Utility of the Serum C-reactive Protein for Detection of Occult Bacterial Infection in Children

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Objective: To assess the utility of serum C-reactive protein (CRP) as a screen for occult bacterial infection in children.

Methods: Febrile children ages 3 to 36 months who visited an urban children’s hospital emergency department and received a complete blood cell count and blood culture as part of their evaluation were prospectively enrolled from February 2, 2000, through May 30, 2001. Informed consent was obtained for the withdrawal of an additional 1-mL aliquot of blood for use in CRP evaluation. Logistic regression and receiver operator characteristic (ROC) curves were modeled for each predictor to identify optimal test values, and were compared using likelihood ratio tests.

Results: Two hundred fifty-six patients were included in the analysis, with a median age of 15.3 months (range, 3.1-35.2 months) and median temperature at triage 40.0°C (range, 39.0°C-41.3°C). Twenty-nine (11.3%) cases of occult bacterial infection (OBI) were identified, including 17 cases of pneumonia, 9 cases of urinary tract infection, and 3 cases of bacteremia. The median white blood cell count in this data set was 12.9 $/H_10^9/µL$ (range, 3.6-39.1 $/H_10^9/µL$), the median absolute neutrophil count (ANC) was 7.12 $/H_10^9/L$ (range, 0.56-28.16 $/H_10^9/L$), and the median CRP level was 1.7 mg/dL (range, 0.2-43.3 mg/dL). The optimal cut-off point for CRP in this data set (4.4 mg/dL) achieved a sensitivity of 63% and a specificity of 81% for detection of OBI in this population. Comparing models using cut-off values from individual laboratory predictors (ANC, white blood cell count, and CRP) that maximized sensitivity and specificity revealed that a model using an ANC of 10.6 $/H_10^9/L$ (sensitivity, 69%; specificity, 79%) was the best predictive model. Adding CRP to the model insignificantly increased sensitivity to 79%, while significantly decreasing specificity to 50%. Active monitoring of emergency department blood cultures drawn during the study period from children between 3 and 36 months of age showed an overall bacteremia rate of 1.1% during this period.

Conclusions: An ANC cut-off point of 10.6 $/H_10^9/L$ offers the best predictive model for detection of occult bacterial infection using a single test. The addition of CRP to ANC adds little diagnostic utility. Furthermore, the lowered incidence of occult bacteremia in our population supports a decrease in the use of diagnostic screening in this population.

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The diagnosis of occult bacteremia in children remains a challenging clinical problem. Prior studies have established that between 1.6% and 8% of children 3 to 36 months of age with temperatures 39°C or higher will have bacteremia, defined as growth of a pathogen in a blood culture. Discrimination on the basis of clinical findings has not been sufficiently sensitive or specific to direct therapy. Thus, laboratory screening tests are often used to identify a subpopulation at significant risk for bacteremia to merit prophylactic antibiotic therapy. Currently, the best laboratory predictors of bacteremia are the white blood cell count (WBC) and the absolute neutrophil count (ANC), with comparable sensitivities and specificities in the range of 70% to 86%. Measurement of C-reactive protein (CRP), an acute-phase protein synthesized by hepatocytes, is valuable in distinguishing systemic bacterial infection from viral infections in both immunocompetent and immunodeficient hosts. After the onset of inflammation or acute tissue injury, CRP synthesis increases within 4 to 6 hours, doubling every 8 hours thereafter, and peaking at 36 to 50 hours after the onset of inflammation. C-reactive protein levels remain elevated with ongoing inflammation and tissue destruction, but with resolution, they decline rapidly because of a relatively short half-life of 4 to 7 hours. The rapid kinetics of CRP metabolism seem to closely parallel the degree of injury and repair, thereby supporting its value as an acute measure of disease activity. Furthermore, the test is relatively inexpensive, can be run quickly, and requires a small aliquot of serum, obtainable by fingerstick. Auto-
mated chemistry analyzers are beginning to offer CRP in their test menus.10,11

While several studies have looked at the usefulness of CRP in the neonatal population, few studies have been done to assess the performance of CRP for the detection of bacteremia or occult bacterial infection (OBI) in children. Four reports have suggested that CRP may offer superior diagnostic accuracy compared with WBC in the detection of bacteremia or OBI.12-15

This study prospectively compared the accuracy of serum CRP with that of WBC and ANC for the detection of bacteremia and OBI in febrile young children, and investigated the contribution of other variables such as patient age, temperature, and duration of illness on the utility of these tests. The “best” test was determined by maximum area under the curve (AUC) criteria. The study also assessed whether adding CRP testing to those results obtained from the WBC and the differential improved the diagnostic accuracy of these tests.

