ARTICLE

Incidence of Occult Bacteremia Among Highly Febrile Young Children in the Era of the Pneumococcal Conjugate Vaccine

A Study From a Children's Hospital Emergency Department and Urgent Care Center

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Background: The optimal diagnostic approach to and management of well-appearing, highly febrile young children has been a matter of debate owing to the possibility of clinically inapparent, or occult, bacteremia (OB). The most common causative organism of OB is *Streptococcus pneumoniae*. Universal immunization with a heptavalent pneumococcal conjugate vaccine (PCV7) has recently been implemented, but there are limited data on the impact of this vaccine on the incidence of OB.

Objective: To evaluate the incidence of OB in the era of routine use of PCV7.

Methods: We conducted a retrospective cohort study of highly febrile (temperature, 39°C) children between the ages of 2 months and 36 months who had blood cultures performed in the emergency department or urgent care center between December 11, 2001, and March 5, 2003, and were discharged to home at the time of the initial visit.

Results: Of 329 blood cultures obtained from children who met inclusion criteria and did not meet exclusion criteria, 3 (0.91%; 95% confidence interval, 0%-1.9%) yielded a pathogenic bacterium; all were *S pneumoniae*. Neither an elevated total white blood cell count, an elevated absolute neutrophil count, nor an increased percentage of bands was highly predictive of OB. Blood cultures positive for organisms were more commonly due to contaminants (4; 95% confidence interval, 0%-2.4%) than pathogens.

Conclusions: In the PCV7 era, OB is uncommon in highly febrile children 2 to 36 months of age. With continued use of PCV7, the routine practice of obtaining blood cultures and complete blood cell counts may no longer be indicated in previously healthy, well-appearing, highly febrile children 2 to 36 months of age, particularly those who have received at least 1 dose of PCV7.

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THE OPTIMAL DIAGNOSTIC approach to and management of well-appearing but highly febrile young children have long been a matter of debate because of the possibility of clinically inapparent, or occult, bacteremia (OB). Prior to the introduction in 1990 of the *Haemophilus influenzae* type b (Hib) conjugate vaccine for infants, 3% to 10% of highly febrile, non–toxic-appearing children between the ages of 2 months and 36 months without a focus of infection were found to have OB.[1-11] The risk was higher among children with elevated white blood cell (WBC) counts.[7,9,11] Fifty to ninety percent of episodes were caused by *Streptococcus pneumoniae*, 3% to 25% were caused by Hib, and a small percentage was caused by other bacterial species, including *Salmonella* species and *Neisseria meningitidis*.[2,4-7,10-12] Although OB is at times self-limited, there is a potential for OB to progress to serious bacterial infections such as meningitis. The likelihood of OB progressing to meningitis depends on the causative organism, with a 7% to 13% risk of Hib OB progressing to meningitis[12,13] compared with 1% to 4% for *S pneumoniae* OB.[12,14,15] Consequently, some authors recommended that appropriate management of children between 2 months and 36 months of age with high fever without a source include obtaining blood for culture and a WBC measurement, with empirical antibiotic therapy for patients with a WBC count greater than 15 000/μL[3,5,13,16-18] because this criterion defined a subgroup of febrile children at increased risk for OB.

Routine vaccination of infants with the Hib conjugate vaccine has largely eliminated this bacterium as a cause of severe infectious morbidity and mortality in the United States.[19] In 2000, a heptavalent pneumococcal conjugate vaccine (PCV7) was licensed and recommended for routine administration to all infants and young

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children.[20,21] Prior to vaccine licensure, the 7 serotypes included in the vaccine accounted for 80% of cases of invasive infections in young children in the United States and Canada.[22] In a randomized, controlled trial, PCV7 resulted in an 89% reduction in invasive pneumococcal disease among children younger than 1 year; in 75% of the cases of invasive disease, OB was the clinical manifestation of disease.[23] During the initial postlicensure years, studies have shown a 65% to 80% decrease in the incidence of invasive pneumococcal infections among children younger than 3 years.[24-26] The significant reduction in cases of invasive *S pneumoniae* infection warranted a reassessment of the current incidence of OB, as well as a reevaluation of the predictive value of an elevated WBC count for the presence of OB. In this study, we evaluated a cohort of febrile, non–toxic-appearing young children evaluated in an emergency department or urgent care center to determine the incidence of OB and the distribution of total leukocyte counts and absolute neutrophil and band counts in patients with or without OB.

