Pneumococcal Bacteremia in Febrile Infants Presenting to the Emergency Department Before and After the Introduction of the Heptavalent Pneumococcal Vaccine

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Study objective: Fever is among the most common presenting complaints of infants and children younger than 3 years who present to the emergency department (ED). The evaluation and management of the febrile child is evolving rapidly. We compare the proportion of pneumococcal bacteremia between febrile infants and children younger than 3 years who had and had not received the heptavalent pneumococcal vaccine and who had received blood culture tests in our ED.

Methods: We performed a nonconcurrent prospective observational cohort study, with a standardized medical record review to collect data of patients treated in the ED of a tertiary care military hospital during 24 months. Patients were eligible if they were younger than 36 months and had a temperature greater than or equal to 100.4°F (38°C). A data collection sheet was used to abstract age, temperature, and whether CBC count and blood cultures were obtained. Heptavalent pneumococcal vaccine status and blood culture results were obtained through review of the computerized medical record. Descriptive analysis was used for comparing the 2 groups. Group size analysis was based on the prevalence of occult bacteremia caused by *Pneumococcus* before the introduction of heptavalent pneumococcal vaccine. Interobserver variation was assessed by independent review of 10% of abstracted records. The main outcome measure was the proportion of positive pneumococcal blood cultures in infants and children younger than 3 years who had received at least 1 vaccination of heptavalent pneumococcal vaccine versus those who had not.

Results: Three thousand five hundred seventy-one patients met entry criteria; 1,428 had blood cultures obtained, and 833 of them received at least 1 immunization of heptavalent pneumococcal vaccine. All groups were similar in age, sex, and temperature. Positive blood culture results, including probable contaminants, were obtained for 4.2% (58/1,383) of the patients. In the heptavalent pneumococcal vaccine group, there were 0 of 833 (0%) positive pneumococcal blood cultures compared with 13 of 550 (2.4%) in the unimmunized group ($P<.001$; 95% confidence interval 1.4% to 3.3%).

Conclusion: Pneumococcal bacteremia was found to be lower in our patients who had received the heptavalent pneumococcal vaccine than in the patients who had not. [Ann Emerg Med. 2007;49: 772-777.]

0196-0644/$-see front matter

doi:10.1016/j.annemergmed.2006.10.026

INTRODUCTION

Background

Fever is among the most common presenting complaints of infants and children younger than 3 years who present to the emergency department (ED).[1,2] The evaluation and treatment of the febrile child is changing rapidly as a result of the amount of research conducted, the introduction of *Haemophilus influenzae* type b and *Streptococcus pneumoniae* (heptavalent pneumococcal vaccine) vaccines, and ever-evolving diagnostic technologies and therapies. Heptavalent pneumococcal vaccine

Editor's Capsule Summary

What is already known on this topic

The introduction of the heptavalent pneumococcal vaccine has reduced the incidence of invasive pneumococcal disease, but the effects on emergency practice are not fully elucidated.

What question this study addressed

The authors compared the occurrence of bacteremia among children younger than 36 months who had and had not received heptavalent pneumococcal vaccine.

What this study adds to our knowledge

None of 833 vaccinated children compared with 13 of 550 (2.4%) unvaccinated children had pneumococcal bacteremia. The heptavalent pneumococcal vaccine appears to be associated with significant reductions in the prevalence of pneumococcal bacteremia.

