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Changing Epidemiology of Bacteremia in Infants Aged 1 Week to 3 Months

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WHAT'S KNOWN ON THIS SUBJECT: Approximately 1.1% to 5.9% of febrile infants aged <90 days have bacteremia, but the incidence of bacteremia in this age is unknown. *Escherichia coli*, group B *Streptococcus*, and *Staphylococcus aureus* are the leading causes of bacteremia.

WHAT THIS STUDY ADDS: Bacteremia occurs in 2.2% of infants who have a blood culture drawn. The incidence rate of true bacteremia was 0.57 in 1000 full-term births. The most common pathogens were *Escherichia coli* (56%), group B *Streptococcus* (21%), and *Staphylococcus aureus* (8%).

abstract

BACKGROUND: Bacteremia in young infants has remained an important ongoing concern for decades. Despite changes in prenatal screening and infant immunizations, the current epidemiology of this problem has received little attention.

METHODS: We conducted a retrospective analysis of all blood cultures collected at Kaiser Permanente Northern California on full-term, previously healthy infants presenting for care between 1 week to 3 months of age for whom a blood culture was drawn from January 1, 2005, through December 31, 2009.

RESULTS: During the study period, 4255 blood cultures were collected from 160 818 full-term infants. Only 2% of all blood cultures were positive for pathogens (93/4255), whereas 247 positive cultures were due to contaminants. The incidence rate of true bacteremia was 0.57 in 1000 full-term births. The most common pathogen was *Escherichia coli* (56%). Ninety-eight percent of infants with *E coli* bacteremia had a urinary tract infection. Group B *Streptococcus* and *Staphylococcus aureus* were the second and third most common pathogens, respectively. There were no cases of *Listeria monocytogenes* bacteremia or meningococcemia and only 1 case of enterococcal bacteremia. Ampicillin resistant pathogens accounted for 36% of organisms.

CONCLUSIONS: Our study indicates bacteremia in young infants occurs infrequently and in only 2.2% of those who had a blood culture drawn. On the basis of the epidemiology of pathogens found in this large cohort, these data suggest a change in currently recommended presumptive antibiotic coverage in 1-week to 3-month-old infants with suspected bacteremia. *Pediatrics* 2012;129:e590–e596

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KEY WORDS

bacteremia, infant, antibiotic resistance, group B *Streptococcus*, *Escherichia coli*

ABBREVIATIONS

CSF—cerebral spinal fluid
GBS—group B *Streptococcus*
KPNC—Kaiser Permanente Northern California
UTI—urinary tract infection
WBC—white blood cell

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Bacteremia in young infants, although uncommon, has been a challenging problem for decades because potentially serious consequences in this age group. Most studies have focused on febrile infants, were completed before implementation of changes in prenatal screening for group B *Streptococcus* (GBS), and are not population based. Although ~1.1% to 5.9% of febrile infants <90 days have bacteremia,[1–11] the incidence of bacteremia in this age group is unknown. Surveillance data are available for GBS and *Listeria monocytogenes*,[12,13] but there are no published incidence data for other pathogens. Existing prospective studies have been designed to report rates of bacteremia in febrile infants. Including only febrile infants may miss cases of bacteremia occurring in hypothermic or euthermic but ill-appearing infants.

Although late-onset bacteremia occurring after 7 days appears to be decreasing, there has been a paucity of bacteremia studies published in the past decade. Studies from the 1980s consistently report higher rates of bacteremia compared with those from the early 2000s, 3.5% to 4% vs <3%, respectively.[3–6,8,10–12,14] Many factors affect the rate, epidemiology, and risk factors of bacteremia, including differences in perinatal care (eg, intrapartum antibiotics), immunization policies with resultant herd immunity, food safety, and emergence of new pathogens.

METHODS

Approval to conduct this study was granted by the Institutional Review Board of Kaiser Permanente Northern California (KPNC). Informed consent was waived.

Study Design

This study was a retrospective review of the computerized medical database containing all blood culture results in full-term infants aged 1 week to 3 months obtained at KPNC between January 1, 2005, and December 31, 2009. A review of the computerized database identified subject medical record number, name, gender, date of birth, date of cultures obtained, age, race, ethnicity, location of blood culture acquisition (clinic, emergency department or hospital), and organism(s) identified in blood cultures.