METHODS

We surveyed the medical records of all children 2 to 36 months of age who had a blood culture performed during a visit to the emergency department or urgent care center of Schneider Children's Hospital (New Hyde Park, NY) between December 11, 2001, and March 5, 2003, a period beginning 16 months after PCV7 was recommended for routine administration to all infants and young children.[20,21] We analyzed the medical records of the subgroup of children who had a maximum temperature by history or measurement during the visit of at least 39°C but were not hospitalized at the time of the visit. We excluded children who had received antibiotics within 4 days prior to the visit because they may have had a falsely negative blood culture. We also excluded children who were diagnosed with a focal bacterial infection other than acute otitis media (AOM) at the initial visit (specifically, urinary tract infection, radiographically confirmed pneumonia, abscess, cellulitis, or lymphadenitis); had blood cultures performed as part of the evaluation for appendicitis, septic arthritis, or intussusception; or had an underlying condition that put them at increased risk for bacteremia: an immunologic abnormality (sickle cell disease, congenital or acquired immunodeficiency), complex congenital heart disease, or the presence of a long-term vascular catheter or a ventriculoperitoneal shunt. We recorded the age, the clinical diagnosis at the time of the visit, and the results of laboratory testing including complete blood cell count and differential cell count, urinalysis, urine culture, blood culture, and antigen testing of nasal washes for respiratory syncytial virus (RSV) and influenza, as well as the results of cultures performed at subsequent emergency department or urgent care visits or hospitalizations within 7 days following the initial visit. Approval to perform this study was obtained from the institutional review board of Long Island Jewish Medical Center (New Hyde Park).

Blood for culture was obtained by a pediatric emergency department nurse or resident after the skin was prepared with povidone-iodine. A volume of one half to 1 mL of blood was injected into a single Bactec Peds/F blood culture bottle (Becton, Dickinson and Company, Franklin Lakes, NJ) that was incubated in the continuously monitored BACTEC 9240 instrument. Bottles that alarmed were removed, sampled for gram staining, and subcultured. Colonies were identified using standard methods. Bacterial species that were considered pathogens included *S pneumoniae*, *H influenzae* type b, *Staphylococcus aureus*, and *N meningitidis*. Coagulase-negative staphylococci, nonpneumococcal α-hemolytic streptococci, and *Bacillus* species (other than *Bacillus anthracis*) were considered contaminants, as was *Enterococcus* species in the absence of simultaneous recovery from a urine culture. *Streptococcus pneumoniae* isolates were serotyped by latex particles sensitized with monospecific typing serum samples (Statens Serum Institut, Copenhagen, Denmark) and observed for agglutination.[27]

RESULTS

A blood culture was obtained from 631 children 2 to 36 months of age who were not admitted to the hospital at the time of their initial visit. Three hundred two children (48%) were excluded for the following reasons: antibiotic use within 4 days prior to the visit (n=105), maximum temperature less than 39°C (n=133), known or suspected bacterial source other than AOM (n=44), and increased risk of bacteremia due to an underlying condition (n=20). Of the remaining 329 children, results of a complete blood cell count were available for 324 (98%); and results of a manual differential cell count, for 277 (84%).

Three blood cultures (0.91%; 95% confidence interval [CI], 0%-1.9%) obtained at the time of evaluation of the 329 episodes yielded a pathogen, all *S pneumoniae*. The clinical diagnosis in all 3 episodes with bacteremia was fever without a source. Blood cultures from 4 children (1.2%; 95% CI, 0%-2.4%) yielded contaminants: *Streptococcus intermedius*, *Staphylococcus haemolyticus* and *Bacillus* species, *Staphylococcus epidermidis*, and *Enterococcus faecalis*. Of the 326 children with negative cultures or contaminants, the clinical diagnoses were fever with no source or a mild upper respiratory tract infection (n=259); acute gastroenteritis (n=32); AOM (n=30); and a recognizable viral syndrome (croup, bronchiolitis, or respiratory symptoms with a positive rapid test for RSV or influenza antigen) (n=5).

Table 1 shows the relationship between parameters in the complete blood cell count and the risk of OB. Almost 97% of those with a WBC count greater than or equal to 15000/μL had blood cultures negative for organisms, as did nearly 93% of the children with WBC counts greater than or equal to 20000/μL. Similarly, more than 99% of the children with at least 5% bands and nearly 98% of the children with at least 10% bands had blood cultures negative for organisms. The laboratory parameter with the highest positive predictive value (PPV), (11%) was an absolute neutrophil count greater than or equal to 15000/μL.

