Risk of Bacteremia for Febrile Young Children in the Post–Haemophilus influenzae Type b Era

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Objectives: To determine the risk for bacteremia, in the post–Haemophilus influenzae type b era, in a prospective cohort of well-appearing febrile children 3 to 36 months of age with no obvious source of infection; and to compare the predictive abilities of objective criteria in identification of children with occult pneumococcal bacteremia from those at risk.

Design: All children seen from 1993 through 1996, 3 to 36 months of age with a temperature of 39.0°C or higher, no identified source of infection (except otitis media), and discharged to home were considered to be at risk for occult bacteremia and included in the study.

Setting: Urban pediatric emergency department.

Results: Of 199,868 patient visits to the emergency department, 11,911 children were considered to be at risk for occult bacteremia. Blood cultures were obtained from 9,465 (79%). A total of 149 blood cultures contained pathogenic organisms, indicating a rate of occult bacteremia of 1.57% (95% confidence intervals: 1.32%-1.83%). White blood cell count and absolute neutrophil count were the best predictors for occult pneumococcal bacteremia. Using a white blood cell count cutoff value of 15 cells × 10^9/L (sensitivity, 86%; specificity, 77%; and positive predictive value, 5.1%) would result in the treatment of approximately 19 nonbacteremic children for each bacteremic child treated.

Conclusions: The prevalence of occult bacteremia in children 3 to 36 months old with temperatures of 39.0°C or higher and no obvious source of infection is 1.6%. The white blood cell and absolute neutrophil counts are the most accurate predictors of occult pneumococcal bacteremia and when available should be used if presumptive antibiotic therapy is being considered.

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The appropriate management of the young febrile child remains an area of great debate. Although most children with fever have self-limited viral infections, previous studies have suggested that 3% to 5% of well-appearing children with no obvious source of infection will have occult bacteremia, and that about 10% of children with bacteremia will develop more severe illnesses such as sepsis, meningitis, pneumonia, osteomyelitis, and septic arthritis.²,³ Appropriate antimicrobial therapy administered to children at risk for bacteremia reduces the incidence of sequelae,³,⁴ but distinguishing children with bacteremia from those with self-limited viral illnesses has been quite difficult.⁵,⁶ In fact, by definition, a child with occult bacteremia is clinically indistinguishable from the well-appearing febrile child (or the bacteremia would not be occult). Because clinical judgment has been used to prescreen patients before entering “occult bacteremia guidelines,” such guidelines have relied on additional objective aids to diagnosis such as the white blood cell count (WBC). Published practice guidelines calling for empiric ceftriaxone therapy of selected children with WBC counts of 15 × 10^9/L or greater deemed at risk for occult bacteremia⁸ have recently been challenged. Specifically, recent commentaries have advocated that treatment be either withheld entirely or administered only to children with a WBC count of 20 × 10^9/L or greater.⁹

The purposes of this article are 2-fold: (1) to determine the prevalence of occult bacteremia in a cohort of febrile children 3 to 36 months of age after the introduction of the Haemophilus influenzae type b conjugate vaccine and (2) to provide data from which to assess the risk of Streptococcus pneumoniae bacteremia in well-appearing young children, so that proponents of antibiotic administration to selected febrile children are able to choose optimal criteria.

RESULTS

STUDY POPULATION

There were 199,868 patient visits to the ED from January 1, 1993, to December 31, 1996. Children between the ages of 3 and 36 months accounted for 70,142 of the
PATIENTS AND METHODS

POPULATION

The following prospectively gathered information regarding patient visits to the emergency department (ED) of an urban tertiary care, children's hospital with 24-hour, pediatric emergency medicine–trained attending coverage was obtained from the computerized database at the hospital: medical record number, ED encounter number, date of birth, date of visit, sex, race, chief complaint, temperature at initial evaluation, disposition (admitted to the hospital or discharged to home), diagnoses, WBC, differential cell count, and blood culture results.