Kaiser Permanente is the largest health maintenance organization in the United States, with >2.4 million members in Northern California. During the study period, 53% of enrolled women of childbearing age were Caucasian, 6% were African American, 23% were Asian, and 14% were other. Eighteen percent identified their ethnicity as Latino. The household income was $50,000 to $100 000 and >$100 000 in 48% and 28% of women, respectively. Six percent were insured through Medi-Cal. (Medi-Cal is California's Medicaid program. It is a public health insurance program that provides health care services for low-income individuals.)[15]

Potential cases were defined as infants with positive blood cultures collected in the outpatient setting, emergency department, or first 24 hours of hospitalization. Additional blood cultures obtained within 3 days of a positive or negative blood culture were not considered a unique episode and were not included in the analysis unless they identified a new pathogen. Subjects were previously healthy and full term, defined as ≥37 weeks at birth. Blood cultures obtained after an episode of clinically significant bacteremia were excluded. Infants with underlying medical conditions were excluded.

To analyze clinically significant bacteremia, all organisms identified in blood cultures were classified as either a likely contaminant or a potential pathogen. Bacterial isolates such as coagulase-negative staphylococci, *Micrococcus* species, and diphtheroids were considered contaminants.

Fever was defined as a recorded temperature >100.4°F (38.0°C) rectally. Documentation of a temperature ≥100.4°F by parent before arrival to medical care qualified as a fever. Ill appearance at presentation was a physician's description as "toxic," "lethargic," "ill appearing," "nonresponsive," or "inconsolable."

To assess concomitant urinary tract infection (UTI) and meningitis, white blood cell (WBC) count, urinalysis, cerebral spinal fluid (CSF) analysis, urine and CSF culture results were assessed if obtained within 2 days of blood culture acquisition in all infants with a clinically significant positive blood culture. Urinalysis results were considered positive if the specimen contained leukocyte esterase and/or had ≥5 WBCs per high powered field. UTI was defined as a catheterized urine culture with ≥10 000 colony-forming units of a single organism per milliliter. Bacterial meningitis was defined as a positive CSF culture with or without CSF pleocytosis (WBC >20, infants 1–4 weeks; WBC >6, infants >4 weeks–3 months).

A case-control retrospective review of the medical record identified risk factors (eg, WBC count, pyuria, clinical signs) associated with bacteremia. Cases were defined as infants with clinically significant positive blood cultures. Controls were defined as infants with negative or clinically insignificant blood cultures and were selected from the pool of negative blood cultures. The case and control were matched 1:1 on age of culture acquisition (±1 week), time of year of culture acquisition (±1 months), and gender. Controls were equal in number to cases and chosen with the closest match to cases as described above.

Statistical Analysis

The overall incidence rate of bacteremia among infants 1 week to 3 months was calculated and reported. χ^2 tests

were used to compare the incidence rates by age, gender, and type of organism. A Cochran-Armitage test for trend was used to examine the incidence rate by year. We conducted both univariate and multivariate analyses on the matched case-control substudy to identify risk factors (age, WBC count, and type of organism) for positive cultures. Paired *t* tests were used for continuous variables and McNemar tests were used for categorical variables. A conditional logistic regression was performed to examine the risk factors for the positive cultures. The statistical program was SAS 9.1.

RESULTS

During this 5-year study, 160 818 full-term infants were born at KPNC; 4757 blood cultures were obtained from 4296 infants aged 1 week to 3 months old. Due to underlying medical conditions, 207 blood cultures from 174 infants were excluded. An additional 295 blood cultures were obtained within 3 days of an original culture and excluded because they did not identify a new pathogen. This resulted in 4255 blood cultures in 4122 infants. The location of blood culture acquisition was 1742 in outpatient clinics, 1583 in the emergency department, and 930 in the inpatient setting. Of these 4255 blood cultures, 340 (8%) were positive. However, only 2% of all blood cultures were positive for pathogens (93/4255), whereas 247 positive cultures were due to contaminants (Fig 1). There was a significantly higher rate of contaminants in cultures obtained from the emergency department (133/247) compared with those obtained elsewhere ($P = .002$).

