

Risk of Bacteremia in Young Children With Pneumonia Treated as Outpatients

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Background: Blood cultures are often obtained as part of the evaluation of children with pneumonia. There are few data regarding the risk of bacteremia with pneumonia in children since introduction of the *Haemophilus influenzae* type b vaccine.

Objective: To evaluate the risk of bacteremia in young children with pneumonia who were treated as outpatients.

Methods: A retrospective cohort study of 580 children aged 2 to 24 months who were evaluated by blood culture in a tertiary care children's hospital emergency department between February 1, 1993, and May 31, 1996, and discharged with the diagnosis of pneumonia.

Results: The mean patient age was 14.1 months; 339 patients (58.4%) were boys. Thirty-eight patients (6.6%) reported the use of oral antibiotics before initial emergency department evaluation. The prevalence of bacter-

emia was 1.6% (95% confidence interval, 0.7%-2.9%). *Streptococcus pneumoniae* was the causative organism in all 9 cases. The serotype was available for 8 of 9 cases. Six (75%) of 8 cases of *S pneumoniae* bacteremia were caused by serotypes included in the current heptavalent pneumococcal conjugate vaccine, which was not available at the time of this study. The contamination rate was 1.9% (95% confidence interval, 1.0%-3.4%). The mean \pm SD time to blood culture positive for organisms in a continuously monitored system was significantly shorter for pathogens (13.9 ± 1.3 hours) than for contaminants (21.2 ± 6.1 hours; $P = .01$).

Conclusions: Children aged 2 to 24 months with pneumonia who are treated as outpatients are at low risk of bacteremia. Widespread use of the pneumococcal conjugate vaccine may further decrease the incidence of bacteremia in this population.

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BLOOD CULTURES are often obtained as part of the outpatient evaluation of children with pneumonia. The risk of bacteremia with pneumonia in this population is unclear. In the pre-*Haemophilus influenzae* type b vaccine era, Bonadio¹ noted that bacteremia was present in 1 (1%) of 86 children with pneumonia. Only 2 (1.8%) of 109 children evaluated by Ramsey et al² had bacteremia. Meanwhile, other researchers³⁻⁵ found rates of bacteremia ranging from 7.7% to 9.6% in children with pneumonia; *H influenzae* and *Streptococcus pneumoniae* were the most common bacterial pathogens identified. These previous studies included children treated as outpatients and those requiring hospitalization. They also included children of a wide age distribution. Given the potentially high risk of bacteremia, even in children who did not require hospitalization, experts recommended obtaining blood cultures on

children with pneumonia who were to be treated in the outpatient setting.⁶

Since introduction of the *H influenzae* type b vaccine, few data have become available regarding the risk of bacteremia with pneumonia in children. We performed a retrospective cohort study to determine the occurrence of bacteremia in young children with pneumonia who were treated as outpatients.

METHODS

STUDY DESIGN AND SETTING

This retrospective cohort study included children aged 2 to 24 months with pneumonia who had blood cultures drawn in an urban tertiary care children's hospital emergency department (ED) (The Children's Hospital of Philadelphia) between February 1, 1993, and May 31, 1996. A subset of this cohort of children with pneumonia is included in a previously described population of children with febrile seizures.⁷ At the time of the study, the ED cared

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for approximately 54 000 children annually. The institutional review board of The Children's Hospital of Philadelphia approved the study.

Standard practice during the study was to obtain blood cultures from children 2 to 24 months of age who had temperatures of 39.0°C or higher, but it did not include routine complete blood cell counts. The decision to obtain blood cultures on children 2 to 24 months of age with pneumonia and temperatures less than 39.0°C was made at the discretion of the attending physician. During a subset of the study that accounts for one third of the enrollment time, 82% of children with temperatures of 39.0°C or higher were documented to have blood cultures obtained.⁸ Blood cultures were obtained by ED nurses using sterile techniques and were inoculated into pediatric blood culture bottles (Pedi-Bac T; bioMérieux, Durham, NC). A single bottle containing supplemented brain heart infusion broth with 0.02% sodium polyanethol sulfonate was inoculated for each blood culture ordered. Standard procedure in the ED was to inoculate 0.5 to 1.0 mL. Through a pneumatic tube delivery system, blood cultures were routinely received in the laboratory within an hour of when they were obtained and were immediately loaded into the blood culture instrument. The microbiology laboratory used a microbial detection system (BacT/Alert; bioMérieux) to process all blood cultures. The BacT/Alert system monitored carbon dioxide production within each bottle every 10 minutes, 24 hours per day. Bottles identified as positive were immediately removed from the instrument, 24 hours per day, and an aliquot was taken for gram stain and subculture. The ED was notified immediately of the positive culture result and was given information from the gram stain. Bacterial isolates were identified by conventional procedures. Only information from the gram stain, however, was available at the time of the initial report of positive culture results to the ED. Routine protocol included contacting families of all children with positive blood culture findings for reevaluation.

