Epidemiology of Bacteremia in Febrile Infants Aged 60 Days and Younger

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Study objective: To describe the current epidemiology of bacteremia in febrile infants 60 days of age and younger in the Pediatric Emergency Care Applied Research Network (PECARN).

Methods: We conducted a planned secondary analysis of a prospective observational study of febrile infants 60 days of age and younger presenting to any of 26 PECARN emergency departments (2008 to 2013) who had blood cultures obtained. We excluded infants with significant comorbidities or critically ill appearance. The primary outcome was prevalence of bacteremia.

Results: Of 7,335 screened infants, 4,778 (65.1%) had blood cultures and were enrolled. Of these patients, 84 had bacteremia (1.8%; 95% confidence interval [CI] 1.4% to 2.2%). The prevalence of bacteremia in infants aged 28 days or younger (47/1,515) was 3.1% (95% CI 2.3% to 4.1%); in infants aged 29 to 60 days (37/3,246), 1.1% (95% CI 0.8% to 1.6%). Prevalence differed by week of age for infants 28 days of age and younger (0 to 7 days: 4/156, 2.6%; 8 to 14 days: 19/356, 5.3%; 15 to 21 days: 15/449, 3.3%; and 22 to 28 days: 9/554, 1.6%). The most common pathogens were *Escherichia coli* (39.3%; 95% CI 29.5% to 50.0%) and group B streptococcus (23.8%; 95% CI 16.0% to 33.9%). Bacterial meningitis occurred in 19 of 1,515 infants 28 days of age and younger (1.3%; 95% CI 0.8% to 2.0%) and 5 of 3,246 infants aged 29 to 60 days (0.2%; 95% CI 0.1% to 0.4%). Of 84 infants with bacteremia, 36 (42.9%; 95% CI 32.8% to 53.5%) had urinary tract infections (*E coli* 83%); 11 (13.1%; 95% CI 7.5% to 21.9%) had bacterial meningitis.

Conclusion: The prevalence of bacteremia and meningitis among febrile infants 28 days of age and younger is high and exceeds that observed in infants aged 29 to 60 days. *E coli* and group B streptococcus are the most common bacterial pathogens. [Ann Emerg Med. 2018;71:211-216.]

Risque de **bactériémie** occulte (sepsis/méningite) chez enfant fébrile et sinon aspect normal:
- 0-7 jours de vie: 2,6%
- 8-14 jours de vie: 5,3%
- 15-21 jours de vie: 3.3%
- 22-28 jours de vie: 1,6%
- 29-60 jours de vie: 1.1%

Parmis ceux qui ont une bactériémie, on aura 43% d'infection urinaire, 13% d'infection de méningite.

Risque de **bactériémie** occulte (sepsis/méningite) chez enfant fébrile avec sinon un aspect normal:
- < 28 jours de vie: 1,3%
- 29-60 jours de vie: 0,2%

INTRODUCTION

Background

In young infants, fever can be the only sign of serious bacterial infections. Although higher rates have been reported in the past, current US data suggest that 2% of infants younger than 2 months and presenting with fever with no source have bacteremia, and 0.3% to 0.4% have bacterial meningitis.[1-4] This decrease from previous reports is likely a result of group B streptococcus peripartum antibiotic prophylaxis and herd immunity resulting from *Streptococcus pneumoniae* immunization.[1-6] Many febrile infants undergo comprehensive laboratory evaluations, including cultures of the blood, urine, and often cerebrospinal fluid, followed by use of empiric broad-spectrum antibiotics and inpatient hospitalization.[7]

Among infants older than 28 days, the literature reports variation in management in both emergency department (ED) and office settings. Because bacteremia and bacterial meningitis rates have decreased during the past decade, some clinicians are more selectively using laboratory testing to screen for bacterial illnesses in young febrile infants.[4-6,8] Although bacteremia and bacterial meningitis are relatively uncommon, missed diagnoses can have serious long-term sequelae. Additional up-to-date information about the prevalence and epidemiology of

†Participating centers and investigators are listed in the Appendix.