STUDY POPULATION

Patients treated in the ED between January 1, 1993, and December 31, 1996, were considered initially for inclusion in our study population of subjects at risk for occult bacteremia if they were between 3 and 36 months of age and had a triage temperature of 39.0°C or higher recorded in the ED by rectal or tympanic measurement. Subsequently, we excluded children who were (1) admitted to the hospital, transferred to another facility, or died during the visit; (2) discharged with a diagnosis of a specific viral infection (croup, bronchiolitis, varicella, Coxsackievirus, herpangina, or stomatitis); (3) diagnosed with a focal bacterial infection, other than otitis media (pneumonia, abscess, cellulitis, meningitis, sinusitis, ostitis, pylonephritis, lymphadenitis, cholangitis, mastoiditis, impetigo, scarlet fever, streptococcal pharyngitis, or urinary tract infection); (4) known to have a chronic illness or known immunodeficiency that would alter the approach to febrile illness such as leukemia, agranulocytosis, aplastic anemia, aplasia, atrial fibrillation, congenital heart anomalies, congestive heart failure, cystic fibrosis, human immunodeficiency virus infection, Lyme disease, Kawasaki disease, nephrotic syndrome, and sickle cell anemia. Laboratory tests were performed as part of the ED visit in accordance with the standard protocol in the department for patients meeting risk criteria for occult bacteremia. Children with otitis media were included because previous publications have documented a similar rate of occult bacteremia regardless of the presence of otitis media. The data were analyzed with and without these children to confirm that this was true of our population.

CHART AUDIT

To ensure the accuracy of the data derived from the database, we audited consecutive records from all visits during the first week of each month of 1996. We additionally reviewed these medical records for evidence of recent antibiotic therapy or immunization within the previous 48 hours.

DEFINITION OF INFECTIONS

True-positive cultures were defined as group A streptococci, group B streptococci, *Haemophilus influenzae* type b, *Neisseria meningitidis*, *Salmonella* species, and *Streptococcus pneumoniae*.

LABORATORY METHODS

White blood cell counts were performed using Bayer Technicon H3 Systems (Bayer Diagnostic, Tarrytown, NY) equipment. Blood cultures were performed using a recommended 1 to 3 mL of blood in a BACTEC PEDS PLUS media bottle and were read visually and by BACTEC NR660 equipment or BACTEC PEDS PLUS/F culture media and the model BACTEC 9240 continuous-monitoring system (Becton Dickinson, Tarrytown, NY). Anaerobic cultures were not routinely obtained.

DATA ANALYSIS

Five variables were evaluated for univariate association with occult pneumococcal bacteremia: age, temperature, WBC, absolute neutrophil count (ANC), and absolute band count (ABC). The manual differential cell count was used to obtain values for the ANC and ABC. If a manual differential cell count was not available, the results of the automated differential cell count were used in our analysis.

Age and temperature were considered categorical variables for the purposes of statistical analysis while WBC, ANC, and ABC were analyzed as continuous variables. Categorical variables were analyzed with the χ² tests and univariate logistic regression. Means of continuous variables were compared using the Student t test. Continuous variables were also analyzed independently using logistic regression. Confidence intervals (CIs) were calculated for rates and proportions. Sensitivities and specificities were calculated for each variable at different cutoff values and receiver operating characteristic (ROC) curves were constructed. The ROC plots may be compared using both qualitative and quantitative methods. On visual inspection, an ROC plot lying above and to the left of another plot indicates greater diagnostic accuracy. A quantitative global measure of the diagnostic accuracy of a laboratory test is the area under the curve (AUC). Values range from 0.5 (a test with no discrimination) to 1.0 (a test with perfect discrimination). For each ROC curve, the AUC and SE were calculated using nonparametric methods. To compare 2 independent curves, the χ² test was used to assess any statistical difference between 2 curves. Statistical analyses were performed using Stata 5.0 for the Macintosh computer. Permission to review patient records was granted by the institutional review board.

Of these 11,911 patient visits to the ED, 8974 (75%) had a complete blood cell count done and 8782 (74%) had a differential cell count performed. A manual differential cell count was performed in 7471 (63%) and an automated differential cell count was completed in the remainder of patients. Blood cultures were drawn in 9465 (79%) of the patient visits. Blood cultures were less likely to be drawn when a diagnosis of otitis media was made (71% vs 84%, P<.01). Of 246 blood cultures from which organisms were isolated,
149 were considered pathogens: *S pneumoniae* in 137 (92%), *Salmonella* species in 7 (5%), *N meningitidis* in 2 (1%), group A streptococci in 2 (1%), and group B streptococci in 1 (1%). *Haemophilus influenzae* type b was not isolated from the blood of any of these children. The prevalence of occult bacteremia in this population of 9465 children 3 to 36 months of age with a temperature of 39.0°C or higher and no obvious source of infection is 1.57% with a 95% CI of 1.32%-1.83%. Of those children with positive findings on blood culture, the most common diagnoses were fever (n=78), otitis media (n=46), and unspecified viral infection (n=19). Occult pneumococcal bacteremia occurred in 1.55% (95% CI: 1.11%-1.99%) of children without otitis media. The risk of occult pneumococcal bacteremia alone is 1.45% (95% CI: 1.28%-1.89%) of children with otitis media compared with 1.59% (95% CI: 1.21%-1.97%) of children without otitis media. Because there was no significant difference between the groups, patients with otitis media were included in subsequent analyses. All subsequent analyses will focus on pneumococcal bacteremia alone.

