Prevalence of Occult Bacteremia in Children Aged 3 to 36 Months Presenting to the Emergency Department with Fever in the Postpneumococcal Conjugate Vaccine Era

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Abstract

Objectives: The goal of this study was to identify the prevalence of occult bacteremia (OB) in well-appearing, previously healthy children aged 3 to 36 months who present to the emergency department (ED) with fever without source in the post–pneumococcal conjugate vaccine (PCV) era.

Methods: This was a retrospective cohort study of children presenting to an urban pediatric ED between July 1, 2004, and June 30, 2007. Children were included if they were aged 3 to 36 months, febrile, and previously healthy; had no source of infection on examination; had a blood culture drawn; and were discharged from the ED. Outcome measures were rates of OB and contaminant rates.

Results: A total of 8,408 children met all inclusion criteria. There were 21 true-positives, yielding an OB rate of 0.25% (95% confidence interval [CI] = 0.16% to 0.37%). There were 159 contaminant cultures yielding a contaminant rate of 1.89% (95% CI = 1.61% to 2.19%), or a ratio of 7.6 contaminants for each true-positive. There were 14 included patients who grew *Streptococcus pneumoniae* from the blood, for a rate of 0.17% (95% CI = 0.09% to 0.27%).

Conclusions: Given the current rate of OB in the post-PCV era, it may no longer be cost-effective to send blood cultures on well-appearing, previously healthy children aged 3 to 36 months who have fever without source.

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The evaluation of well-appearing febrile children has been an area of intense research and debate for decades. A subset of these patients, 3- to 36-month-old children presenting to an outpatient setting with fever without a source (FWS), has been the subject of increased scrutiny over the past few years as the introduction of the pneumococcal conjugate vaccine (PCV) has led to a dramatic decrease in the prevalence of occult pneumococcal bacteremia. Guidelines published as far back as 2000 had recommended eliminating the workup for occult bacteremia (OB) once an effective pneumococcal vaccine had been widely utilized.[1] Authorities have also suggested that the evaluation for OB would no longer be necessary should the overall disease prevalence fall below 1%.[1,2] A cost-effectiveness analysis published in 2001 concluded that no workup would be the most cost-effective approach to febrile 3- to 36-month children once the OB rate fell below 0.5%.[3] Several studies published using post-PCV data have suggested that the prevalence of pneumococcal bacteremia in well-appearing febrile children aged 3 to 36 months is currently in the range of 0.24% to 0.91% and that overall OB prevalence in the same group is in the range of 0.65% to 0.91%.[4–7] Yet, despite published guidelines, expert opinion, and published post-PCV immunization rates, studies have shown that a large proportion of pediatric providers in ambulatory centers continue to evaluate these children for OB by utilizing blood cultures.[4–8] Possible reasons for this include a lack of a clear post-PCV fever guideline, worries about legal repercussions from missed OB, and concerns about the sample sizes and

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study design of the aforementioned studies, leading to an inaccurate estimate of OB rates in febrile children.

The goal of this study was to identify the prevalence of OB in well-appearing, previously healthy children aged 3 to 36 months who present to the emergency department (ED) with fever in the post-PCV era. It was hoped that these data would augment recent studies that have demonstrated a steady decline in the rate of OB and add evidence that these findings are geographically robust. In addition, because the PCV is administered in divided doses, we also wanted to determine if there was a different prevalence rate based on age.

METHODS

Study Design

This was a retrospective cohort study. The protocol was approved by the institutional review board at Phoenix Children's Hospital, and a waiver of informed consent was obtained.

Study Setting and Population

This study involved a large, urban, free-standing children's hospital. It is a tertiary care center with approximately 55,000 ED visits per year. The primary data source was the ED billing database, which includes all patient demographics, discharge diagnoses, and billable procedures. This electronic database is hospital-based and patients can be identified by location of presentation. During the study period it was still standard practice at this institution to send blood cultures on well-appearing, 3- to 36-month-old children presenting to the ED with a temperature ≥39°C and no recognized source on physical exam. The initial database search included all children aged 3 months (90 days) to 36 months who presented to the ED between July 1, 2004, and June 30, 2007, and met both of the following criteria: had a blood culture obtained in the ED and had a diagnosis (primary or otherwise) of ''pyrexia'' (this is the coded diagnosis for children with FWS at this institution). Patients were then excluded if they were admitted to the hospital (assumed not well-appearing) or if their diagnosis list contained any of the following: indwelling venous catheter, any identifiable bacterial source of infection (except acute otitis media), croup, stomatitis, herpangina, varicella, or any chronic disease that may predispose to infection (e.g., cancer, immunodeficiency), but not including asthma. In addition, any child with an indwelling foley catheter or suprapubic catheter was excluded.