How this might change clinical practice

We need to reexamine the merits of strategies that recommend searching for occult pneumococcal bacteremia in well-appearing febrile children.

is usually administered at 2, 4, 6, and 12 to 15 months of age. Heptavalent pneumococcal vaccine became available in early 2000, and widespread use in our institution was established by late 2001. The full extent of the impact of these ongoing changes is not yet known.[3-5]

Importance

Fifty percent of pediatric ED visits are for infants and children younger than 36 months, and of these visits, 15% to 25% are for evaluation of fever.[6] Twenty percent of these patients presenting for medical evaluation because of a fever have no identifiable source for their infection or a self-limited viral infection.[2,6,7] Furthermore, up to 3% of well-appearing infants and children younger than 3 years have identifiable bacteria when their blood is cultured.[2,8,9] After the implementation of the *H influenzae* type b vaccine, more than 90% of the bacteria isolated in the blood of these patients was *Pneumococcus*.[5,9,10] Recently, a heptavalent pneumococcal vaccine has become available to cover the most common serotypes of the bacteria and in initial studies has been found to be at least 90% efficacious in preventing associated invasive infections.[7,11-14]

Goals of This Investigation

The purpose of this study was to compare the prevalence of pneumococcal bacteremia between febrile infants and children younger than 3 years who had and had not received the heptavalent pneumococcal vaccine and who had received blood culture tests in our ED. We conducted a nonconcurrent prospective observational cohort study, using standardized medical record review to collect data, of patients presenting to our ED from November 2000 to October 2002. This period included patients who had received heptavalent pneumococcal vaccine and those who had not. Our hypothesis was that those patients who had received heptavalent pneumococcal vaccine would have fewer blood cultures positive for *Pneumococcus* compared with those who had not received the vaccine.

MATERIALS AND METHODS

Study Design

We performed a nonconcurrent prospective observational cohort study, using a standardized medical record review to collect data of all patients treated in the ED during a 24-month period from November 2000 through October 2002. Institutional review board approval was obtained.

Setting

Our ED, a tertiary care military hospital, experiences an average of 55,000 patient visits annually; 27% of the patients are children.

Selection of Participants

Patients were screened if they were younger than 36 months and had a temperature greater than or equal to 100.4°F at home or in the ED. Temperature was recorded rectally in all patients reporting to the ED; however, any report of temperature at home of 100.4°F (38°C) or greater by any method was also considered acceptable. All patients who met these inclusion criteria were included, regardless of disposition. Patients were excluded if they did not receive blood tests for cultures during their evaluation or if their vaccine status was unknown. Patients were identified by reviewing all written emergency treatment records of patients 3 years or younger who presented to the ED and had a fever at home or in the ED. Electronic medical records were reviewed for further laboratory data and immunization status.

Methods of Measurement

Reviewers received formal training in medical record review methods, but there was no external monitoring of the performance of the reviewers. Abstracted data were defined by the reviewers before the study. Medical records were screened, and the following were abstracted onto an explicit data collection sheet: age, temperature in the ED, and whether blood cultures were obtained during the ED evaluation. Heptavalent pneumococcal vaccine immunization status and blood culture results were obtained through review of the computerized medical record. The reviewers were not blinded to the study objectives; however, heptavalent pneumococcal vaccine immunization status and blood culture results were obtained independently of data derived from review of the medical records to limit subjective bias. A coinvestigator reviewed 10% of the records to determine interobserver variation (κ) with all 3

of the abstracted data points (age, temperature, and whether blood cultures were obtained).

Patients who had blood drawn for cultures were divided into 2 groups: those who had received at least 1 heptavalent pneumococcal vaccine vaccination and those who had not. A positive blood-culture result was defined as any pathogen that grew out and was reported positive by our laboratory. The Bactec Peds Plus/F culture vials and system (Becton Dickinson Diagnostic Instrument Systems, Sparks, MD) are used in our institution. If the culture was positive, the bacterium was grown on medium for identification. Positive cultures were divided into 3 groups: *Pneumococcus*, other pathogens, and probable contaminants.[14-16]

For both groups that had blood drawn for cultures, a single reviewer further reviewed the discharge diagnosis, disposition, and whether antibiotics were given. The diagnoses were divided into 6 categories: fever, upper respiratory infection (URI), acute gastroenteritis, otitis media, urinary tract infection (UTI), and pneumonia.