**Table 1** describes characteristics of patients with and without occult pneumococcal bacteremia. Patients with pneumococcal bacteremia were found to have higher temperatures, WBCs, ANCs, and ABCs than those without bacteremia.

### UNIVARIATE ANALYSIS

The risk of occult pneumococcal bacteremia was significantly lower in the 3- to 6-month-old age group than in older age groups (**Figure 1**). The 3- to 6-month-old age group had an odds ratio (OR) for pneumococcal bacteremia of 0.22 (95% CI: 0.07-0.71) compared with the 12- to 24-month-old age group. The 6- to 12-month-old (OR 1.06; 95% CI: 0.73-1.55) and 24- to 36-month-old (OR 0.75; 95% CI: 0.46-1.23) age groups showed no significant differences in the odds ratios when compared with the 12- to 24-month-old group.

**Figure 2** shows an increased prevalence of bacteremia at higher temperatures. When compared with the 39.0°C to 39.4°C temperature group, the 40.0°C to 40.4°C, 40.5°C to 40.9°C, and 41.0°C to 42.0°C temperature groups showed significantly higher risks for bacteremia with ORs of 1.90 (95% CI: 1.13-3.21), 2.6 (95% CI: 1.5-4.5), and 3.7 (95% CI: 1.9-7.3), respectively.

### ROC CURVES

Rates of bacteremia also increased with increasing values of WBC, ANC, and ABC. Univariate logistic regression for each of these variables showed significant association with occult pneumococcal bacteremia (Pearson χ² probability for goodness of fit >0.99 for WBC, ANC, and ABC).

**Table 2** shows risk profiles for occult pneumococcal bacteremia using incremental cutoffs of WBC and temperature. To select a decision threshold for WBC, we examined the sensitivity/specificity pairs for various points on the ROC curve. **Table 3** shows the sensitivity, specificity, positive predictive value, and the percentage of all eligible children above the threshold value for various cutoff points of WBC.

### CHART AUDIT

A total of 586 patients visited the ED in the 12 weeks represented by the first week of each month of 1996. Of these...
patients, 8 (1.4%) were found to have an incorrectly coded discharge diagnosis recorded in the computer database. Eighty-nine patients (15.2%) were recently or currently being treated with antibiotics and 1 patient had been immunized within the previous 48 hours.

Our study is the first large cohort study to document the rate of occult bacteremia, in the post–*H influenzae* type b era, among an unselected population of children typically considered at risk for occult bacteremia. All 3- to 36-month-old highly febrile children were included unless they required hospital admission from that visit (so as not to include “toxic” or ill-appearing children in this analysis) or had a specific viral or bacterial diagnosis other than otitis media. Before introduction of the *H influenzae* type b conjugate vaccines, this organism accounted for 13% of occult bacteremia in this age group and 42% of the complications identified at follow-up. We found that in our area where immunization rates are high we had complete elimination of *H influenzae* type b from our population. *Streptococcus pneumoniae* now accounts for 92% of all cases of occult bacteremia with *Salmonella* species; *N meningitidis*, group A streptococci, and group B streptococci are responsible for the rest.

The rate of occult bacteremia found in our study (1.6%) is lower than previously reported and cannot be completely explained by the disappearance of *H influenzae* type b. Approximately 15% of the children in our study group had been recently vaccinated or were already receiving antibiotics at the time the blood culture was drawn (exclusion criteria for many previous studies) and if these children are at lower risk of bacteremia, we may slightly underestimate the risk of bacteremia in the rest of the population. However, removing these 15% from the study denominator would not alone account for the reduced rate of bacteremia found in our study. We postulate that much of the reduced rate seen is because of our high rate of drawing blood cultures. Blood cultures were obtained in a much higher proportion of children than seen in previous studies (79% vs 10%-40%). These studies likely experienced some clinical selection bias in the drawing of cultures that may have caused a higher rate of positivity.

The low rate of bacteremia in the 3- to 6-month-old age group has been noted previously and may be the result of lower nasal colonization rates and passive immunity conferred by maternal antibodies. Nonetheless, this is the peak age for the development of pneumococcal meningitis. Therefore, we continue to be cautious with this group.