**PATIENTS AND METHODS**

Children visiting the emergency department of Children’s Hospital of The King’s Daughters (Norfolk, Va), a free-standing, urban children’s hospital, who were between 3 and 36 months of age were eligible for participating this study. All febrile children who met entry criteria and required a complete blood cell count (CBC) and blood culture as part of their evaluation were eligible for enrollment. The determination as to whether a CBC and blood culture were drawn, as well as other laboratory testing (including urinalysis and culture and chest radiograph), was made by the pediatric emergency medicine attending physician who was supervising the patient, and was based on standard guidelines adopted for the management of fever without apparent source in children of this age group.16 Patients were excluded if they had taken any oral or parenteral antibiotics within 48 hours of the visit, or had a known case of bacteremia during the previous 48 hours. Immunodeficient patients were enrolled, but analyzed separately.

Informed consent was obtained for each patient for the withdrawal of an additional 1-mL aliquot of blood sampled simultaneously for CRP measurement. C-reactive protein levels were measured using a heterogeneous immunnoassay format; normal values using this assay are 0 to 0.9 mg/dL. Housestaff and attending staff were informed that CRP levels were being analyzed for study purposes only. Data recorded on each patient included age, temperature in triage, length of existing febrile illness (in hours), history of antibiotic use in the past 48 hours, and history of immunodeficiency.

Blood cultures were processed using the Bactec F system (Beckton Dickinson Diagnostics, Sparks, Md) with constant surveillance for 5 days. Results of total WBC, ANC, and CRP levels were recorded and used to compute the sensitivity, specificity, and positive and negative predictive values of these results with the outcome of interest—OBI. Occult bacterial infection was defined as bacteremia, pneumonia, or urinary tract infection in which no focal abnormalities were evident on physical examination. Bacteremia was defined as growth of a pathogen in a catheterized urine specimen, or 10⁵ or more colony-forming units per cubic milliliter of a single organism in a bagged urine specimen.

**STATISTICAL ANALYSIS**

Distributions of demographic variables were evaluated for normality using the Shapiro-Wilk test. Comparison of nonnormally distributed variables was made using the Wilcoxon rank sum test for equality of distributions. Categorical variables were compared using χ² analysis. The distributions of each test were assessed, and where the test values followed a log-linear relationship, simple and multiple logistic regression using backward elimination was performed so that the full model included exploratory tools all demographic variables, laboratory tests, and appropriate interactions as predictors of OBI. Absolute neutrophil count, WBC, and CRP level were assumed to be independent. Variables were removed from the model if the significance was greater than P = .05. Receiver operator characteristic (ROC) curves were fit for WBC, ANC, and CRP individually, and for combinations of WBC and CRP or ANC and CRP as paired screens. The ROC curves were fit first using the observed levels of the tests, and compared using the maximum area AUC criteria. Next, cut-off points for each test were determined by simultaneously maximizing the sensitivity and specificity. The ROC curves were fit using these cut-off points and compared using maximum AUC criteria and likelihood ratio tests where appropriate. Positive and negative predictive values with 95% confidence intervals (CIs) were tabulated. Finally, a model was fit for CRP, keeping sensitivity at 0.80 or higher to determine the specificity of such a test. All analyses were performed using STATA 6.0 (STATA Corp, College Station, Tex), with the exception of ROC curve comparisons, which were made using MedCalc 6.14 (MedCalc Software, Mariakerke, Belgium).

**SAMPLE SIZE ESTIMATION**

Sample size was estimated by establishing the null hypothesis that a CRP value of greater than 2.0 mg/dL will prove to be no more sensitive than the sensitivity of a WBC greater than 15 × 10⁹/L. If we assume that the sensitivity of the test using WBC will be 70% and that the test using CRP will be 95%, 36 patients with OBI would be required to detect this absolute difference of 25% with α = .05 and 80% power. Assuming a 14% OBI rate (6% UTI, 5% pneumonia, and 3% bacteremia), 257 patients would need to be enrolled.