Of 4255 blood cultures, 92 (2.2%) were positive with a pathogen (Fig 1). The incidence rate of true bacteremia was 92 in 160 818 or 0.57 per 1000 full-term births. Eighty-six of 92 infants with

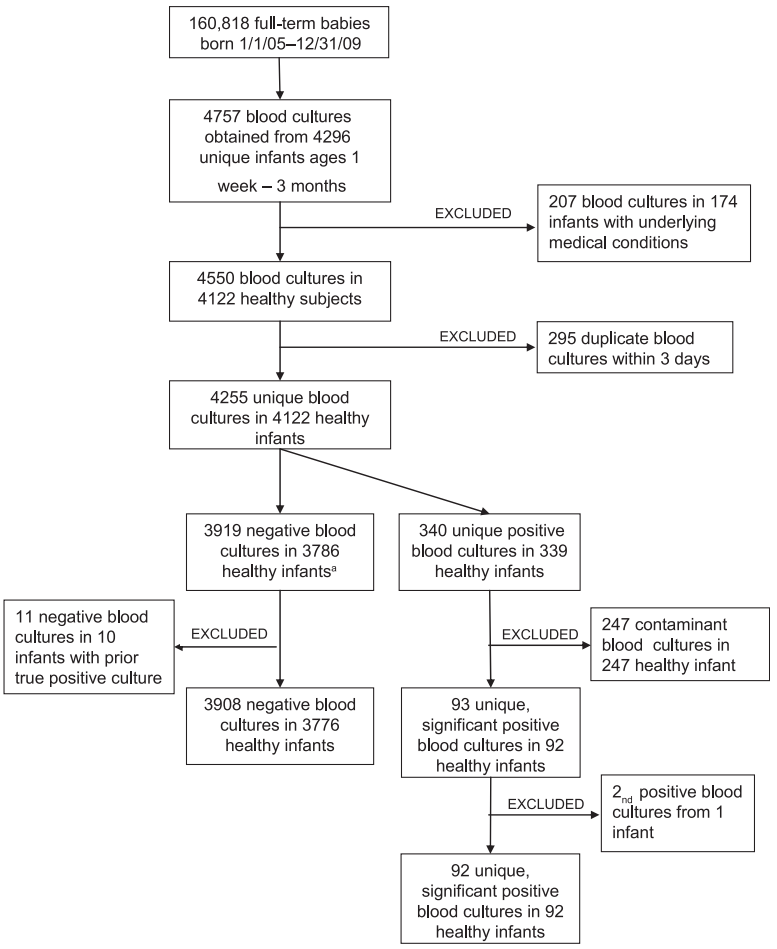

FIGURE 1
Flow diagram of excluded infants and blood cultures. [a] Three infants with 4 blood cultures before positive culture are in both negative and positive boxes.

bacteremia had documentation of temperature. Six of 86 (7%) had no documented fevers by parental history or during initial medical care including 2 hypothermic infants who expired soon after presentation. Eighty-four infants with bacteremia had clinical descriptions recorded at presentation. Sixteen (18.6%) were described as ill appearing. Of the 10 infants with meningitis, 1 was afebrile with an axillary temperature of 100°F at home. Seven of the 10 were ill appearing at presentation.

Gender, race, ethnicity, and age were not independent risk factors for bacteremia (Table 1). Bacteremia was more likely to be identified in infants during 7 to 28 days compared with 29 to 60 and 61 to 92 days (2.84%, 1.92%, and 2.14%, respectively), but this difference was not statistically significant. Over the 5 years of the study, there was no statistically significant change in the incidence of bacteremia. There were no cases of *L monocytogenes* or *Neisseria meningitidis* bacteremia. Ampicillin-resistant pathogens accounted for 33 of 92 (36%) of the identified pathogens. Only infants with *Escherichia coli*, GBS, and *Streptococcus pneumoniae* bacteremia had concomitant meningitis (Table 2).

Gram-negative organisms accounted for the majority (58/92, 63%) of bacterial pathogens and *E coli* (52/92, 56%) was the most common overall (Table 2). The incidence rate of *E coli* bacteremia was 0.32 in 1000 births and was