### Table 2. Rates of Bacteremia at Different White Blood Cell Count (WBC) and Temperature Cutoffs

<table>
<thead>
<tr>
<th>WBC Cutoff, $10^9$/L</th>
<th>Temperature Cutoff, °C</th>
<th>Row Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4.99</td>
<td>39.0-39.4</td>
<td>40-40.4</td>
</tr>
<tr>
<td>5-9.99</td>
<td>39.5-39.9</td>
<td>40.5-40.9</td>
</tr>
<tr>
<td>10-14.99</td>
<td>41.0</td>
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<tr>
<td>15-19.99</td>
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<tr>
<td>20-24.99</td>
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<tr>
<td>25-29.99</td>
<td></td>
<td></td>
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<tr>
<td>30-50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>22/2389 (0.9)</td>
<td>30/2669 (1.1)</td>
</tr>
</tbody>
</table>

*Each cell reports the number of patients with positive blood culture findings in the numerator, the total number of patients in the denominator, and the percentage of positive blood culture findings in parentheses. The numbers in this table may differ slightly from numbers reported in the text as this table represents only those children for whom both a white blood cell count and a blood culture were obtained.

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Our study refines and expands the relationships of age, temperature, WBC, ANC, and ABC to occult pneumococcal bacteremia. The WBC and ANC performed best in predicting bacteremia. Based on its widespread clinical usage, we chose to evaluate potential cutoff values for WBC as determinants of the risk for bacteremia.

The sensitivity of the WBC in identifying children with occult bacteremia is better than previously reported. Jaffe and Fleisher\textsuperscript{14} found a WBC cutoff value of $15 \times 10^9$/L to have a sensitivity of 0.65 in identifying occult bacteremia due to all pathogens. Kupperman et al\textsuperscript{12} report a WBC cutoff value of $15 \times 10^9$/L to have a sensitivity of 0.79 in identifying occult pneumococcal bacteremia compared with 0.86 in our study. This improvement in sensitivity is likely due, in part, to the higher WBCs typical of pneumococcal bacteremia compared with bacteremia due to other pathogens.

The selection of a cutoff value depends on a number of factors, including the costs of various treatment approaches and their consequences, the prevalence of occult bacteremia, the incidence of morbidity and mortality associated with no treatment, and treatment complications. Previous authors have recommended presumptive antibiotic therapy for children with a WBC greater than $15 \times 10^9$/L\textsuperscript{26} or more recently $20 \times 10^9$/L.\textsuperscript{27}

The recommendation for empiric treatment of children 3 to 36 months of age with temperatures of 39.0°C or higher and a WBC of $15 \times 10^9$/L or greater would, if applied to our entire pediatric population of nearly 200,000 visits, result in empiric antibiotic therapy in fewer than 1% of patients; approximately 19 children without bacteremia would be treated for each child with bacteremia. Recent meta-analyses have estimated a 2.7% to 5.8% risk for developing meningitis in children with occult pneumococcal bacteremia who are not treated with antibiotics at the initial evaluation.\textsuperscript{4,5} Therefore, we can estimate that approximately 500 children would need empiric treatment to prevent 1 case of pneumococcal meningitis. The higher recommended WBC cutoff value of $20 \times 10^9$/L or greater would result in approximately 12 children without bacteremia treated for each child with bacteremia treated (therefore treating approximately 300 children to prevent a case of meningitis), but at the cost of missing more than one half of the children with bacteremia and potentially failing to prevent a similar proportion of cases of meningitis. The optimal cutoff may actually lie between these 2 values and we have presented the data so the clinicians may make an informed decision. A WBC cutoff value of $18 \times 10^9$/L or greater provides a reasonable alternative that would result in lower usage of empiric antibiotics than a WBC cutoff value of $15 \times 10^9$/L. This alternative cutoff value would decrease sensitivity to 64% in favor of an increase in specificity to 87%, thereby reducing the proportion of febrile children who receive empiric treatment from 24% to 14%. The decrease in sensitivity seems justified by the lower prevalence of occult bacteremia and the elimination of \textit{H. influenzae} type b noted in our cohort.

We believe a complete blood cell count and blood culture are useful tools to supplement clinical acumen in evaluating non-toxic-appearing children 3 to 36 months of age with temperatures of 39.0°C or higher without an identifiable source. Although children 3 to 6 months of age appear to be at lower risk for bacteremia, we do not exclude these children from evaluation as they face a higher risk of serious complications when bacteremia is present. Our data provide the clinician with rational criteria for the selection of which young febrile patients, if any, to treat with presumptive antibiotics.

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