RESEARCH ARTICLE

Time to Pathogen Detection for Non-ill Versus Ill-Appearing Infants ≤60 Days Old With Bacteremia and Meningitis

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ABSTRACT

OBJECTIVES: We sought to determine the time to pathogen detection in blood and cerebrospinal fluid (CSF) for infants ≤60 days old with bacteremia and/or bacterial meningitis and to explore whether time to pathogen detection differed for non–ill-appearing and ill-appearing infants.

METHODS: We included infants ≤60 days old with bacteremia and/or bacterial meningitis evaluated in the emergency departments of 10 children's hospitals between July 1, 2011, and June 30, 2016. The microbiology laboratories at each site were queried to identify infants in whom a bacterial pathogen was isolated from blood and/or CSF. Medical records were then reviewed to confirm the presence of a pathogen and to extract demographic characteristics, clinical appearance, and the time to pathogen detection.

RESULTS: Among 360 infants with bacteremia, 316 (87.8%) pathogens were detected within 24 hours and 343 (95.3%) within 36 hours. A lower proportion of non–ill-appearing infants with bacteremia had a pathogen detected on blood culture within 24 hours compared with ill-appearing infants (85.0% vs 92.9%, respectively; $P = .03$). Among 62 infants with bacterial meningitis, 55 (88.7%) pathogens were detected within 24 hours and 59 (95.2%) were detected within 36 hours, with no difference based on ill appearance.

CONCLUSIONS: Among infants ≤60 days old with bacteremia and/or bacterial meningitis, pathogens were commonly identified from blood or CSF within 24 and 36 hours. However, clinicians must weigh the potential for missed bacteremia in non–ill-appearing infants discharged within 24 hours against the overall low prevalence of infection.

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Febrile infants ≤60 days of age evaluated in the emergency department (ED) routinely undergo blood and cerebrospinal fluid (CSF) collection to evaluate for bacteremia and bacterial meningitis, respectively.[1] Approximately two-thirds of febrile infants in the ED do not meet low-risk criteria[2] and are therefore hospitalized[1] for up to 48 hours while awaiting culture results. Automated blood culture systems[3] permit earlier detection of bacteremia, which has allowed for hospital discharge within 24 to 36 hours at some institutions for infants whose bacterial culture results remain negative.[4]

Safe discharge from the hospital, however, is contingent on the timely detection of bacterial pathogens. In a previous multicenter investigation of febrile infants ≤90 days of age, 91% of pathogenic organisms were identified on blood culture within 24 hours and 96% were identified within 36 hours.[5] Although detection of CSF pathogens still largely relies on conventional agar plating, 81% of bacterial pathogens were detected on CSF culture within 36 hours.[6] However, because well-appearing infants are the most likely candidates for earlier hospital discharge, further investigation is needed to determine if the time to bacterial culture positivity varies by an infant's clinical appearance. If the vast majority of blood and CSF pathogens are detected within 24 hours in well-appearing infants, a result of this data could be shorter length of hospital stay for a large number of infants.

Our objective with this study was to determine the time to pathogen detection in blood and CSF for infants ≤60 days of age with bacteremia and/or bacterial meningitis (ie, invasive bacterial infection [IBI]) in a large multicenter study. Additionally, we explored whether time to detection of IBI differed for non–ill-appearing and ill-appearing infants.

METHODS

Study Design

We performed a planned secondary analysis of a cross-sectional study of infants ≤60 days of age with IBI evaluated in the ED of 1 of 11 children's hospitals. We limited this subanalysis to the 10 sites with available time to culture positivity. Study approval with a waiver of informed consent and permission for data sharing was obtained from each site's institutional review board.

Study Subjects

We included infants ≤60 days of age with an ED visit to a participating site between July 1, 2011, and June 30, 2016. Infants were included if they had a blood and/or CSF culture result positive for an a priori–determined pathogen (Supplemental Table 4) that was not treated as a contaminant. We identified potentially eligible infants by querying each hospital's microbiology laboratory or electronic medical record system for positive results of blood and/or CSF bacterial cultures. Infants with blood and/or CSF culture results positive for known contaminant species or whose positive culture result was documented to have been treated as a contaminant were excluded. Pathogens that grew only from CSF broth cultures were also excluded given the diagnostic ambiguity,[7] as were infants with ventriculoperitoneal shunts.

Medical Record Review

For each infant with a culture result positive for a potential pathogen, the medical record was reviewed to confirm eligibility and to extract bacterial culture results, patient characteristics (including age, temperature, clinical appearance, and presence of a skin or soft tissue infection), and whether antibiotics were administered before blood and/or CSF culture collection. A fever was defined as a documented temperature ≥38.0°C (100.4°F) at home, in an outpatient clinic, or in the ED.[2] Ill appearance was defined as any of the following documented in the physical examination performed in the ED: "ill-appearing," "toxic," "limp," "unresponsive," "gray," "cyanotic," "apnea," "weak cry," "poorly perfused," "grunting," "listless," "lethargic," or "irritable." If none of these words were documented, the infant was classified as not ill-appearing.[8] If there was disagreement in documentation of ill appearance between the attending physician and a trainee, the attending physician's documentation was used.

