuable diagnostic tool in the initial evaluation of febrile young children, allowing clinicians to rapidly screen febrile children for occult SBI and determine which children need additional diagnostic tests and antibiotic therapy. Additional research is needed to validate CRP as a screening tool in this setting.

CONCLUSION

Quantitative CRP concentration is a valuable laboratory test in the evaluation of febrile young children who are at risk for OB and SBI, with a better predictive value than the total WBC or ANC. The use of CRP alone or in a multivariate predictive model may enhance clinicians' abilities in the early recognition of clinically undetectable SBI, allowing for a more selective strategy for determining which children need additional diagnostic studies and antibiotic therapy.

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