Two hundred sixty-six patients were enrolled in the study, and 9 were later found to have undetected exclusion criteria and were subsequently excluded (8 with antibiotic use within 48 hours and 1 with known bacteremia within 48 hours). One additional patient was analyzed separately because of a history of immunodeficiency. The median age of the 256 patients included in the analysis was 15.3 months (range, 3.1-35.2 months); median temperature at triage was 40.0°C (range, 39.0°C-41.3°C); median length of illness was 24 hours (range, 0-288 hours). Twenty-nine patients (11.3%) had OBI: 17 with pneumonia, 9 with a urinary tract infection, and 3 with bacteremia. The immunocompromised patient did not have an OBI, and since comparisons based on one subject have questionable validity, the patient was excluded from analysis. No significant demographic or clinical difference was detected between those included in the study and those excluded from analysis. Comparing patients with OBI with
those without, neither age nor length of illness were significantly different (for age and length of illness, \( P = .51 \), and \( P = .10 \), respectively); however, median temperature in triage was significantly higher for those with OBI (\( P = .04 \)).

Distributions of WBC, ANC, and CRP levels for those with and without OBI, as well as those excluded, are presented in Table 1. Median values of each of these tests were significantly higher in patients with OBI than in those without OBI (\( P < .001 \)). Line graphs of the distribution of the test values for patients with and without OBI are provided in the Figure.

Two multiple logistic regression models were fit that included age, temperature, length of illness, CRP, and either ANC (model 1) or WBC (model 2). Backward elimination identified only ANC (or WBC), CRP, and length of illness as independent predictors of OBI. In the first model, each cell increase of 1000 \( \times 10^9 \)/L in the ANC resulted in a risk increase of 1.15 for OBI (odds ratio [OR] = 1.15; 95% CI, 1.07-1.24; \( P = .001 \)) after adjusting for CRP and length of illness. Each 1-mg/dL increase in CRP resulted in a risk increase of 1.12 for OBI (OR = 1.12; 95% CI, 1.04-1.20; \( P = .003 \)), adjusting for ANC and length of illness. Similarly, each 1-hour increase in length of illness resulted in a risk increase of 1.01 for OBI (OR = 1.01; 95% CI, 1.00-1.03; \( P = .01 \)), adjusting for ANC and CRP. In the second model, each cell increase of 1000 \( \times 10^9 \)/L in the WBC resulted in a 1.15 risk increase for OBI (OR = 1.15; 95% CI, 1.07-1.23; \( P = .001 \)) after adjusting for CRP and length of illness. Each 1-mg/dL increase in CRP resulted in a 1.12 increase in risk of OBI (OR = 1.12; 95% CI, 1.04-1.21; \( P = .003 \)), adjusting for WBC and length of illness. Similarly, each 1-hour increase in length of illness resulted in a risk increase of 1.01 for OBI (95% CI, 1.00-1.02; \( P = .05 \)), adjusting for WBC and CRP.

The ROC curves were constructed, and “best” tests were determined for ANC, WBC, and CRP using the criteria that the AUC be maximized. These models are summarized in terms of sensitivity, specificity, and positive and negative predictive values (PPV and NPV, respectively) in Table 2. The WBC, CRP, and ANC performed quite similarly with little discernible difference. When using the criteria that either the CRP cut-off value be greater than or equal to 3.1 mg/dL or a WBC threshold of at least 17.1 \( \times 10^9 \)/L, the sensitivity of the screen increased from 0.69 (95% CI, 0.51-0.89) to 0.76 (95% CI, 0.59-0.92), while the specificity dropped from 0.80 (95% CI, 0.75-0.85) to 0.58 (95% CI, 0.51-0.64). Similarly, using the criteria that CRP levels be at least 3.6 mg/dL or the ANC threshold be at least 10.5 \( \times 10^9 \)/L increased sensitivity of the test from 0.69 (95% CI, 0.51-0.87) to 0.79 (95% CI, 0.64-0.95) with a commensurate drop in specificity from 0.79 (95% CI, 0.73-0.84) to 0.50 (95% CI, 0.43-0.56). As evidenced by the overlap in CIs, no change in sensitivity was statistically significant; however, the drop in specificity with the addition of CRP to both ANC and WBC criteria was significant. There was also an insignificant drop in PPV with the addition of a CRP marker to both WBC and ANC, while NPV remained constant with 95% rule-out probability.