It is standard practice at our hospital ED to send a single aerobic blood culture on febrile children undergoing evaluation for OB. Pediatric culture bottles require 1 to 5 mL of blood. Blood cultures are continuously monitored using the BacTec 920 machine (Becton Dickinson, Franklin Lakes, NJ). Positive culture bottles are identified and further subcultured. Blood is routinely obtained by ED nurses or ED technicians.

Study Protocol

The laboratory database was searched to determine the final blood culture results for each included patient. For all cultures where growth occurred, the name of the organism was recorded. A member of the pediatric infectious disease (ID) department then reviewed all positive blood cultures. Each organism was labeled as ''true pathogen,'' ''contaminant,'' or ''more information needed.'' Organisms generally not considered pathogens in healthy individuals (e.g., coagulase-negative *Staphylococcus aureus*) were labeled as contaminants. Those which are always considered pathogenic when isolated from a venipuncture (e.g., *Streptococcus pneumoniae*) were labeled as pathogens. Those organisms that may be considered true pathogens, depending on the clinical scenario (e.g., *Morexalla catarrhalis*), were labeled as ''more information needed.'' The chart of each patient whose blood grew an organism labeled ''more information needed'' was then reviewed by the pediatric ID subspecialist to make a final determination of ''true pathogen'' or ''contaminant.'' The charts of all patients with a final ''true pathogen'' label were then reviewed to determine if they actually represented occult infection. Children who were determined, based on chart review, to have an excludable diagnosis or who were determined to not be well-appearing on initial exam, were excluded from the final OB calculation. Not well-appearing on initial exam, while a vague term, was defined a priori as any of the following terminology found on physical exam documentation: ill-appearing, unwell, lethargic, less responsive, or toxic. These terms may be construed by different observers as meaning different things, but overall they send a message that the child was not well-appearing.

Data Analysis

Data were entered into the SPSS statistical software and analyzed by a trained biomedical statistician (SPSS, Chicago, IL). Descriptive statistics were used to characterize the sample. Results were reported as an overall rate of OB, rate of *S. pneumoniae* OB, contaminant rate, and OB rates by age (3 to <12 months, 12 to <24 months, and 24 to <36 months). Ninety-five percent confidence intervals (CI) for each rate were also reported. The 95% CIs were calculated using the arcsine transformation, which increases accuracy with small proportions. The p-value for comparisons among the three age groups was calculated using the chi-square test.

RESULTS

Between July 1, 2004, and June 30, 2007, a total of 10,043 children aged 3 to 36 months presented to the ED with a diagnosis of febrile illness, had a blood culture drawn, and were discharged from the ED. The ethnic background of those enrolled was 65% Hispanic, 24% white, and 11% other. Of those enrolled, 67% had public insurance, 25% had private insurance, and 8% had no insurance.

Of the 10,043 patients, 1,630 children had an excludable final diagnosis and were removed from subsequent analysis. Of the 8,413 remaining blood cultures, 185 grew an organism. Of these, 159 were determined to be contaminants (Table 1), and 26 to be true pathogens (Table 2). Two cultures required chart review by the ID specialist to determine final classification: *Neisseria* species not gonorrhea or meningitides was classified as a

Table 1
Blood Culture Contaminants

Organism	*n*
Coagulase-negative *Staphylococcus*	96
Alpha-hemolytic *Streptococcus*	15
Diphtheroids	12
Mixed flora	10
Micrococcus sp.	8
Bacillus sp.	5
Streptococcus mitis	3
Gamma-hemolytic *Streptococcus*	2
Micrococcus luteus	2
Eikenella corrodens	1
Lactobacillus sp.	1
Neisseria (not gonorrhea or meningitides)	1
Streptococcus salivarius	1
Streptococcus sanguinis	1
Streptococcus viridans	1
Total	159

Table 2
Blood Culture Pathogens

Organism	*n*
S. pneumoniae	17
H. influenzae (not Type B)	3
E. coli	2
Group A *Streptococcus*	1
M. catarrhalis	1
S. aureus	1
Salmonella Group G	1
Total	26

Table 3
Positive Blood Cultures, Contaminant Rates, and True Pathogen Rates

	Cases	*n*	Rate (%)	95% CI
Before exclusions				
Total-positive	231	10,043	2.30	2.02, 2.60
Total contaminant	192	10,043	1.91	1.66, 2.19
Total true	39	10,043	0.39	0.28, 0.52
After diagnosis exclusions				
Positive	185	8,413	2.20	1.90, 2.53
Contaminant	159	8,413	1.89	1.61, 2.19
True	26	8,413	0.31	0.20, 0.44
After chart exclusions				
Positive	180	8,408	2.14	1.85, 2.46
Contaminant	159	8,408	1.89	1.61, 2.20
True	21	8,408	0.25	0.16, 0.37
S. pneumoniae only				
Total *S. pneumoniae*	20	10,043	0.20	0.12, 0.30
After exclusions	14	8,408	0.17	0.09, 0.27

CI = confidence interval.