Editor's Capsule Summary

What is already known on this topic

Serious bacterial infections can be subtle in infants.

What question this study addressed

What is the probability of bacteremia in 7,335 well-appearing febrile infants aged 60 days and younger from whom blood cultures were obtained in 26 emergency departments in the United States?

What this study adds to our knowledge

In this prospective cohort study, the prevalence of bacteremia was 3% in febrile infants 28 days and younger and 1% in febrile infants aged 29 to 60 days.

How this is relevant to clinical practice

Complete laboratory evaluation is warranted for febrile children younger than 29. For those 29 days and older, however, the risk of meningitis was 1 in 500. Physicians will likely differ in their approach to this risk, depending on case specifics.

bacteremia and bacterial meningitis among young, febrile infants would help to inform clinical evaluation and decisionmaking.

The age of the infant appears to be a potential contributing factor to the prevalence of bacterial infections and to decisions about laboratory testing. The purpose of this study was to describe the epidemiology of bacteremia stratified by week of age in febrile infants aged 60 days and younger from a geographically diverse sample of previously healthy infants treated in US pediatric EDs. As a secondary aim, we report the epidemiology of associated bacterial meningitis and urinary tract infections.

MATERIALS AND METHODS

Study Design and Setting

This was a planned secondary analysis of a prospective observational study that enrolled infants aged 60 days and younger with temperatures greater than 38°C (100.4°F) and who had blood cultures obtained as part of standard clinical care.[9] The study was conducted in 26 EDs participating in the Pediatric Emergency Care Applied Research Network (children's hospitals [18] and general academic medical centers [8]) between December 2008 and May 2013.[9,10] The study was approved by the institutional review boards at all sites, and we obtained written informed consent from the guardians of all infants.

Selection of Participants

We included infants aged 60 days and younger with temperatures 38°C (100.4°F) or greater (measured at home, in the clinic, or in the ED) and who had blood cultures obtained as part of standard clinical care and were enrolled in the parent ribonucleic acid (RNA) biosignatures study.[9] For the parent study, staff enrolled a convenience sample of eligible infants at various times of day, and there were no processes to account for all eligible patients. Infants who were critically ill, as well as those with congenital heart disease, prematurity (<36 weeks' gestation), inherited or acquired immunodeficiency, indwelling devices or catheters, or receipt of antibiotics in the preceding 48 hours, were excluded.[9,10] All clinical care, including laboratory testing, antibiotics, and disposition, was at the discretion of the treating providers.

Methods of Measurement

Trained staff collected the following data at enrollment: age and sex, qualifying temperature (measured at home, in the clinic, or in the ED), Yale Observation Scale score, laboratory data (CBC count with differential, urinalysis, cerebrospinal fluid studies, and viral studies), imaging reports, and study site, visit date, and disposition. We abstracted bacterial cultures (blood, urine, and cerebrospinal fluid) from the medical record.

Outcome Measures

Our primary outcome was bacteremia, defined as growth of pathogenic bacteria in the blood culture. We also evaluated for concomitant bacterial meningitis, defined as growth of pathogenic bacteria in the cerebrospinal fluid, and concomitant urinary tract infection (defined below). All concurrent bacterial infections were by definition associated with the same organism and were assumed to be indicative of systemic dissemination of the same pathogen. Growth of multiple types of bacteria or those not commonly considered pathogens (eg, coagulase-negative staphylococcus, diphtheroids, bacillus species) were categorized as contaminants. The 3 study principal investigators (pediatric emergency and pediatric infectious disease physicians [PVM, NK, OR]) classified bacterial growth as pathogens or contaminants by consensus. In the parent study of RNA biosignatures, there were 13 patients for whom the blood cultures could not be categorized definitively; for example, growth of multiple organisms in which one could have been a pathogen, or positive Gram's stain without identification on culture. Although these most likely reflected contaminants, these 13 patients were excluded from the parent study and this subanalysis. We defined urinary tract infection in a catheter specimen as

culture growth of pathogenic bacteria greater than 50,000 colony-forming units/mL or greater than 10,000 colony-forming units/mL associated with a positive urinalysis result (>5 WBCs/high-power field, positive nitrate, or leukocyte esterase) and in a suprapubic aspiration specimen as greater than 1,000 colony-forming units/mL. We contacted the family of each enrolled infant who did not have a lumbar puncture completed in the ED and who was discharged to home 8 to 30 days after the ED visit to ascertain whether the infant remained well (and therefore bacterial meningitis was excluded clinically).