Due to the biological rise and decay rate of CRP, the timing of presentation was included in regression models. This is of special interest since most patients in our study group, 219 overall (81%), and 25 of those with OBI (81%), came to the emergency department for treatment 12 or more hours after the onset of illness. No significant difference in Table 1. Demographic and Clinical Comparisons*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients With OBI (n = 29)</th>
<th>Patients Without Non-OBI (n = 227)</th>
<th>Excluded Patients† (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mo</td>
<td>13.5 (4.3-33.6)</td>
<td>15.5 (3.1-35.2)</td>
<td>19.7 (5.3-26.1)</td>
</tr>
<tr>
<td>Temperature, °C†</td>
<td>40.2 (39.0-41.2)</td>
<td>40.0 (39.0-41.3)</td>
<td>39.7 (39.0-40.6)</td>
</tr>
<tr>
<td>Length of illness, h</td>
<td>24 (4-240)</td>
<td>24 (0-288)</td>
<td>24 (12-96)</td>
</tr>
<tr>
<td>WBC (thousands)†</td>
<td>19.7 (6.4-39.1)</td>
<td>11.4 (3.6-33.9)</td>
<td>9.0 (4.8-26.2)</td>
</tr>
<tr>
<td>CRP†</td>
<td>5.6 (0.7-43.3)</td>
<td>1.5 (0.2-31.1)</td>
<td>2.7 (1.2-7.8)</td>
</tr>
<tr>
<td>ANC†</td>
<td>13.8 (2.6-26.4)</td>
<td>6.6 (0.6-28.2)</td>
<td>4.9 (1.3-17.6)</td>
</tr>
</tbody>
</table>

*All data are presented as median (range). OBI indicates occult bacterial infection; WBC, white blood cell count; CRP, C-reactive protein; and ANC, absolute neutrophil count.
†Indicates significant difference between patients with and without OBI.
‡No significant differences were detected between those included in the analysis and those excluded.
was detected in the distribution of CRP levels between patients presenting within 12 hours of onset of illness compared with at least 12 hours after illness. The sensitivity of CRP to detect OBI among patients seen at least 12 hours after onset of illness only slightly exceeds that for patients seen within 12 hours (0.68 vs 0.67, respectively), with a proportional drop in specificity (0.81 vs 0.85, respectively).

Three (1.1%) of the 256 studied analysis patients had occult bacteremia; there were two cases of *Streptococcus pneumoniae* bacteremia, and 1 case of *Salmonella* infection. To ensure that the prevalence of occult bacteremia mirrored that in our overall emergency department, we reviewed the microbiology reports from all of children 3 to 36 months of age who had a blood culture done during the period from February 2000 to February 2001. Seventeen hundred seventy-two cultures were drawn during this year; there were 38 pathogens (2.1%) and 38 contaminants (2.1%). A comparison between the bacteremia rates in the study population vs the overall emergency department population revealed that there was no significant difference (*P* = .26).

### COMMENT

While CRP offers many theoretical advantages as a screening test for OBI, we did not find any advantage in using this test in lieu of the ANC. The sensitivity, specificity, and PPV and NPV profiles of these tests are extremely similar. While the addition of CRP testing to that of WBC or ANC provides a slightly better screening profile for ruling out occult bacterial infection, this comes at the cost of a decrease in specificity. At our institution, direct and indirect costs for a CBC amounts to $17.32 per case, and the total cost of CRP is $21.94 per case, meaning that if 1800 patients require this screening annually, as in our emergency department, they would have 204 cases of OBI, of which the ANC screen would detect 141 cases (69% sensitivity), while the ANC/CRP screen would detect 162 cases (79% sensitivity). This would lead to an additional cost of $40000 to detect 21 additional cases of OBI. Furthermore, despite the added cost of this 2-test approach, the ANC and CRP model “rules out” only 798 of 1396 febrile patients, which is a marked reduction in specificity compared with that of ANC alone.

Comparing the distributions of CRP, ANC, and WBC provides further evidence as to the limited usefulness of CRP as a screening test (Figure). While the lines for patients with OBI and those without OBI clearly separate at WBC and ANC levels that are greater than normal, this pattern is not seen with CRP until extremely high values are reached. The distribution of CRP suggests that many patients without OBI will still have an elevated CRP, thus leading to a high percentage of false-positive results using this screening method. Stated another way, to achieve a screening sensitivity of 85% for OBI, using CRP would necessitate setting the cut-off point so low (0.7 mg/dL) that the specificity (23%) would be impractical.