Primary Data Analysis

Descriptive analysis was used for comparing 2 groups of febrile infants and children younger than 3 years: those who had received heptavalent pneumococcal vaccine and those who had not. Group size analysis was based on the prevalence of occult bacteremia caused by *Pneumococcus* before the introduction of heptavalent pneumococcal vaccine in febrile infants and children younger than 3 years (estimated to be 4.0% [95% confidence interval [CI] 1.9% to 7.1%]).[6,12-15] Given a hypothesized vaccine effectiveness rate of 90%, we estimated that with a power of 90% and an α of 0.05, we would need approximately 500 patients in each arm of the study to validate this.

The Stata 7.0 (StataCorp, College Station, TX) statistical package was used for data entry and analysis. Fisher's test and χ^2 analysis was used for binomial outcomes; $P<.05$ was taken for significance.

RESULTS

Three thousand five hundred seventy-one patients met inclusion criteria. Of these, 9 were not included, because of errors in abstracting patient identification. Of the remaining 3,562, 1,428 had blood cultures obtained as part of their ED evaluation. Immunization records were unavailable for 45 of these patients, resulting in 1,383 patients who were further evaluated (Figure). These patients were divided into 2 groups: immunized (833 patients) versus nonimmunized (550 patients), with the immunized groups representing patients who had received at least 1 heptavalent pneumococcal vaccine vaccination. Within this group of immunized patients, the average age was 11 months (SD±0.5 months), and 61% of these patients were younger than 6 months. The unimmunized group had an average age of 10 months (SD±0.5 months), and 54% of these patients were younger than 6 months. Demographics for both groups are listed in Table 1.

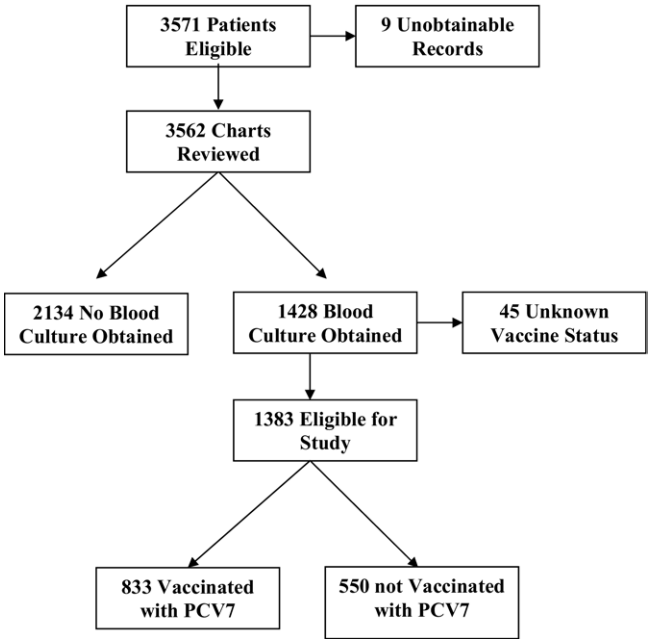

Figure. Patient enrollment.

Table 1. Patient demographics.

Patient demographics	Immunized (n=833)	Unimmunized (n=550)
Sex, male (%)	425 (51)	286 (52)
Age, median (25^{th}/75^{th} IQR)	12 (6/19)	11 (7/22)
Age range (%, 95% CI)		
0–28 days	0 (0, 0–0.5)	22 (4.0, 2.7–6.0)
29–90 days	50 (6.0, 4.6–7.8)	45 (8.2, 6.2–10.8)
3–36 mo	783 (94, 92.2–95.4)	483 (87.8, 84.8–90.3)
Temperature, median (25^{th}/75^{th} IQR)	101.9°F (38°C) [100.9°F (38.3°C)/ 102.9°F (39.4°C)]	102.3°F (39.1°C [100.8°F (38.2°C/ 102.9°F (39.4°C)]
PCV7 received, No. (%, 95% CI)		
1	400 (48.0, 44.6–51.4)	
2	217 (26.1, 23.2–29.1)	
3	100 (12.0, 10.0–14.4)	
4	116 (13.9, 11.7–16.4)	
Positive culture results (%, 95% CI)		
All organisms	17 (2.0, 1.3–3.2)	41 (7.5, 5.5–10.0)
S pneumoniae	0 (0, 0–0.5)	13 (2.4, 1.4–4.2)

IQR, Interquartile range; *PCV7,* heptavalent pneumococcal vaccine.