TABLE 1 Characteristics of Infants With and Without Bacteremia

Variable	Infants With Bacteremia					Infants Without Bacteremia	*P* Value[a]
	E coli *n* = 52 (%)	GBS *n* = 19 (%)	*S aureus* *n* = 7 (%)	Other *n* = 14 (%)	Overall *n* = 92 (%)	*n* = 4030 (%)	
Male	36 (69)	9 (47)	4 (57)	10 (71)	59 (64)	2246 (56)	.1086
Race							
White	21 (40)	9 (47)	5 (71)	6 (43)	41 (45)	1848 (46)	.3697
African American	2 (4)	4 (21)	0 (0)	3 (21)	9 (10)	359 (9)	
Asian/Pacific Islander	14 (27)	4 (21)	1 (14)	4 (29)	23 (25)	760 (19)	
Other/unknown	15 (29)	2 (11)	1 (14)	1 (7)	19 (20)	1072 (27)	
Hispanic	19 (37)	3 (16)	1 (14)	4 (29)	27 (29)	1387 (34)	.3112
Age (d)							
Median (interquartile range)	39 (50)	24 (17)	34 (32)	33 (34)	32 (33)	40 (36)	.2215
7–28 d	19 (36.5)	12 (63)	3 (43)	5 (36)	39 (42)	1373 (34)	.2361
29–60 d	19 (36.5)	6 (31.5)	3 (43)	6 (43)	34 (37)	1769 (44)	
61–92 d	14 (27)	1 (0.5)	1 (14)	3 (21)	19 (21)	888 (22)	

[a] *P* value reflects infants with bacteremia to those without.

TABLE 2 Bacterial Pathogens in 92 Infants With Bacteremia

Pathogen	*n* (%)	Median Age (Range)	Median WBC Count K/uL (IQR)	Ampicillin Resistance *n* (%)	UTI N (%)	Concomitant Meningitis *n* (%)
Gram-positive						
GBS	19 (21)	23 (11–82)	5.8 (10)	0/19 (0)	1/17 (6)	5/17 (29)
S aureus	7 (8)	34 (12–75)	15.8 (9.5)	6/7 (86)	0/6 (0)	0/4 (0)
Streptococcus pyogenes	1 (1)	32 (32)	14.2 (0)	0/1 (0)	0/1 (0)	0/1 (0)
Enterococcus faecalis	1 (1)	41 (41)	13.4 (0)	0/1 (0)	ND	ND
Viridans streptococci	3 (3)	20 (17–61)	10.7 (11.3)	0/3 (0)	0/3 (0)	0/2 (0)
S pneumoniae	3 (3)	71 (30–81)	25.9 (7.1)	0/3 (0)	0/2 (0)	1/2 (50)
Gram-negative						
E coli	52 (56)	39 (7–92)	14.2 (9.7)	23/52 (44)	47/48 (98)	4/38 (11)[a]
Klebsiella sp	2 (2)	20 (9–32)	10.3 (8.7)	2/2 (100)	1/1 (100)	0/2 (0)
Citrobacter sp	1 (1)	27 (27)	13.6 (0)	1/1 (100)	1/1 (100)	0/1 (0)
Salmonella sp	2 (2)	37 (24–51)	14.9 (0.5)	0/2 (0)	0/1 (0)	0/2 (0)
Moraxella	1 (1)	53 (53)	9.2 (0)	1/1 (100)	0/1 (0)	0/1 (0)

IQR, interquartile range; ND,.

[a] Two patients with *E coli* bacteremia and UTI had abnormal CSF analysis. Both had CSF obtained before antibiotics and were not treated for bacterial meningitis.

evenly spread throughout the first 3 months of life. Thirty-six (69%) were male. With univariate analysis, male gender was a predictor of *E coli* bacteremia ($P = .05$). By using multivariate logistic regression comparing age, gender, and race, no predictor was statistically significant. Gender approached statistical significance ($P = .058$). Strains were resistant to ampicillin (23/52, 44%), gentamicin (3/52, 5.8%), and cefazolin (1/52, 2%). All 3 gentamicin-resistant strains were also ampicillin resistant. There were no ceftriaxone resistant strains of *E coli*.

Of the 52 infants with *E coli* bacteremia, 47 had a urinalysis, 48 had a urine culture, and 38 had a CSF culture and analysis. Forty-seven of 48 infants (98%) had a concomitant UTI. In infants with *E coli* bacteremia, urinalysis with positive leukocyte esterase was a strong predictor of *E coli* UTI with 42 of 47 (89%) positive. Four of 38 infants had concomitant *E coli* meningitis. Of the 14 infants without CSF obtained, all received short-course antibiotics without relapse or sequelae. Three of the 4 meningitis cases were pan-sensitive *E coli*, and 1 case was ampicillin resistant. All 4 cases occurred in male infants aged 23 to 41 days (median: 35.5 days).