Primary Data Analysis

We report the rates of bacteremia and concurrent bacterial infections by age, with 95% confidence intervals (CIs), using the exact binomial method. Statistical analyses were performed with SAS (version 9.4; SAS Institute, Inc., Cary, NC).

RESULTS

Of 7,335 infants approached, 4,778 (65.1%) had blood cultures performed; 84 culture results were positive (1.8%; 95% CI 1.4% to 2.2%) (Figure). Of enrolled patients who met inclusion criteria for the current analysis (4,761), 1,515 (32%) were aged 28 days and younger and 2,074 (44%) were girls. The race and ethnicity distribution was white (57%), black (24%), Asian (3%), other (9%), and unknown (7%); 30% reported Hispanic ethnicity. A total of 4,771 patients had information about meningitis: 3,559 had a cerebrospinal fluid culture obtained in the ED and an additional 1,212 had absence of meningitis confirmed through follow-up (7 patients had missing cerebrospinal fluid information).

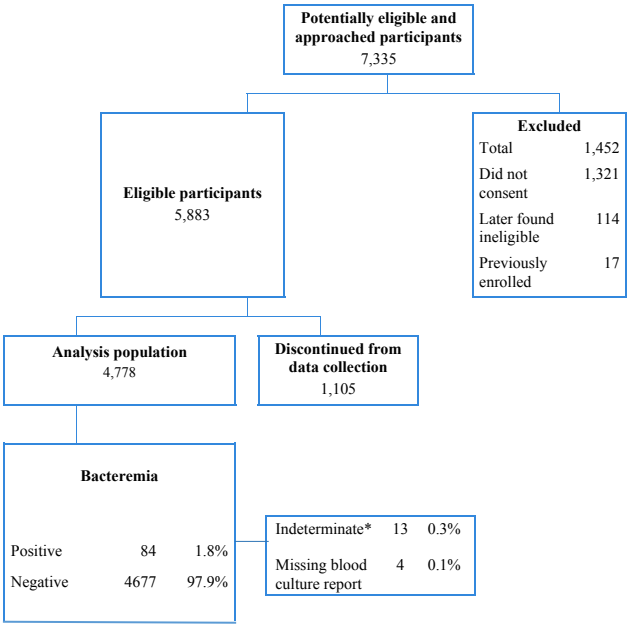

Figure. Patient enrollment. *"Indeterminate" included cultures with multiple organisms in which one could have been a pathogen, or positive Gram's stain but no identified organism.

The spectrum and frequency of bacterial species causing bacteremia, as well as bacterial coinfections, are demonstrated in Table 1. Eleven infants (13.1%; 95% CI 7.5% to 21.9%) had associated bacterial meningitis, and 36 (42.9%; 95% CI 32.8% to 53.5%) had concurrent urinary tract infections. Of the 33 infants whose blood cultures grew *Escherichia coli*, 30 (91%) had concurrent urinary tract infections. Urine cultures were missing for 104 patients. Group B streptococcus accounted for 24% of the bacteremia and 54% of the concurrent bacterial meningitis, of which 5 of 11 cases of bacterial meningitis were in infants younger than 28 days. *Staphylococcus aureus* accounted for 13% of the bacteremia. An additional 13 infants received a diagnosis of bacterial meningitis and had negative blood culture results. The cerebrospinal fluid cultures of these infants grew *E coli* (n=3), *Enterococcus faecalis* (n=3), group B streptococcus (n=3), *Klebsiella oxytoca* (n=1), *Listeria monocytogenes* (n=2), and *S aureus* (n=1). In 3 infants, the cerebrospinal fluid grew contaminant organisms, and in one case the culture report was missing.