The κ value for the temperature value was 0.99 (95% CI 0.98 to 1.00). The κ value for the age value was 0.99 (95% CI 0.98 to 1.0). The κ value for whether or not blood cultures were obtained was 1.0.

Two thousand one hundred thirty-four patients in our cohort were not eligible, because no blood culture was obtained.

This group was older, with a mean age of 26 months (SD±1.4) and presented with a lower temperature of 101.4°F (SD±0.4) [38.6°C (SD ± 0.2)].

Positive blood cultures were found in 4.2% of infants and children entered into the study (58/1,383). Pneumococcal bacteremia was detected in 0 of 833 (0%) patients who had received at least 1 heptavalent pneumococcal vaccine compared with 13 of 550 (2.4%) patients who had not ($P<.001$; 95% CI 1.4% to 3.3%). The only other pathogen that yielded positive blood cultures in the heptavalent pneumococcal vaccine group was *Enterococcus* (2/17). The following were considered contaminants: coagulase-negative *Staphylococcus* (11/17), α-*Streptococcus* (2/17), γ-*Streptococcus* (1/17), and *S milleri* (1/17). In the unimmunized group, there were no other pathogens that yielded positive blood cultures. The following were considered contaminants: coagulase-negative *Staphylococcus* (17/41), α-*Streptococcus* (2/41), *Acinetobacter* (2/41), *Staphylococcus aureus* (2/41), *S milleri* (1/41), *Neisseria mucosa* (1/41), *Propionibacter* (1/41), *Bacillus* sp. (1/41), and diphtheroids (1/41), which is consistent with other recently published data (Table 2).[14,15]

The immunized group of patients had the following diagnoses recorded on the emergency treatment record: fever (57.7%), URI (14.2%), acute gastroenteritis (9.8%), UTI (5.0%), and pneumonia (6.8%). These patients were given intravenous or intramuscular antibiotics at 38.4%. The admission rate for this group of patients was 2.6%, and all were aged 3 to 36 months. Refer to Table 3 for diagnoses in patients with positive cultures.

The unimmunized group had the following diagnoses recorded on the emergency treatment record: fever (53.1%), URI (16.0%), acute gastroenteritis (10.5%), otitis media (11.1%), UTI (4.2%), and pneumonia (5.1%). Intravenous or intramuscular antibiotics were given at 34.0%. The admission rate for this group was 6.9%, which included neonates (4.0%) and children aged 3 to 36 months (2.9%). Refer to Table 3 for diagnoses in those patients with positive cultures.

Table 2. Positive culture result details.

Positive Culture Results	Immunized	Unimmunized
S pneumoniae		
0–28 days	0	0
29–90 days	0	5
3–36 mo	0	8
Other likely pathogens		
0–28 days	0	0
29–90 days	1	0
3–36 mo	1	0
Probable contaminants		
0–28 days	1	2
29–90 days	3	5
3–36 mo	11	21

Table 3. Final diagnoses in patients with positive culture results.

Positive Culture Results	Immunized	Unimmunized
S pneumoniae		
0–28 days	0	0
29–90 days	0	Bacteremia (2/5)
		Pneumonia (3/5)
3–36 mo	0	Bacteremia (3/8)
		Pneumonia (4/8)
		Otitismedia (1/8)
Other likely pathogens		
0–28 days	0	0
29–90 days	UTI (1/1)	0
3–36 mo	UTI (1/1)	0
Probable contaminants		
0–28 days	Fever (1/1)	Fever (2/2)
29–90 days	Fever (3/3)	Fever (4/5)
		UTI (1/5)
3–36 mo	UTI (2/11)	UTI (5/21)
	Pneumonia (2/11)	Pneumonia (4/21)
	Otitis media (3/11)	Otitis media (6/21)
	URI (3/11)	URI (4/21)
	AGE (1/11)	AGE (2/21)

AGE, Acute gastroenteritis.