GBS was the second most common pathogen (19/92, 21%; Table 2). The incidence rate of late-onset GBS bacteremia was 0.11/1000 births. Only 1 case occurred from 2 to 3 months. By using a Cochran-Armitage Trend test compared with no bacteremia, there was a significant trend toward a decreasing incidence with age with the respective rates of positive blood cultures being 8.6 per 1000, 3.4 per 1000, and 1.1 per 1000 ($P = .02$). Maternal GBS status was known in 18 of 19 at delivery. Eleven of 18 (61%) had positive screening. Of 19 cases of GBS bacteremia, 5 of 17 (29%) had concomitant meningitis, and 2 deaths occurred. Of the infants with meningitis, 2 of 5 were boys, aged from 14 to 82 days (median: 22 days), and 1 case occurred outside the neonatal period (>30 days).

S aureus was the third most common organism (7/92, 8%) with no cases of methicillin-resistant *S aureus* (Table 2). Compared with infants without bacteremia, there was no statistically significant difference in age, gender, or race. Five of the 7 infants underwent a full workup to determine a source of *S aureus* bacteremia including bone scan and echocardiogram. Associated osteomyelitis occurred in 1 case, endocarditis occurred in no cases, and there was 1 death due to overwhelming *S aureus* sepsis. One case had concomitant influenza A. One infant's mother had

mastitis. The 5 infants with bacteremia without a source received 2 weeks of antibiotics, and all recovered without complications.

There were 3 cases of *S pneumoniae* bacteremia (Table 2). Two infants had CSF obtained, and 1 had concomitant meningitis. There were no cases of neonatal *S pneumoniae*. All cases were penicillin, ampicillin, and ceftriaxone susceptible.

Controls for comparison of peripheral WBC counts were age, gender, and time of year of blood culture acquisition matched with cases. All 92 infants with bacteremia had a concurrent complete blood count obtained, but data on absolute neutrophil count was not available. Cases had an average WBC count of 13.82 K/uL (range: 1.90–42.30, SD: 7.24), whereas matched controls had an average WBC of 10.77 K/uL (range: 2.90–37.30, SD: 5.96; $P = .0012$). The average WBC of all subjects with *E coli* was 15.58 K/uL (SD: 7.33), with GBS was 8.26 K/uL (SD: 5.82), with *S aureus* was 14.17 K/uL (SD: 4.98) and with *S pneumoniae* was 23.9 K/uL (SD: 3.94). Only *E coli* had statistically higher WBC than controls. The number of cases of other pathogens was too small to detect any actual differences.

DISCUSSION

This large case series was unique in analyzing the incidence and epidemiology of bacteremia in healthy full-term infants aged 1 week to 3 months. The incidence rate of late-onset bacteremia was 92 in 160 818 or 0.57 per 1000 full-term births. *E coli*, GBS, and *S aureus* bacteremia occurred in 0.32, 0.11, and 0.04 per 1000 full-term births, respectively. This incidence was stable over the 5 study years. Before this study, the incidence of late-onset bacteremia was unknown. Compared with Centers for Disease Control and Prevention surveillance data,[12] we have documented a lower incidence of GBS bacteremia.

Our study had some limitations. This was a retrospective review of all blood cultures obtained in full-term infants aged 1 week to 3 months old. Despite using *International Classification of Diseases, Ninth Revision* codes to identify infants with underlying medical problems, some may have been missed. The demographics of KPNC may not represent all of Northern California or the United States. Acquisition of a blood culture was at the clinician's discretion and was obtained for reasons other than fever. KPNC is an established health maintenance organization with the vast majority of patients receiving all their care from a KPNC facility. If a bacteremic infant was ill, the infant would likely return to a KPNC facility for follow-up. Therefore, most clinically significant bacteremia would eventually be captured. Some bacteremic infants may have been treated with antibiotics without a blood culture, and so an episode of bacteremia may have been missed. Even with these limitations, we feel confident that our study accurately reported incident rates of bacteremia by capturing bacteremic infants presenting to care and analyzing all blood cultures received at the microbiology laboratory.

