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Powell, Elizabeth C
Mahajan, Prashant V
Roosevelt, Genie
et al.

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Epidemiology of Bacteremia in Febrile Infants 60 Days of Age and Younger

Elizabeth C. Powell, MD, MPH[1], **Prashant V. Mahajan, MD, MPH, MBA**[2], **Genie Roosevelt, MD**[3], **John D. Hoyle Jr, MD**[4], **Rajender Gattu, MD**[5], **Andrea T. Cruz, MD, MPH**[6], **Alexander J. Rogers, MD**[7], **Shireen M. Atabaki, MD**[8], **David M. Jaffe, MD**[9], **T Charles Casper, PhD**[10], **Octavio Ramilo, MD**[11], and **Nathan Kuppermann, MD, MPH**[12] **the Febrile Infant Working Group of the Pediatric Emergency Care Applied Research Network (PECARN)**

[1]Division of Emergency Medicine, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL

[2]Departments of Emergency Medicine and Pediatrics, University of Michigan, Ann Arbor, MI

[3]Department of Pediatrics, Children's Hospital Colorado, Denver, CO

Corresponding author: Elizabeth C. Powell, Division of Emergency Medicine, Department of Pediatrics, Northwestern University, Ann & Robert H. Lurie Children's Hospital of Chicago, 225 E. Chicago Ave, Chicago, IL 60611.

[4]Departments of Emergency Medicine and Pediatrics, Western Michigan University, Kalamazoo, MI

[5]Department of Pediatrics, University of Maryland, Baltimore, MD

[6]Sections of Emergency Medicine and Infectious Diseases, Department of Pediatrics, Texas Children's Hospital, Baylor College of Medicine, Houston, TX

[7]Departments of Emergency Medicine and Pediatrics, University of Michigan, Ann Arbor, MI

[8]Division of Emergency Medicine, Department of Pediatrics, Children's National Medical Center, The George Washington School of Medicine and Health Sciences, Washington, DC

[9]Associate Executive Director, Department of Education, American Academy of Pediatrics, Elk Grove Village, IL

[10]Department of Pediatrics, University of Utah, Salt Lake City, UT

[11]Division of Pediatric Infectious Diseases and Center for Vaccines and Immunity, Nationwide Children's Hospital and The Ohio State University, Columbus, OH

[12]Departments of Emergency Medicine and Pediatrics, University of California, Davis, School of Medicine, Sacramento, CA

Abstract

Study Objective—To describe the current epidemiology of bacteremia in febrile infants 60 days-old 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-old presenting to any of 26 PECARN emergency departments (EDs) (2008 –2013) who had blood cultures obtained. We excluded infants with significant comorbidities or critically-ill appearances. 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, 84 had bacteremia (1.8%; 95% CI 1.4–2.2%). The prevalence of bacteremia in infants 28 days-old (47/1,515) was 3.1% (95% CI 2.3–4.1%) and in infants 29–60 days-old (37/3,246) was 1.1% (95% CI 0.8–1.6%). Prevalence differed by week of age for infants 28 days (0–7 days: 4/156, 2.6%), (8–14 days: 19/356, 5.3%), (15–21 days: 15/449, 3.3%), (22–28 days: 9/554, 1.6%). The most common pathogens were *Escherichia coli* (39.3%; 95% CI 29.5–50.0%) and *group B streptococcus* (23.8%; 95% CI 16.0–33.9%). Bacterial meningitis occurred in 19/1515 infants 28 days-old (1.3%; 95% CI 0.8–2.0%) and 5/3,246 infants 29–60 days-old (0.2%; 95% CI 0.1–0.4%). Of 84 infants with bacteremia, 36 (42.9%; 95% CI 32.8–53.5%) had urinary tract infections (*Escherichia coli* 83%); 11 (13.1%; 95%CI 7.5–21.9%) had bacterial meningitis.

Conclusion—The prevalence of bacteremia and meningitis among febrile infants 28 days-old is high and exceeds that observed in infants 29–60 days old. *Escherichia coli* and *group B streptococcus* are the most common bacterial pathogens.