LIMITATIONS

Limitations to our study include the expected errors associated with medical record review. However, recommended strategies were used.[17] Errors that were unavoidable included incomplete medical records, reliance on electronic records, and the movement of military families.

Our main objective was to review blood culture results. We hoped to include all patients with fever regardless of final diagnosis or presenting complaint. Clinical outcome was not obtained on our patients, and we were unable to obtain follow-up information. The lack of follow-up data caused us to be blind to the fact that patients who did not have blood cultures obtained in the ED could have had a bacterial disease, even bacteremia, at their first ED visit. We also could not discover whether the patients had recently finished a course of antibiotics. We did not expect, however, that clinicians would have prescribed antibiotics at a higher rate to patients who had not received heptavalent pneumococcal vaccine, especially because they would have been treated before the use of heptavalent pneumococcal vaccine in our institution. Additionally, if clinicians were to prescribe antibiotics to unimmunized patients more frequently, it would tend to reduce the size of differences in the number of pathogens between the groups.

At the time of the study, most ED physicians at our hospital followed previous guidelines, as recommended by Baraff et al,[8] which included blood cultures. The results of these cultures, if positive, often demanded further intervention. It was our intention to study the results of these cultures once heptavalent pneumococcal vaccine was introduced.

During the study, the decision whether to obtain blood cultures on all febrile children between 3 and 36 months of age was in flux and led to the exclusion of 60% of eligible patients. Examining the excluded group, we found that they represented

older children with lower presenting temperatures, which may have put them at lower risk for occult bacteremia.

As expected in retrospective record review, some patients were lost because of unforeseen problems in data collection. Further, the vaccination status was unknown for a small percentage of patients (3.1%). However, the military health care system allowed for excellent data collection and examination of immunization status in our subjects.

Additionally, we could not differentiate the occult bacteremia cases from the toxic-appearing child. Missing information from the medical record could have misclassified cases and may underestimate the true prevalence of vaccinated children in the cohort.

Of course, we understand that positive blood cultures may not equal occult bacteremia or sepsis. However, we were studying the results of a specific vaccine, heptavalent pneumococcal vaccine, and found that in our cohort it effectively eradicated positive pneumococcal blood cultures in patients who had received at least 1 vaccination.

DISCUSSION

The evaluation of febrile infants continues to evolve. Bacteremia rates are now much lower in febrile infants and children, placing well-appearing patients who have been found to have fever without a source at a lower risk of occult bacteremia.[7,12-15] It has been previously reported that 2 vaccinations may be protective.[18] Our limited retrospective review provides some evidence that febrile children aged 3 to 36 months who have received at least 1 heptavalent pneumococcal vaccine may be protected from pneumococcal bacteremia.

The currently licensed vaccine (Prevnar; Wyeth Pharmaceuticals, Philadelphia, PA) is active against only 7 of the 90 serotypes of *S pneumoniae*, but according to previous studies it has dramatically reduced the risk of invasive disease resulting from *S pneumoniae* in young children by 90%.[12] Furthermore, other authors have stated that infants younger than 6 months who have not received at least 3 doses of heptavalent pneumococcal vaccine may have incomplete immunity and warrant a more complete evaluation.[19-21] Widespread use of heptavalent pneumococcal vaccine, along with the other routine childhood vaccines, may prevent disease by providing direct and indirect immunity, as well as reduce the use of antibiotics.[5,13,16,22] Current recommendations in the evaluation of well-appearing febrile infants and children aged 3 to 36 months who have received at least 2 in the series of 4 of both *H influenzae* type b and heptavalent pneumococcal vaccine need to include urinalysis.[3]