PARTICIPANTS

Potential study participants were identified using microbiology laboratory data from the BacT/Alert system. Patients 2 to 24 months of age were included if they were diagnosed as having pneumonia confirmed by chest radiography, had a blood culture obtained during the initial ED evaluation, and were discharged after evaluation. The diagnosis of pneumonia was determined by documentation of attending pediatric emergency medicine physician evaluation of the chest radiograph on the ED chart or by attending pediatric radiologist report of infiltrate on the chest radiograph. Patients were excluded if during initial ED evaluation they (1) were known to have an underlying condition that predisposed them to bacteremia (eg, sickle cell anemia, oncologic disease, immunodeficiency, or indwelling central catheter), (2) underwent lumbar puncture (used as a proxy for clinical suspicion of meningitis, sepsis, or clinically evident bacteremia), or (3) had an illness requiring hospitalization.

MEASURED OUTCOMES AND PROTOCOL

Bacteremia was defined as a blood culture obtained from a patient at initial ED presentation that was positive for pathogenic bacteria. Bacteria that were considered pathogenic included *S pneumoniae*, *Staphylococcus aureus*, group A streptococci, *Enterococcus* species, *Neisseria meningitidis*, Enterobacteriaceae, *Salmonella* species, *Moraxella catarrhalis*, *Pseudomonas* species, *H influenzae*, *Campylobacter* species, and *Escherichia coli*. Bacteria that were considered contaminants included coagulase-negative *Staphylococcus* species, α -hemolytic strep-

tococci, *Micrococcus* species, *Clostridium* species, *Corynebacterium* species, and *Neisseria* species other than *N meningitidis* or *Neisseria gonorrhoeae*. Time to positive culture was measured and recorded in hours and tenths of hours.

STATISTICAL METHODS

Continuous variables are described using mean \pm SD and 95% confidence intervals (CIs). Discrete variables are described using counts and percentages, with binomial exact 95% CIs. Continuous variables were analyzed using the Wilcoxon 2-sample test. Categorical variables were analyzed using the χ^2 test or Fisher exact test. Relative risks with exact 95% CIs were calculated. Statistical significance was determined a priori as $P < .05$.

RESULTS

Blood cultures were obtained in 667 children diagnosed as having pneumonia and discharged from the ED after evaluation. A chest radiograph was not performed in 76 children (11.4%), and these children were excluded from further analysis. None of the 76 children excluded from further study had bacteremia. Eleven (1.6%) of the 667 children had underlying conditions, including congenital heart disease ($n=4$), static encephalopathy ($n=3$), hydrocephalus with ventriculoperitoneal shunt ($n=2$), cystic fibrosis ($n=1$), and tuberculosis ($n=1$), and were also excluded from further analysis. Of the remaining 580 children, 339 (58.4%) were boys. The mean patient age was 14.1 ± 5.1 months (median, 14.0 months; range, 2-24 months). Most children were 6 months or older (96.9%). The mean temperature was $39.9^\circ\text{C} \pm 0.8^\circ\text{C}$, and 524 patients (90.3%) had a temperature of 39.0°C or higher at initial evaluation. Thirty-eight patients (6.6%) reported the use of oral antibiotics before initial ED evaluation. Concurrent acute otitis media was diagnosed during the initial ED visit in 169 children with pneumonia (29.1%). After being diagnosed as having pneumonia, 571 (98.4%) of the 580 children were documented to have been prescribed antibiotics.

The prevalence of bacteremia was 1.6% (95% CI, 0.7%-2.9%); *S pneumoniae* was the causative organism in all 9 cases. The serotype was available for 8 of 9 cases (Table). Six (75%) of 8 cases of *S pneumoniae* bacteremia were caused by serotypes included in the current heptavalent pneumococcal conjugate vaccine, which was not available at the time of this study. All *S pneumoniae* isolates were sensitive to penicillin exposure. The rate of contamination was 1.9% (95% CI, 1.0%-3.4%). Cultures with pathogenic bacteria became positive in less time (13.9 ± 1.3 hours) than contaminated cultures (21.2 ± 6.1 hours; $P = .01$).