Our results differ from some other recent investigations. In 1986, Peltola and Jaakkola used a case-control design to study CRP values in 73 children with culture-positive bacteremia and compared them with 73 patients with systemic viral infections. Their CRP levels were higher than 2.0 mg/dL in 65 of 73 children who had bacteremia and were less than this value in 56 of 73 with a viral illness, suggesting a high sensitivity and specificity for this level of CRP to detect a bloodstream infection. More recently, Pulliam et al evaluated CRP in 77 children aged 1 to 36 months who had fever and no localizing signs, and found that a CRP value of 7 mg/dL provided a sensitivity of 79% and a specificity of 91% for the detection of OBI. Using the cut-off point of Pulliam et al (7 mg/dL) would have identified only 37% of those with OBI in our population—an unacceptably low sensitivity. While both prior studies demonstrated very good to excellent sensitivities of the CRP, neither of these designs allowed for the determination of true-PPVs or true-NPVs of CRP, as the incidence of disease in these populations was much higher than in the general emergency department population. Furthermore, neither of these studies looked at the added diagnostic utility of adding the CRP test to existing screening tests.

While the initial goal of this study was to test the usefulness of CRP as a screening tool for occult bacteremia, the low incidence of this disorder in our population made this objective impractical. A review of the microbiology records at our hospital showed a slightly higher incidence of OBI in our general emergency department population than in our study group, though both values were quite low. Our rates of bacteremia mirror those recently reported by Alpern et al. In light of such a low incidence of occult bacteremia, whether any screening test should be done for this disorder is now debatable.

Some might argue that it is unnecessary to use a non-specific laboratory test such as CRP to screen for infections such as pneumonia and urinary tract infection, as these infections can be diagnosed through more specific laboratory studies. While that argument has its merit,
that combines CRP results with those of either WBC or ANC insignificantly increases the sensitivity of these screens for the detection of OBI, but at roughly twice the cost. With the routine use of the conjugate pneumococcal vaccine, the incidence of bacteremia in fully immunized children is now quite low, thus arguing for a changing management approach that relies more on clinical follow-up than on screening laboratory testing.

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REFERENCES


What This Study Adds

Previous work in the neonatal literature has suggested that serial measurements of serum CRP can be very useful in identifying neonatal infection. A recent study has suggested that CRP may hold promise in predicting children who are likely to have an OBI. This study contributes to the ongoing literature regarding the detection of occult bacteremia and OBI in children. It questions the usefulness of a single CRP value in identifying OBI in children, and highlights the decreasing incidence of occult bacteremia in this population.
The author of the editorial writes that the goal for palliative care is to achieve the best quality of life for patients and their families. However, she does not address the question of communication with an older child about his or her imminent death, nor does she address ways to measure a child’s quality of life. A close look at the development and behavior of the child should be incorporated in any future evaluation of pediatric palliative care issues.

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In reply

In his letter to the editor, Dr Nitschke raises an important point regarding informing a child of his or her impending death. Although not reported on directly in our article, we did ask parents whether their child was informed of his or her impending death. Many parents cited that their child was too young to talk about the fact that he or she was dying. Other parents stated that they themselves were emotionally unable to raise the issue. Some parents expressed regret at not having had these discussions with their child and were tortured by thoughts about potential fear and anxiety they might have faced. A few parents were able to talk directly with their child and give him or her the opportunity to choose how to spend what time was left. These situations were the exception rather than the rule. In addition, it seemed rare that someone other than parents talked to the child about dying.

There are many things to consider when thinking about communicating with a child about his or her death. What is the cultural background of the family and beliefs about how much a child should be told? What are the spiritual beliefs and dynamics of the family and how will they affect the discussion of the child’s imminent death? What is the emotional and developmental stage of the child? Who will be there to support the child through these discussions if parents and family members are unable to address these issues? How are we obligated to respond when a child asks us directly what is happening even if the parents have indicated that they prefer not to have the child know?

Clearly, the death of a child is the most torturous of life events. It is an area that deserves our attention and resources. Further study into the means by which we can improve the palliative phases of treatment for both the patient and family must be undertaken. As Dr Nitschke so rightly points out, our attempts to ameliorate care must address not only the family but also pay particular attention to the experience of the child.

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Correction
Errors in Reporting White Blood Cell and Absolute Neutrophil Counts. In the article titled “Utility of the Serum C-reactive Protein for Detection of Occult Bacterial Infection in Children” published in the September issue of the ARCHIVES (2002;156:905-909), there are several mispresentations of the white blood cell (WBC) and absolute neutrophil count (ANC) values in the abstract, as well as in “Patients and Methods” and “Results” section. For example, in the abstract, where the median WBC value reads, “12.9 × 10⁹/L,” the “×10⁹” should be “×10³”. All instances of WBC and ANC values should, therefore, be reported as thousands of cells per microliter.

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