Table 4
OB Rates by Age Group

	Cases	*n*	Rate (%)*	95% CI
3 to <12 months	12	4,653	0.26	0.14, 0.43
12 to <24 months	5	2,993	0.17	0.06, 0.36
24 to <36 months	4	762	0.52	0.15, 1.21

CI = confidence interval; OB = occult bacteremia.
*p-Value for difference among age groups is 0.21.

contaminant, and *M. catarrhalis* was classified as a true pathogen. Of the 26 remaining true-positives, 5 more were excluded on chart review: 2 children described as ''ill-appearing,'' 1 child described as ''ill-appearing'' with a complex medical history, 1 child who was hypoxemic and diagnosed with pneumonia, and 1 child who was referred by the primary care physician for a positive blood culture. The final results after exclusions gave a total positive blood culture rate of 2.14% (95% CI = 1.85% to 2.46%), contaminant rate of 1.89% (95% CI = 1.61% to 2.20%), and a true pathogen rate of 0.25% (95% CI = 0.16% to 0.37%; Table 3). There were 7.6 contaminants for each true pathogen. There were 20 total and 14 included patients whose cultures grew *S. pneumoniae*, yielding a rate of *S. pneumoniae* OB of 0.17% (95% CI = 0.09% to 0.27%). Because the study laboratory does not serotype *S. pneumoniae*, those data were unavailable.

Because the PCV is administered in divided doses, the results were also tabulated based on smaller age categories to determine if incomplete vaccination status is a confounding factor. When broken down by age, the 3- to <12-month group had an OB rate of 0.26% (95% CI = 0.14% to 0.43%), the 12- to <24-month group had an OB rate of 0.17% (95% CI = 0.06% to 0.36%), and the 24- to <36-month group had an OB rate of 0.52% (95% CI = 0.15% to 1.21%; Table 4). There was not a significant difference among the age groups (p = 0.21).

DISCUSSION

Recently published literature has revealed that many pediatric providers continue to routinely use the complete blood count and blood culture as diagnostic tools in the evaluation of well-appearing, previously healthy children aged 3 to 36 months presenting with FWS.[4–8] As discussed previously, there are a number of reasons why this practice has continued despite increasing evidence and recommendations to the contrary.

Our results suggest that the current prevalence of OB in the 3- to 36-month age group is below 1%, probably in the range of 0.16% to 0.37%. Furthermore, the rate of *S. pneumoniae* OB appears to have fallen to the range of 0.09% to 0.27% in our community. Table 3 reveals the results in terms of all of the outpatients and then the subpopulations when we exclude certain patients that were either ''described as ill'' in the records or were found to have chronic diseases. In practice, the clinician wants to know the OB rate on patients that were sent home, so the full data set may be more instructive, as that represents the cohort of patients that clinicians felt could be managed as outpatients. In that case the rate of OB is 0.39% (95% CI = 0.28% to 0.52%). Regardless of which way you choose to look at these results, they show a continued decline in rates of OB when compared with other post-PCV prevalence studies.[4–7]

With a *S. pneumoniae* OB prevalence of 0.17%, we would need to test 588 children to detect one case. Previous studies have shown that without treatment, approximately 4% of children who are bacteremic with *S. pneumoniae*, and who do not receive antibiotics, will go on to develop meningitis.[9–11] Of the children with meningitis, the mortality rate is about 8%, and the occurrence of permanent neurologic sequelae is about 30%.[12,13] Simple calculations show that we would need to test 14,700 children to detect or prevent one case of *S. pneumoniae* meningitis, 49,000 children to prevent one neurologic sequelum, and 184,000 children to prevent one death from *S. pneumoniae* meningitis.

It is also important to consider the additional costs associated with contaminated blood cultures. With a ratio of 7.6 contaminants to each true pathogen, the direct and indirect costs associated with ED callbacks, hospital admissions, antibiotic administration, and repeat cultures must be accounted for. Previous studies have shown that these costs can be considerable.[3,14]

There were other bacterial pathogens besides *S. pneumoniae* recovered from the blood of study subjects during the FWS workup in our population. *Haemophilus influenzae* (not Type B), *Escherichia coli*, *M. catarrhalis*, Group A streptococci, salmonella, and *S. aureus* were all recovered from study patients with FWS. The natural history of OB with these organisms is not as well described as that with *S. pneumoniae*. Another recent OB study yielded other bacterial pathogens, including *Neisseria meningitides*.[5] *N. meningitides* OB is known to be much less common, but often more devastating than invasive disease caused by other organisms, including *S. pneumoniae*.[15–19]

In addition, Herz et al.[5] found that in their population of children routinely immunized with the conjugated pneumococcal vaccine, a white blood cell (WBC) count >15,000 was a poor predictor of bacteremia (sensitivity, 74.0%; specificity, 54.5%). They also noted the incidence of pneumococcal bacteremia has decreased, while *E. coli*, *Salmonella* spp., and *S. aureus* have increased in relative importance, and that they often have a WBC count in the normal range. In their population, the use of the WBC count alone to guide the empiric use of antibiotics was not indicated. While examining the WBC count was not a goal of our study, their results emphasize this test as a poor predictor and as such unnecessary in the evaluation of well-appearing febrile children with a fever and no focus.