The mean temperature was higher in patients with bacteremia ($40.4^\circ\text{C} \pm 0.4^\circ\text{C}$) than in those with negative or contaminated cultures ($39.9^\circ\text{C} \pm 0.8^\circ\text{C}$; $P = .048$). Oral antibiotics were reportedly administered before the ED visit more frequently in patients who were later identified to have bacteremia (22.2%) than in those with negative or contaminated cultures (6.3%), but this difference did not reach statistical significance (relative risk, 0.96; 95% CI, 0.89-1.04). A complete blood cell count was obtained in 30.1% of patients. There was no statistically significant difference in white blood cell

Characteristics of Patients With Pneumonia and *Streptococcus pneumoniae* Bacteremia

Patient No./ Age, mo/Sex	Pretreatment With Antibiotics	Additional Diagnoses	<i>S pneumoniae</i> Serotype	Penicillin MIC, μg/mL	Time to Growth, h
1/10/M	No	Otitis media	6A*	<0.12	12.3
2/11/M	No	Otitis media	6A*	0.03	15.7
3/5/F	No	Otitis media	9V	0.05	15.5
4/10/M	No	Otitis media	14	NA	13.8
5/9/M	Yes	None	14	≤0.03	12.2
6/16/M	Yes	None	14	≤0.03	15.2
7/14/F	No	Otitis media	14	≤0.03	14.2
8/16/F	No	Otitis media	19F	NA	12.5
9†/13/F	No	Otitis media	NA	≤0.03	13.8

Abbreviations: MIC, minimum inhibitory concentration; NA, not available.

*This serotype is not included in the current heptavalent pneumococcal conjugate vaccine.

†A coagulase-negative staphylococcal species was isolated from the repeated blood culture performed on reevaluation.

counts between patients who were later identified as having bacteremia ($24100 \pm 5800 \times 10^3/\mu\text{L}$) and those with negative or contaminated cultures ($19800 \pm 9000 \times 10^3/\mu\text{L}$; $P = .32$). There were no statistically significant differences in age or sex between patients who were later identified as having bacteremia and those with negative or contaminated cultures. Two patients with bacteremia (patients 5 and 6) received amoxicillin before the ED visit. The *S pneumoniae* blood culture isolates from both of these patients were sensitive to penicillin exposure.

When children who had received antibiotics before their initial ED evaluation were excluded from analysis, the prevalence of bacteremia was 1.3% (95% CI, 0.5%-2.6%). The rate of contamination was 2.0% (95% CI, 1.0%-3.6%). There was no longer a difference in mean temperature between patients with bacteremia ($40.3^\circ\text{C} \pm 0.5^\circ\text{C}$) and those with negative or contaminated cultures ($40.0^\circ\text{C} \pm 0.8^\circ\text{C}$; $P = .11$). There were still no statistically significant differences in mean white blood cell count, age, or sex between patients with bacteremia and those with negative or contaminated cultures.

All 9 patients with pathogenic bacteria isolated from blood cultures had documented follow-up in the ED. Repeated blood cultures were performed on reevaluation in 8 of the 9 patients with bacteremia. All the cultures were negative for pathogenic bacteria; a coagulase-negative staphylococcal species was isolated from one repeated blood culture. No other studies were performed in those patients. All 9 patients with bacteremia were prescribed antibiotics after their initial evaluation. This regimen was not changed on reevaluation. Although no patient with bacteremia ultimately required hospital admission, 5 (45%) of 11 patients with contaminated cultures were admitted after reevaluation. Three patients were admitted to the hospital for treatment of dehydration, and 2 patients were admitted owing to worsening respiratory distress. Blood cultures were repeated in all 5 of these patients and were negative. One of these patients was toxic appearing and underwent lumbar puncture when reevaluated. The results of the lumbar puncture were unremarkable. None of the patients were diagnosed as having meningitis.

COMMENT

This study updates the risk of bacteremia associated with pneumonia in the post-*H influenzae* vaccine era by documenting the current low prevalence of bacteremia in children treated as outpatients. We excluded children who required hospitalization after initial evaluation and those with a specific underlying condition (eg, sickle cell disease or an indwelling central catheter) that predisposed them to bacteremia.