The 3 cases of OB occurred in 2 children. Patient 1 (aged 9 months) was infected with serotype 22F (not included in PCV7). He was treated empirically with an intramuscular dose of ceftriaxone and seen the following day to receive a second dose, at which time he was clinically improved. Patient 2 had 2 episodes of pneumococcal OB 1 month apart, occurring at ages 20 months and 21 months. He had not received PCV7. His first episode was caused by a penicillin-susceptible serotype 4 strain, a serotype included in PCV7. He received intravenous ceftriaxone at the time of the initial visit and an intramuscular dose the following day. When the positive blood

Table 1. Sensitivity, Specificity, and Predictive Value of Laboratory Tests for Diagnosis of Occult Bacteremia in Highly Febrile Children*

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
WBC count ≥15 000/μL†	100	71	3.2	100
WBC count ≥20 000/μL†	100	88	7.1	100
Bands ≥5%‡	33	56	0.83	99
Bands ≥10%‡	33	84	2.2	99
ANC ≥10 000/μL†	100	77	3.8	100
ANC ≥15 000/μL†	100	92	10.7	100

Abbreviations: ANC, absolute neutrophil count; WBC, white blood cell.
*Data are given as percentage.
†Results based on 324 cases.
‡Results based on 277 cases.

Table 2. Comparison of Data and Methodology From the Current Study With Those of the 3 Studies Conducted in the Post–Hib Conjugate Vaccine, Pre-PCV7 Era*

	Lee and Harper[29] (n = 9465)	Alpern et al[30] (n = 5901)	Bandyopadhyay et al[31] (n = 1202)	Current Study (n = 329)
Incidence of OB, % (95% CI)	1.6 (1.3-1.8)	1.9 (1.5-2.3)	3.1 (2.2-4.2)	0.91 (0-1.9)
PPV of WBC count >15 000/μL, % (95% CI)	5.1 (4.2-6.1)	NA	NA	3.2 (0-6.7)
PPV of WBC count >20 000/μL, % (95% CI)	8.1 (6.3-10.4)	NA	NA	7.1 (0-14.9)
Age range, mo	3-36	2-24	2-36	2-36
Definition of fever (°C)	39	39	39	39

Abbreviations: CI, confidence interval; Hib, *Haemophilus influenzae* type b; NA, not available; OB, occult bacteremia; PCV7, heptavalent pneumococcal conjugate vaccine; PPV, positive predictive value; WBC, white blood cell.
*Sample size indicates the number of episodes of high fever.

culture was reported, he was recalled, another blood culture was obtained, and he was prescribed orally administered cefuroxime. Two days later, the blood culture results remained negative and cefuroxime treatment was discontinued. Twenty-three days after cefuroxime therapy was discontinued, he had a fever without a focus and was treated with intramuscular ceftriaxone. Blood culture yielded *S pneumoniae*; the isolate was not available for serotyping. The patient was never admitted to Schneider Children's Hospital, however, and further details of his subsequent course are not available.

COMMENT

To our knowledge, this study is the first to evaluate the incidence of OB in the PCV7 era. The starting date was chosen to be approximately 1½ years after licensure of PCV7 and after approximately 1 year of routine use. We did not determine the proportion of patients in our cohort who had been appropriately immunized with PCV7. However, the Nassau County Department of Health (Mineola, NY) performs audits of immunization of children in Nassau County, a county included in the catchment area of our hospital. Of 185 children audited from 16 primary care practices during mid 2002, a weighted average of only 28% of infants had received 3 doses of PCV7 by 7 months of age, and 66% had received 3 doses of PCV7 by 12 months of age (written communication, Abby J. Greenberg, MD, Nassau County Department of Health, to L.G.R., April 2003). The low incidence of pneumococcal OB we observed despite data suggesting a relatively low rate of PCV7 immunization in our community may be due to herd-type immunity associated with a reduction in carriage of vaccine serotypes in immunized children[24] and/or to the ability of even 1 dose of PCV7 to provide significant protection against pneumococcal pneumonia.[28] The incidence of OB among highly febrile young children in our study was lower than in all studies conducted prior to routine administration of Hib conjugate vaccine, with all but 1 of these differences statistically significant (χ^2 data not shown).[1-11] Also, the incidence of OB was lower in our study than in each of the 3 studies conducted since routine use of Hib conjugate vaccine, albeit only significantly lower than the incidence observed in 1 of the 3 (**Table 2**).[29-31]

We found that the 3.2% PPV of a WBC count greater than or equal to 15 000/μL was lower than that observed in each of the 4 pre–Hib conjugate vaccine studies in which this was evaluated (8.7%, 24%, 11%, and 15%) and significantly lower than in 3 of the 4 ($P<.05$, χ^2)[2,7,9,11] pre–Hib vaccine studies that had also evaluated this test: listed chronologically, 8.7%, 24%, 11%, and 15%. The lower PPV is most likely the result of a lower incidence of bacteremia. Additionally, the PPV was comparable to that calculated by Lee and Harper,[29] authors of the only other post-Hib study that evaluated this test (Table 2).