Background

In young infants, fever can be the only sign of serious bacterial infections. Although higher rates have been reported in the past, current United States data suggest that 2% of infants younger than 2 months old presenting with fever with no source have bacteremia, and 0.3–0.4% 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 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 medical literature reports variation in management in both emergency department (ED) and office settings. As bacteremia and bacterial meningitis rates have decreased in 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 diagnosis can have serious long-term sequelae. Additional up-to-date information about the prevalence and epidemiology of bacteremia and bacterial meningitis among young, febrile infants will help to inform clinical evaluation and decision-making.

The age of the infant appears to be a potential contributing factor to the prevalence of bacterial infection 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 60 days of age and younger from a geographically-diverse sample of previously healthy infants treated in United States pediatric EDs. As a secondary aim, we report the epidemiology of associated bacterial meningitis and urinary tract infections.

Methods

Study Design and Setting

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

Selection of Participants

We included infants 60 days old with temperatures 38° C (measured at home, in the clinic, or in the ED) and who had blood cultures performed as part of standard clinical care and were enrolled in the parent RNA Biosignatures study.[9] For the parent RNA 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, and/or receipt of antibiotics in the

preceding 48 hours were excluded. [9,10] All clinical care including laboratory testing in addition to the blood culture, antibiotics, and disposition was at the discretion of the treating providers.

Methods of Measurement

Trained staff collected the following data at the time of enrollment: age and sex, qualifying temperature (location home, clinic, or ED), Yale Observation Scale score (YOS), laboratory data (CBC count with differential, urinalysis, cerebrospinal fluid (CSF) studies, 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 outcomes were 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 CSF, 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 bacteria or those not commonly considered pathogens (e.g. coagulase-negative staphylococcus, diphtheroids, bacillus species) were categorized as contaminants. The three study principal investigators (pediatric emergency and pediatric infectious disease physicians) classified bacterial growth as pathogens or contaminants by consensus. In the parent study of RNA biosignatures, there were 13 patients from whom the blood cultures could not be categorized definitively. For example, growth of multiple organisms where one could have been a pathogen, or positive Gram stain without growth on culture. Although these most likely reflected contaminants, these 13 patients were excluded from the parent study RNA analysis and this sub analysis. We defined urinary tract infection in a catheter specimen as culture growth of pathogenic bacteria 50,000 colony forming units (cfu)/ml or 10,000 cfu/ml associated with a positive urinalysis (>5 white blood cells per high power field, positive nitrate, or leukocyte esterase) and in a suprapubic aspiration specimen as 1000 cfu/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 8–30 days after the ED visit to ascertain whether the infant remained well (and therefore bacterial meningitis was excluded clinically).

Statistical analysis

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

Results

Of 7,335 infants approached, 4,778 (65.1%) infants had blood cultures performed; 84 cultures were positive (1.8%; 95% CI 1.4–2.2%) (Figure 1). Of enrolled patients who met inclusion criteria for the current analysis (4,761), 1,515 (32%) were 28 days old and 2,074 (44%) were girls. The race/ethnicity distribution was white (57%), African American (24%),

Asian (3%), other (9%) and unknown (7%); 30% reported Hispanic ethnicity. A total of 4,771 had information about meningitis: 3,559 had a CSF culture obtained in the ED and an additional 1,212 had absence of meningitis confirmed through follow-up (7 patients had missing CSF information).