The rate of bacteremia was 2.2%, which was 0.1% to 0.5% lower than other publications from the past decade[1–5,10] but higher than another large study with a rate of 1.1%.[11] Differences in rates are likely due to study design, setting, and population. We included infants who were full term, previously healthy, aged 1 week to 3 months. Other studies included late preterm infants and infants <1 week old, which increased the likelihood of bacteremia. Although recognizing these may not have been pathogens, we also included viridans group streptococcal and enterococcal bacteremia cases that were treated by clinicians. Blood cultures were obtained at the clinician's discretion, and 7% of infants with bacteremia did not have documented fever. We assumed a greater proportion of infants without bacteremia also did not have fever. Similar to other publications, we saw no cases of *L monocytogenes* or *N meningitidis* bacteremia.[4,5]

In our KPNC study on infants aged 3 months to 3 years, we reported *E coli* as the leading cause of bacteremia in infants during the first year of life.[16] This pathogen was also the most common cause of bacteremia in younger infants, and we continued to see a strong association with UTI.

Until the past several years, GBS had been considered the most common pathogen in young infants in the United States.[17] Similar to other studies in the past decade, *E coli* replaced GBS as the leading cause of culture proven late-onset bacteremia.[3–5,10] Even though other studies report *E coli* as the most common cause of late-onset bacteremia, we found a higher percentage of bacteremia attributable to Gram-negative organisms (63%) and *E coli* (56%) than other studies.[3,5] The reason our rates of *E coli* bacteremia were higher than other published rates (56% vs 25%–45%,[3,5,10] respectively) was most likely multifactorial. Other studies have seen a correlation with intrapartum antibiotics and risk for late-onset serious bacterial infections and ampicillin resistant pathogens.[18] We question whether there was increased *E coli* and Gram-negative bacteremia secondary to excellent maternal screening for GBS and resultant increased use of intrapartum antibiotics.

We were likely reporting more cases of *E coli* and fewer cases of GBS. The incidence of late onset GBS was 0.11 in 1000 births, which was one-third of Centers for Disease Control surveillance rates last reported for 1996 through 2004.[12] The lower incidence was likely due to many reasons other

than years of the study. It was well established that African American race, prematurity, infants not discharged from the hospital after birth, and cultures obtained more than 24 hours of hospitalization were risk factors for GBS.[19] By including only full term previously healthy infants presenting to care, we excluded infants with higher rates of GBS. KPNC has very high rates of maternal GBS screening and use of intrapartum antibiotics which may decrease horizontal transmission of GBS. KPNC also had a considerably lower African American population which may further lower the rates of GBS.

Ampicillin-resistant pathogens accounted for 36% of cases including 1 case of *E coli* meningitis. There were no cases of *L monocytogenes* bacteremia and only 1 case of enterococcal bacteremia. This resistance pattern raised the question of whether ampicillin should be included as initial antibiotics in infants with suspected bacteremia. Our study included infants from all of Northern California and may not be generalizable to recommend antibiotic changes for the United States. However, we have identified a discordance between standard empirical coverage and organism susceptibility. We doubt infants in Northern California need ampicillin as part of the empirical regimen. In addition, we find it disconcerting that *E coli* strains from 3 bacteremic infants were resistant to both gentamicin and ampicillin. At the very least, if Gram-negative meningitis is suspected, therapy should include cefotaxime. Therapy is not adequate to cover the third most frequently identified pathogen, *S aureus*. We propose that if infants present with signs of skin and soft tissue infection, endocarditis, osteomyelitis, or other concerns for *S aureus*, therapy is tailored to treat this pathogen. If changes are made to empirical antibiotics, they should include ampicillin-resistant Gram-negatives and *S aureus*. Additional studies are underway to determine risk factors for ampicillin-resistant pathogens in our patient population.

CONCLUSIONS

This large cohort study has identified a shift in the epidemiology of bacteremia in term infants. Although bacteremia was a rare occurrence in infants, it did occur in 0.57 of 1000 full-term births. GBS bacteremia is no longer the leading cause of bacteremia but occurs most frequently in the first month of life, and 29% had concomitant meningitis. *E coli* is now the leading cause of bacteremia, and *S aureus* follows GBS. These 3 organisms are now responsible for 85% of bacteremia cases. There were no cases of *L monocytogenes* bacteremia and 1 case of enterococcal bacteremia, and 36% of pathogens were ampicillin resistant. On the basis of the pathogens found and antibiotic susceptibilities, we suggest new strategies are for presumptive treatment of bacteremia and question whether ampicillin still needs to be part of every empirical antibiotic regimen in infants 1 week to 3 months old.

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