Urinary tract infection (UTI) was defined as either (1) a urine culture obtained by catheterization that had growth of ≥50 000 colony-forming units (CFUs)/mL of a single pathogen or 10 000 to 50 000 CFUs/mL of a single pathogen with an abnormal urinalysis (ie, positive nitrite or leukocyte esterase on urine dipstick or >5 white blood cells [WBCs] per high-powered field on urine microscopy)[9,10] or (2) growth of ≥100 000 CFUs/mL of a single pathogen on urine culture from a bagged urine specimen or from an unknown collection method, if the pathogen was simultaneously identified in the blood.[11,12] An abnormal peripheral WBC count was defined as a WBC count of <5000/μL or >15 000/μL.[2] CSF pleocytosis was defined by using the following age-based norms: CSF WBC count of ≥20 cells per mm^3 for infants ≤28 days of age and CSF WBC count of ≥10 cells per mm^3 for infants 29 to 60 days of age.[13]

Primary Outcome

We defined bacteremia and bacterial meningitis as the growth of a pathogen in the culture of blood or CSF, respectively. The primary outcome was the time to positivity of (1) blood culture and/or (2) CSF Gram-stain or culture. For infants with bacteremia, time to detection was defined as the time from specimen collection to the time of the first notification of a pathogen in blood culture. For infants with bacterial meningitis, time to detection was defined as the time from specimen collection to the time of the first notification of a pathogen on either Gram-stain or culture.

We excluded eligible cases without documented time to bacterial growth. During the 5-year study period, all participating hospitals had 24-hour blood culture monitoring systems with immediate provider notification for positive culture results.

Statistical Analysis

Categorical variables were described by using frequencies and percentages. Times to positivity for blood culture results were described with median, interquartile range, and range values. We used the Mantel-Haenszel hazard ratio (HR) with 95% confidence intervals (CIs) to compare the time to detection of blood culture on the basis of ill appearance and repeated analyses limiting the cohort to include only infants with fever. Additionally, we used a χ^2 test to compare the proportion of blood pathogens detected at 24 hours on the basis of ill appearance. As CSF cultures are examined once daily at most institutions, time to positivity was described as the proportion of pathogens detected at 24 hours and compared for infants with and without ill appearance by using a Fisher's exact test. Statistical significance was determined as a 2-sided P value $<.05$. Statistical analyses were performed by using Stata Data Analysis and Statistical Software version 15.0 (Stata Corp, College Station, TX) and GraphPad Prism version 7.0 (GraphPad Software, La Jolla, CA).

RESULTS

During the 5-year study period, we identified 1186 blood cultures and 337 CSF cultures with growth of bacteria. A total of 438 infants had a blood and/or CSF culture positive for an a priori–defined pathogen. After medical record review, we excluded 7 infants without an ED visit, 3 with a ventriculoperitoneal shunt, 4 with growth of bacteria from CSF broth culture only, and 37 with bacteria treated as contaminants. Of the remaining 366 infants with bacteremia, 6 (1.6%) were excluded because of missing time data, as were 3 (4.6%) of the 65 infants with bacterial meningitis. Among the 381 included infants, 42 (11.0%) had both bacteremia and meningitis. Demographics and clinical characteristics of included infants are listed in Table 1. Approximately one-third of infants with bacteremia and just over half with bacterial meningitis were ill-appearing.

TABLE 1 Characteristics of Infants With Bacteremia and/or Bacterial Meningitis

Characteristic	Bacteremia (n = 360), n (%)	Bacterial Meningitis (n = 62), n (%)
Demographics		
Age group		
≤28 d	192 (53.3)	42 (67.7)
29–60 d	168 (46.7)	20 (32.3)
Female sex	150 (41.7)	31 (50.0)
Clinical characteristics		
Fever	296 (82.2)	52 (83.9)
Ill-appearing	126 (35.0)	34 (54.8)
Concomitant infection		
UTI	105 (29.1)	2 (3.2)

Bacteremia

Time to blood culture positivity ranged from 2 to 98 hours with a median of 14 hours (interquartile range 12–17.5). Time to pathogen detection was similar for infants ≤28 days and 29 to 60 days of age (median 14 vs 13 hours, respectively) and for those who received antibiotic pretreatment compared with those who did not (median 15 vs 14 hours). Overall, 316 (87.8%) pathogens were detected on blood culture within 24 hours, and 343 (95.3%) were detected within 36 hours.

Time to detection was shorter for ill-appearing infants compared with that of non–ill-appearing infants (median 13 vs 14 hours; HR 1.55; 95% CI: 1.21–1.98; Fig 1). Results were similar when limited to infants with fever (HR 1.39; 95% CI: 1.05–1.83). A lower proportion of non–ill-appearing infants had a pathogen detected on blood culture within 24 hours compared with ill-appearing infants (199 out of 234 [85.0%] vs 117 out of 126 [92.9%]; P = .03).