The spectrum and frequency of bacterial species causing bacteremia, as well as bacterial co-infections are demonstrated in Table 1. Eleven infants (13.1%; 95% CI 7.5–21.9%) had associated bacterial meningitis and 36 (42.9%; 95% CI 32.8–53.5%) 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 5/11 were in infants 28 days old. *Staphylococcal aureus* accounted for 13% of the bacteremia. An additional 13 infants were diagnosed with bacterial meningitis and had negative blood cultures. The cerebrospinal fluid cultures of these infants grew *Escherichia coli* (n=3), *Enterococcus faecalis* (n=3), *Group B Streptococcus* (n=3), *Klebsiella oxytoca* (n=1), *Listeria monocytogenes* (n=2), and *Staphylococcal aureus* (n=1). In 3 infants the CSF 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 8–14 days old. Among infants 28 days-old there was week-to-week variation in bacteremia prevalence; prevalence overall was 3.1% (95% CI 2.3–4.1%) vs 1.1% (95% CI 0.8–1.6%) among infants 29–60 days-old. Among the infants 29–60 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 1.9–6.7%. Of the 24 cases of bacterial meningitis, 19 occurred in infants 28 days-old and younger (1.3%, 95% CI 0.8–2.0%) and 5 were in infants 29 days-old and older (0.2%, 95% CI 0.1–0.4%). 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 consent rate of 60%–70% may also have allowed for a study sample with potentially biases 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] While all enrolled infants had blood cultures obtained, not all had CSF samples collected, potentially resulting in missed bacterial meningitis. However, all young infants managed without performing 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 60 days old evaluated in United States EDs, the overall prevalence of bacteremia was 1.8%, and *Escherichia coli* and *Group B streptococcus* were the most common pathogens identified. The prevalence was higher among infants in the first four weeks of life than in the older infants. Among the infants 29–60 days old, the frequency was lower overall and we observed no significant variation by week of age among that group. 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: 1) the data reported in the present study were prospectively gathered, allowing for real-time evaluation and data queries; 2) all infants were enrolled in the ED and had blood cultures obtained; and 3) the study included multiple sites, allowing for broad geographic representation and ample sample sizes at each week of age.

Escherichia coli was the most common etiologic agent of bacteremia in our study population. This is similar to the epidemiology in the current reported literature. [1,3,4] *Escherichia coli* urinary tract infections were the most frequent identified site infections among infants with bacteremia. The rates of bacteremia that we report, and 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 Streptococcus pneumoniae. The exclusion of critically-ill infants (by study protocol) also contributed to the lower rates of bacteremia than in other reported literature. Of note, the prevalence of contaminated blood cultures in young febrile infants collected in the ED setting 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 are important contributing factors in determining the best approach to the diagnostic evaluation and disposition of young febrile infants. Bacteremia prevalence was highest in infants 28 days. Although lower in infants 29–60 days old, 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 28 days old, and there were no cases of bacterial meningitis after the 6th week of life.

Conclusion

In this large, prospective cohort study of febrile infants 60 days-old and younger the overall prevalence of bacteremia was 1.8 %. We found *Escherichia coli* to be the most frequent etiology of bacteremia, followed by *Group B streptococcus*, *Staphylococcus aureus*, and *Enterobacter cloacae*, together accounting for 81% of pathogenic positive blood cultures. In infants 28 days and younger the prevalence of bacteremia and bacterial meningitis was

higher than that observed in infants 29 days and older and a low threshold for complete laboratory evaluation and hospitalization for the youngest group is warranted.