The prevalence of bacteremia by week of age is demonstrated in Table 2. The highest frequency was among infants aged 8 to 14 days. Among infants aged 28 days and younger, there was week-to-week variation in bacteremia prevalence; prevalence overall was 3.1% (95% CI 2.3% to 4.1%) versus 1.1% (95% CI 0.8% to 1.6%) among infants aged 29 to 60 days. Among infants aged 29 to 60 days, there was little variation in prevalence of bacteremia by week of age. The frequency of contaminated samples (n=182) by week of age ranged from 1.9% to 6.7%. Of the 24 cases of bacterial meningitis, 19 occurred in infants aged 28 days and younger (1.3%; 95% CI 0.8% to 2.0%), and 5 were in infants aged 29 days and older (0.2%; 95% CI 0.1% to 0.4%). There were no cases of bacterial meningitis in infants older than 42 days (6 weeks).

LIMITATIONS

The study has some limitations related to infant enrollment and laboratory testing. The study population was a convenience sample based on the availability of research or clinical staff to approach families and complete enrollment procedures. We do not know how many eligible subjects were not approached. The intent was to enroll infants at risk of infection because of young age, but who otherwise were not critically ill appearing. Because there were no specific criteria or definition for critically ill, there was likely some variation in how it was defined. The

Table 1. Bacteremia pathogens and concurrent bacterial infections by age.

	Bacteremia, No. (%)*		Concurrent UTI, No. (%)†		Concurrent Bacterial Meningitis, No. (%)†	
	≤28 Days	>28 Days	≤28 Days	>28 Days	≤28 Days	>28 Days
N	47 (56.0)	37 (44.0)	18 (38.3)	18 (48.6)	9 (19.1)	2 (5.4)
Bacteremia organisms						
E coli	16 (19.0)	17 (20.2)	14 (87.5)	16 (94.1)	1 (6.3)	0
Group B streptococcus	15 (17.9)	5 (6.0)	0	0	5 (33.3)	1 (20.0)
S aureus	5 (6.0)	6 (7.1)	0	0	0	0
E cloacae	2 (2.4)	3 (3.6)	1 (50.0)	2 (66.7)	1 (50.0)	0
K pneumoniae	2 (2.4)	0	1 (50.0)	0	1 (50.0)	0
Enterococcus spp	1 (1.2)	1 (1.2)	0	0	0	0
Neisseria meningitidis	0	2 (2.4)	0	0	0	1 (50.0)
Moraxella spp	0	2 (2.4)	0	0	0	0
L monocytogenes	1 (1.2)	0	0	0	0	0
Citrobacter freundii	1 (1.2)	0	0	0	0	0
Salmonella spp	1 (1.2)	0	1 (100)	0	0	0
Flavobacterium	1 (1.2)	0	0	0	0	0
Lactose-fermenting negative bacilli	1 (1.2)	0	1 (100)	0	0	0
S pneumoniae	1 (1.2)	0	0	0	1 (100)	0
Pseudomonas	0	1 (1.2)	0	0	0	0

UTI, Urinary tract infection.
*The percentages in this column are based on the 84 total patients with bacteremia.
†The percentages in this column are based on the total number of patients with the corresponding bacteremia organism in the matching age group.

consent rate of 60% to 70% may also have allowed for a study sample with potentially biased reported results. However, the rates of bacteremia in the enrolled population reflect those reported in the recent literature, suggesting that our sample is similar and generalizable.[1,3-5] Although all enrolled infants had blood cultures obtained, not all had cerebrospinal fluid samples collected, potentially resulting in missed bacterial meningitis. However, all study patients managed without performance of lumbar punctures had telephone follow-up, and we included in the analysis only those infants in whom we could confirm that bacterial meningitis had not occurred (by either laboratory diagnosis or clinical follow-up). Despite the large sample, few young infants had bacterial meningitis, limiting analysis by week of age. Finally, urine culture results were missing for 2%.