Recent studies have suggested that nonvaccine serotypes of *S. pneumoniae* may be replacing the strains that were most prevalent in the past, both in nasal carriage and in clinical disease.[20,21] Continued surveillance is crucial to help determine the practical significance of these serotype replacements. It is not known whether the cases of OB caused by *S. pneumoniae* in this report represent serotypes included in the vaccine or not.

LIMITATIONS

The limitations of this study include those inherent to a retrospective design, such as selection bias. It is likely that a number of children aged 3 to 36 months presented to the ED with fever during the study period and did not have a blood culture drawn. One might argue that the sicker appearing children may have been more likely to have a blood culture obtained. This would likely overestimate the prevalence of OB, yielding a rate that is actually higher than the true rate. We only looked at children who had fever and a blood culture done. The real denominator is the number of well-appearing children, regardless of whether a blood culture was done. This number is unknown based on the method used to identify subjects. It is likely some children were seen with a fever ≥39°C without a focus who had no laboratory examinations performed. However, during the study period our ED routinely obtained complete blood cell counts and blood cultures in this patient population. Even if we could identify those children who had no testing, it would merely increase the denominator and further decrease the incidence of OB.

There are some scenarios that may impact the likelihood of occult infection, yet could not be determined from the method of data extraction. We were unable to exclude premature infants, children recently hospitalized, or children with recent antibiotic use. The inclusion of these patients may have decreased the accuracy of our ultimate OB calculation.

We excluded children with identifiable sources of infection, chronic disease, or unwell appearance on exam; however, the OB prevalence prior to diagnosis and chart exclusion was 0.39% (95% CI = 0.28% to 0.52%). This is still well below the value of 1% that has been identified in prior studies as the cutoff point at which it becomes impractical to perform diagnostic studies.[1,2]

This study supports prior work looking at the decline of OB post heptavalent pneumococcal conjugate vaccine (PCV7). Stoll et al.[4] enrolled 329 children and, although the overall prevalence of OB was 0.91%, two of the three cases involved a single child who was unimmmunized. Carstairs et al.[7] had a larger study, and they were able to separate out those children who were, and were not, immunized with PCV. Unfortunately, accurate immunization status cannot be reliably extracted from the ED record at our institution. Prior studies have demonstrated that parental recall, immunization cards, and the state registries were all unreliable when compared to the official primary care

Table 5
PCV Vaccine Rates by Age for Maricopa County, Arizona, and the United States

	Maricopa County, AZ	United States
3 months (1+ PCV)	78.7	77.7
5 months (2+ PCV)	69.1	66.2
7 months (3+ PCV)	49.4	46.8
13 months (3+ PCV)	74.9	76.7
19 months (3+ PCV)	84.4	84.0
24 months (3+ PCV)	86.6	85.8

PCV = pneumococcal conjugate vaccine.

record.[22–24] The results presented demonstrate the current prevalence of OB independent of immunization status. We have included vaccine data for Maricopa County, Arizona, and the United States as a whole for comparison (Table 5).[25,26] Practitioners in areas with similar vaccine coverage can probably expect a similar prevalence of *S. pneumoniae* OB.

CONCLUSIONS

Accounting for the results of this and other recent studies on the subject of OB, it is time to reconsider our approach to well-appearing, previously healthy children aged 3 to 36 months presenting to outpatient settings with FWS. Obtaining blood cultures on all of these children may no longer be prudent. It appears that the rate of OB is sufficiently low to preclude laboratory testing in favor of close follow-up. If a child is known to be unimmunized, however, it may still be wise to screen for OB as per previous, pre-PCV recommendations.

It must be stressed that these recommendations would only apply to well-appearing, previously healthy children aged 3 to 36 months presenting with FWS. They should not be applied to children who appear ill, have a history of any disease that may predispose to infection, or have a recognized source of infection on exam. In addition, the authors encourage continued research and surveillance evaluating the prevalence of nonvaccine serotypes of *S. pneumoniae* and other important causes of occult bacterial infection. Should the rates of OB change in the future, these issues would need to be readdressed.

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