The efficacy of the current heptavalent pneumococcal conjugate vaccine against invasive disease caused by vaccine serotypes is 97.4% (95% CI, 82.7%-99.9%).⁹ In the present study, all 9 cases of bacteremia were caused by *S pneumoniae*, and 6 of these were caused by serotypes included in the current heptavalent pneumococcal conjugate vaccine, which was not available at the time of this study. Two of the remaining cases were caused by serotype 6A, which is thought to be cross-reactive with vaccine serotype 6B.¹⁰ Widespread use of the pneumococcal conjugate vaccine may decrease the rate of bacteremia associated with pneumonia in young children treated as outpatients.

Hickey and colleagues¹¹ noted bacteremia in 2.7% of children with pneumonia. However, children up to 21 years of age, a population at low risk for bacteremia, were included in that analysis. Other studies^{2-5,12-14} of childhood pneumonia were conducted before introduction of the *H influenzae* type b vaccine and included patients requiring hospitalization after initial evaluation. The prevalence of bacteremia in this study, although lower than that reported in most other studies of children with pneumonia, is similar to that in recent studies of the prevalence of occult bacteremia by Alpern et al⁸ (1.9%; 95% CI, 1.5%-2.3%) and Lee and Harper¹⁵ (1.6%; 95% CI, 1.3%-1.8%).

In this study, the difference in mean temperature between patients with bacteremia and those with negative or contaminated cultures, although statistically significant, is probably not clinically important. Teele and colleagues⁴ found that the risk of bacteremia in children with pneumonia was even higher if the white blood cell count was elevated. In their study⁴ of 100 children with pneumonia, the prevalence of bacteremia was 15% in children

What This Study Adds

Before introduction of the *H influenzae* type b vaccine, the risk of bacteremia in children with pneumonia was reported to be as high as 9.6%. These studies included children treated as outpatients and those requiring hospitalization representing a wide age distribution. Since introduction of the *H influenzae* type b vaccine, few data have become available regarding the risk of bacteremia with pneumonia in young children.

The data in this study indicate that children aged 2 to 24 months with pneumonia who are well enough to be treated as outpatients are at low risk of bacteremia. Because most cases of bacteremia in this study were due to pneumococcal serotypes included in the currently licensed heptavalent pneumococcal conjugate vaccine, widespread use of the vaccine may further decrease the incidence of bacteremia in this population.

with white blood cell counts of $15000 \times 10^3/\mu\text{L}$ or higher and 5% in children with white blood cell counts less than $15000 \times 10^3/\mu\text{L}$. In our study, the low rate of bacteremia precluded meaningful dichotomous analysis of white blood cell counts between patients with bacteremia and those with negative or contaminated cultures.

This study has several limitations. Approximately 7% of children received antibiotics before ED evaluation, an intervention that may have lowered the risk of bacteremia. Also, children with pneumonia of viral etiology may have been included. These limitations would cause us to underestimate the overall risk of bacteremia in children with pneumonia. However, there was no difference in receipt of oral antibiotics between children with bacteremia and those with negative or contaminated cultures. Furthermore, the risk of bacteremia was unchanged when children who had received antibiotics before the initial evaluation were excluded from analysis. Because our study was a retrospective evaluation of a cohort of patients with pneumonia evaluated by blood culture, we expect that physicians obtained blood cultures from children they considered at highest risk for bacteremia. This may have resulted in overestimation of the prevalence of bacteremia in children with pneumonia but most closely estimates clinical practice. Owing to the retrospective nature of this study, we could not identify the total number of febrile patients evaluated in the ED during the study to evaluate the rate of diagnosis of pneumonia. Also, children with pneumonia from whom a blood culture was not obtained were not included in this study. It is difficult to determine in which direction these factors would have biased the estimate of bacteremia presented.

Some researchers have expressed concern that the decrease in invasive pneumococcal infection caused by the heptavalent conjugate vaccine may only be temporary. Serotypes contained in the vaccine may undergo capsular transformation into other serotypes that can cause disease.¹⁶ Serotype replacement by nonvaccine serotypes has been demonstrated in the middle ear and nasopharynx in children receiving the pneumococcal vaccines.^{17,18} No increase in invasive infection, including

pneumonia, due to vaccine serotypes has been demonstrated thus far.¹⁹

Detection of bacteremia and prevention of serious complications are important goals in the evaluation of young children with pneumonia. The data in this study indicate that children 2 to 24 months of age with pneumonia who are well enough to be treated as outpatients are at low risk for bacteremia. Because most cases of bacteremia in this study were due to pneumococcal serotypes included in the currently licensed heptavalent pneumococcal conjugate vaccine, widespread use of the vaccine may further decrease the incidence of bacteremia in this population.

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