DISCUSSION

In this large prospective cohort of 4,778 previously healthy term febrile infants aged 60 days and younger evaluated in US EDs, the overall prevalence of bacteremia was 1.8%, and *E coli* and group B streptococcus were the most common pathogens identified. The prevalence was higher among infants in the first 4 weeks of life. Among infants aged 29 to 60 days, the frequency was lower overall and we observed no significant variation by week of age. The bacteremia rate in our whole cohort is similar to that in other large cohorts of young febrile infants.[1,4,5] There are differences, however, in study design, setting, and population: the data reported in the present study were prospectively gathered, allowing real-time evaluation and data queries; all infants were enrolled in the ED and had blood cultures obtained; and the study included multiple sites, allowing broad geographic representation and sample sizes at each week of age.

Table 2. Bacteremia by week of age.

Age, Days	Proportion (%, 95% CI)
0–7	4/156 (2.6, 1.0–6.4)
8–14	19/356 (5.3, 3.4–8.2)
15–21	15/449 (3.3, 2.0–5.4)
22–28	9/554 (1.6, 0.9–3.1)
29–35	6/654 (0.9, 0.4–2.0)
36–42	11/774 (1.4, 0.8–2.5)
43–49	5/778 (0.6, 0.3–1.5)
50–56	9/729 (1.2, 0.7–2.3)
57–60	6/311 (1.9, 0.9–4.1)

E coli was the most common causal agent of bacteremia in our study population. This is similar to the epidemiology in the current reported literature.[1,3,4] *E coli* urinary tract infections were the most frequently identified site infections among infants with bacteremia. The rates of bacteremia that we report, as well as the spectrum of pathogens, likely result in part from study inclusion criteria, which involved only previously healthy term infants, high rates of peripartum maternal group B streptococcus screening and treatment, and high population rates of immunization for *S pneumoniae*. The exclusion of critically ill infants (by study protocol) also contributed to rates of bacteremia lower than those found in other reported literature. The prevalence of

contaminated blood cultures collected in the ED from young febrile infants was high and similar to that reported by others.[2,4] There appeared to be no association between week of age and blood culture contamination rates.

The epidemiology of bacteremia and bacterial meningitis is an important contributing factor in determining the best approach to the diagnostic evaluation and disposition of young febrile infants. Bacteremia prevalence was highest in infants aged 28 days or younger. Although lower in infants aged 29 to 60 days, the bacteremia rates did not vary week by week in the second month of life. As expected, bacterial meningitis prevalence was also higher in infants aged 28 days or younger, and there were no cases of bacterial meningitis after the sixth week of life.

In this large, prospective cohort study of febrile infants aged 60 days and younger, the overall prevalence of bacteremia was 1.8%. We found *E coli* to be the most frequent cause of bacteremia, followed by group B streptococcus, *S aureus*, and *Enterobacter cloacae*, together accounting for 81% of pathogenic-positive blood cultures. In infants aged 28 days and younger, the prevalence of bacteremia and bacterial meningitis was higher than that observed in infants aged 29 days and older, and a low threshold for complete laboratory evaluation and hospitalization for the youngest group is warranted.

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Author contributions: ECP, PVM, OR, and NK conceived and designed the study. ECP, PVM, GR, JDH, RG, ATC, AJR, SMA, DMJ, and NK supervised patient enrollment. ECP, PVM, GR, JDH, RG, ATC, AJR, SMA, DMJ, and NK supervised data abstraction. ECP, PVM, TCC, and NK contributed to data analysis. ECP drafted the initial article. ECP, PVM, GR, JDH, RG, ATC, AJR, SMA, DMJ, TCC, OR, and NK approved the final article. PVM, OR, and NK obtained funding. PVM, GR, JDH, RG, ATC, AJR, SMA, DMJ, TCC, OR, and NK revised the final article. TCC had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. ECP takes responsibility for the paper as a whole.

All authors attest to meeting the four ICMJE.org authorship criteria: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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APPENDIX

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