Our study suggests that heptavalent pneumococcal vaccine is protective against pneumococcal bacteremia and may change the approach to the evaluation of well-appearing febrile infants and children aged between 3 and 36 months. In fact, in our limited study, we found no cases of pneumococcal bacteremia in our study group of febrile infants and children younger than 3 years who received heptavalent pneumococcal vaccine, which is in comparison with a similar group of febrile infants and children who had not received heptavalent pneumococcal vaccine, in which 2.4% of blood cultures obtained were positive for *Pneumococcus*.

Similar to other recent literature, our study confirmed a decrease in the amount of pneumococcal bacteremia detected in well-appearing febrile children who had received the heptavalent pneumococcal vaccine vaccine.[13-15] Strengths of our study included that we were able to confirm the immunization status in our study patients. In addition, because of the timing of introduction of heptavalent pneumococcal vaccine in 2000, coupled with initial vaccine shortages, we were able to define large comparable groups of infants and children younger than 3 years who had and had not received the vaccine because this group was evaluated in our ED before the introduction of heptavalent pneumococcal vaccine.

As expected, the proportion of positive cultures of other likely pathogens and contaminants did not differ between vaccinated and unvaccinated groups. However, what is considered a pathogen versus a nonpathogen or contaminant should be a clinical decision, as previously suggested by other authors.[14]

We conclude that, among children younger than 36 months who had fever and received blood cultures, the proportion positive for *S pneumoniae* (0) was lower among those who received the heptavalent pneumococcal vaccine than those who did not.

Supervising editor: David M. Jaffe, MD

Author contributions: KLC, DAT, and ASJ conceived and designed the study and obtained research approval. KLC and DAT supervised the conduct of the trial and data collection. KLC, DAT, and SBK performed data collection. ASJ and RHR provided statistical advice on study design and analyzed the data. KLC drafted the article, and all authors contributed substantially to its revision. KLC takes responsibility for the paper as a whole.

Funding and support: This study was supported by the Clinical Investigations Department of Naval Medical Center San Diego, CA. The study received no outside funding or support.

The views expressed in this article are those of the authors and do not reflect the official policy or position of the Department of the Navy, Department of Defense, or the United States government.

Publication dates: Received for publication January 12, 2006. Revisions received March 25, 2006, and September 22, 2006. Accepted for publication October 31, 2006. Available online March 6, 2007.

Presented at the Society for Academic Emergency Medicine annual meeting, May 2004, Orlando, FL.

Reprints not available from the authors.

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IMAGES IN EMERGENCY MEDICINE

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DIAGNOSIS:

Boerhaave's syndrome (spontaneous esophageal rupture). The majority of transmural esophageal tears are iatrogenic, with Boerhaave's syndrome accounting for only 15% of all cases. It is commonly seen in middle-aged men with excessive dietary or alcoholic intake and typically occurs after forceful emesis. The Mackler triad defines the classic presentation of vomiting, lower thoracic pain, and subcutaneous emphysema. Chest auscultation may reveal signs of pleural effusion or the Hamon's crunch (a crackling sound caused by pneumomediastinum).[1] Erect chest radiograph may show a unilateral effusion, pneumothorax, hydropneumothorax, pneumomediastinum, subcutaneous emphysema, or mediastinal widening. The V-sign of Naclerio is caused by air dissecting the fascial planes behind the heart to form the shape of the letter V. Treatment is with broad-spectrum antibiotics, intravenous fluid resuscitation, and urgent primary surgical repair. Overall mortality is 35%, making it the most lethal gastrointestinal perforation. Diagnosis and surgery within 24 hours carry a 75% survival rate, decreasing to 50% after 24 hours and 10% after 48 hours. A high index of suspicion and familiarity with the clinical and radiologic features are vital if this relatively rare cause of chest pain is to be diagnosed correctly.

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