Acknowledgments

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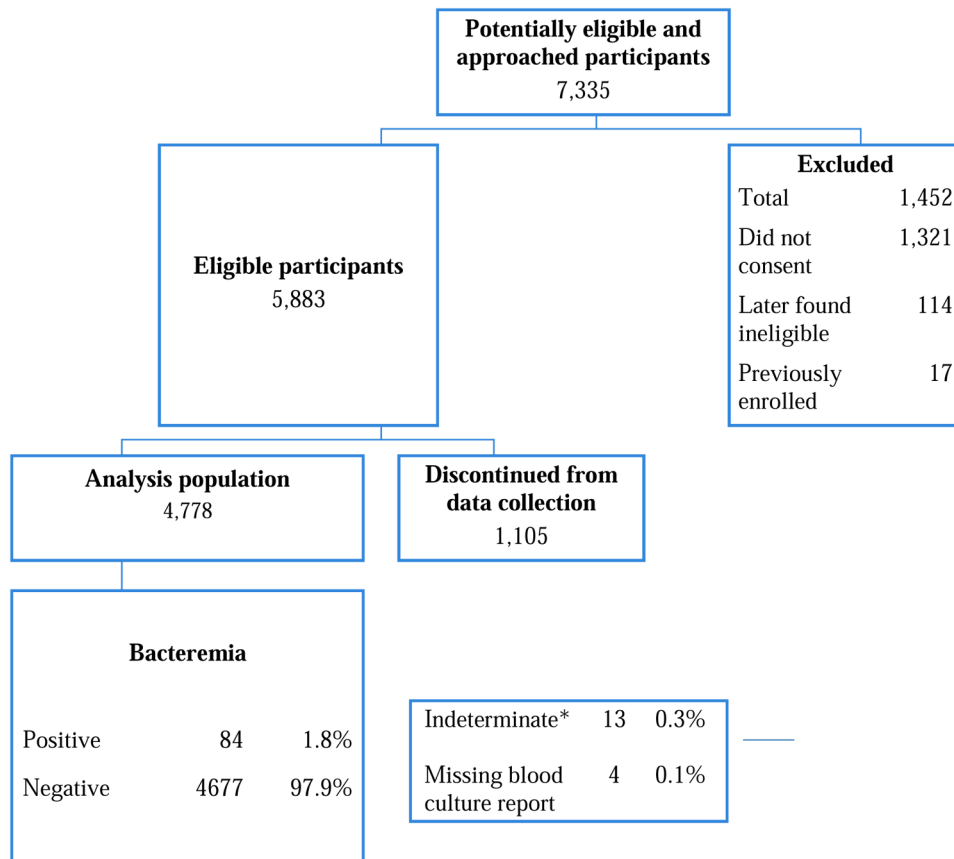
Figure 1.
Patient enrollment
*Indeterminate included cultures with multiple organisms where one could have been a pathogen, or positive gram stain but no bacterial growth

Table 1

Bacteremia pathogens and concurrent bacterial infections by age

	Bacteremia[1]		Concurrent UTI[2]		Concurrent bacterial meningitis[2]	
	28 days	> 28 days	28 days	> 28 days	28 days	> 28 days
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
N	47 (56.0)	37 (44.0)	18 (38.3)	18 (48.6)	9 (19.1)	2 (5.4)
Bacteremia organisms						
Escherichia coli	16 (19.0)	17 (20.2)	14 (87.5)	16 (94.1)	1 (6.3)	0 (0)
Group B *streptococcus*	15 (17.9)	5 (6.0)	0 (0)	0 (0)	5 (33.3)	1 (20.0)
Staphyloccus aureus	5 (6.0)	6 (7.1)	0 (0)	0 (0)	0 (0)	0 (0)
Enterobacter cloacae	2 (2.4)	3 (3.6)	1 (50.0)	2 (66.7)	1 (50.0)	0 (0)
Klebsiella pneumoniae	2 (2.4)	0 (0)	1 (50.0)	0 (0)	1 (50.0)	0 (0)
Enterococcus species	1 (1.2)	1 (1.2)	0 (0)	0 (0)	0 (0)	0 (0)
Neisseria meningitidis	0 (0)	2 (2.4)	0 (0)	0 (0)	0 (0)	1 (50.0)
Moraxella species	0 (0)	2 (2.4)	0 (0)	0 (0)	0 (0)	0 (0)
Listeria monocytogenes	1 (1.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Citrobacter freundii	1 (1.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Salmonella species	1 (1.2)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)
Flavobacterium	1 (1.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Lactose fermenting negative bacilli	1 (1.2)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)
Streptococcus pneumoniae	1 (1.2)	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)
Pseudomonas	0 (0)	1 (1.2)	0 (0)	0 (0)	0 (0)	0 (0)

[1]The percentages in this column are based on the 84 total patients with bacteremia

[2]The percentages in this column are based on the total number of patients with the corresponding bacteremia organism in the matching age group.

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%)