Our limited data set of 3 pneumococcal isolates (with the serotype known for only 2 isolates) is insufficient to determine if serotype replacement, ie, an increase in the proportion of pneumococcal bacteremia episodes caused by serotypes not included in PCV7, will occur following introduction of PCV7. In the randomized trial that supported licensure of PCV7, Black et al[23] observed 6 cases of invasive disease due to serotypes not included in the

What This Study Adds

Children between 2 months and 36 months of age with high fever and no focus of infection have long been considered to be at risk for OB, most commonly due to *S pneumoniae*. General use of a heptavalent pneumococcal conjugate vaccine, available since mid-2000, may markedly reduce the risk of invasive pneumococcal disease in infants and young children. The impact of this vaccine on OB was examined in this study. Of 329 episodes of high fever in children 2 to 36 months of age, there were 3 cases (0.91%; 95% CI, 0%-1.9%) of OB in 2 children, all due to *S pneumoniae*. The incidence of OB may now be sufficiently low that routine performance of complete blood cell count and blood culture in highly febrile children 2 months of age and older who have received at least 1 dose of PCV7 is no longer necessary.

vaccine in the control group and 3 cases in the PCV7 group, findings that do not indicate possible serotype replacement. In a postlicensure evaluation of PCV7, Black et al[24] observed no increase in invasive disease incidence for possibly cross-reacting serotypes or nonvaccine serotypes. Finally, using population-based data from a prospective survey of invasive disease, Whitney et al[26] found a nonsignificant 27% higher rate of invasive pneumococcal disease from serotypes not included in PCV7 in 2001 (post-PCV7 licensure) compared with 1998 and 1999 (prelicensure years). Thus, data available to date do not indicate that nonvaccine serotypes are replacing vaccine serotypes as causes of invasive disease.

Our study has several limitations. We did not determine the number of highly febrile young children who did not have blood obtained for culture; although it was the routine practice of emergency department physicians to obtain blood for culture from such children, the decision to culture was at the discretion of the pediatric emergency department fellow or attending physician. It is unlikely that any of the discharged children developed pneumococcal septicemia or meningitis because a separate review of the records of children 2 to 36 months of age hospitalized with pneumococcal bacteremia or meningitis during the study period revealed 4 children, none of whom had been evaluated and discharged from the emergency department prior to their admission (data not shown). We cannot exclude the small possibility that discharged children were subsequently examined at another hospital. A second limitation is the relatively small sample size, compared with some of the other studies conducted during the pre-PCV7 era.

We included children with AOM, acute gastroenteritis, and viral diagnoses, such as croup and RSV infection. Children with AOM were included because previous studies found that children with AOM had a risk of bacteremia similar to children with no focus for infection.[29] Previous studies of OB have included children with AOM, acute gastroenteritis, and bronchiolitis.[29] We excluded children with recent use of antibiotics because of the possibility that antibiotic therapy resulted in a blood culture negative for organisms in a child with bacteremia. Had we included such patients, our incidence of pneumococcal OB may have been lower than was observed, since none of the 105 children excluded owing to recent antibiotic use had blood cultures that yielded *S pneumoniae* (data not shown).

The potential value of detecting OB needs to be balanced against the costs: the trauma associated with phlebotomy; the financial costs of the blood cultures, complete blood cell counts, and antibiotics; the extra time required for the visit and for the repeat emergency department visits and hospitalizations resulting from contaminant growth[32]; the adverse effects of the antibiotics; and pressure to use antibiotics that promotes bacterial resistance. Lee et al[33] published a cost-benefit analysis of performing blood cultures and complete blood cell counts in children at risk for OB, concluding that such tests would no longer be cost-effective if the post-PCV7 incidence of OB were 0.5% or less, an incidence within the 95% CI of the incidence we observed. With full implementation of universal vaccination of infants and young children, it is possible that the rate of OB as well as the PPV of an elevated WBC count will continue to decrease. Even the current incidence of an OB of 0.91% and a PPV of an elevated WBC count greater than or equal to 15 000/μL of 3.2% may not justify expectant broad-spectrum antibiotics, particularly in light of the benign outcome of most cases of OB.[12,14,15] Thus, the practice of routinely obtaining a blood culture and complete blood cell count may no longer be necessary or cost-effective in the management of previously healthy, well-appearing highly febrile children 2 to 36 months of age who have been immunized with at least 1 dose of PCV7, as a recent case-control study demonstrated 88% vaccine effectiveness after 1 dose.[28]

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