Bacterial Meningitis

Thirty-nine (62.9%) infants with bacterial meningitis had a positive Gram-stain result. Overall, 55 (88.7%) pathogens were detected within 24 hours, and 59 (95.2%) were detected within 36 hours. Of the 14 infants who received antibiotic pretreatment, 13 (92.9%) had pathogens detected within 24 hours, and 100% had pathogens detected within 36 hours. At 24 hours, the proportion of CSF pathogens detected did not differ on the basis of ill appearance (88.2% vs 89.3%; P = 1.0).

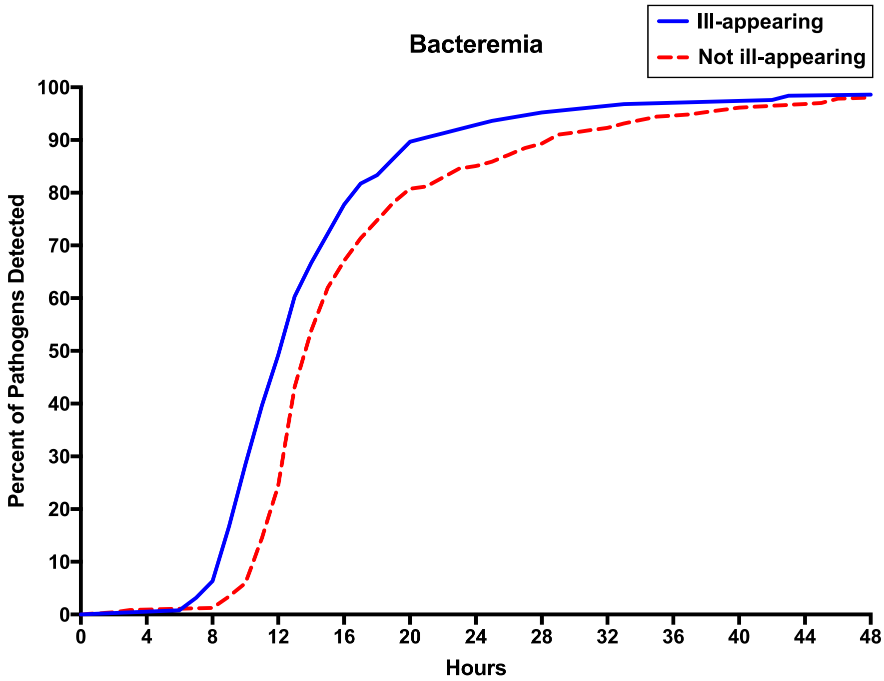

FIGURE 1 Kaplan-Meier survival analysis of pathogens detected by hour for infants ≤60 days of age with bacteremia, stratified by ill appearance.

Delayed Detections in Blood and CSF Cultures

Fifty (13.1%) infants with IBI had blood and/or CSF pathogens identified >24 hours after specimen collection, including 10 with concomitant UTI. Nineteen (5.0%) had pathogens identified >36 hours after specimen collection. Seventeen (89.5%) of these 19 infants had bacteremia without meningitis, 1 had bacteremia and meningitis, and 2 had bacterial meningitis without bacteremia; 2 (10.5%) had a concomitant UTI. The pathogens with time to detection of >24 and >36 hours are listed in Table 2. Of the 19 infants with pathogens detected after >36 hours, 7 (36.8%) had *Staphylococcus aureus*, including 1 infant with a skin or soft tissue infection (cellulitis). Five of the 6 infants with *S aureus* bacteremia identified after >36 hours had time to detection between 40 and 46 hours, whereas 1 had *S aureus* detected at 57 hours. The other infant had growth of *S aureus* from the CSF at 106 hours. Although the culture was not clearly documented to have been treated as a contaminant, the infant was discharged from the hospital before notification of the positive CSF culture results and was not readmitted to the participating site.

Three-quarters of infants with pathogens detected >24 hours after specimen collection were non–ill appearing. However, only 20% were non–ill appearing and had a normal urinalysis and peripheral WBC, with no CSF pleocytosis (Table 3). Of the 19 infants with pathogens detected after >36 hours, 13 (68.4%) were non–ill appearing and 5 (26.3%) were non–ill appearing and had normal laboratory parameters.

TABLE 2 Time to Detection by Pathogen in Infants With Bacteremia and/or Bacterial Meningitis

Pathogen[a,b]	≤24 h, *n* (%)[c]	>24–≤36 h, *n* (%)[c]	>36 h, *n* (%)[c]
Group B *Streptococcus*, *n* = 139	132 (95.0)	5 (3.6)	2 (1.4)
E coli, *n* = 117	106 (90.6)	8 (6.8)	3 (2.6)
S aureus, *n* = 42	24 (57.1)	11 (26.2)	7 (16.7)
Enterococcus spp., *n* = 26	23 (88.5)	2 (7.7)	1 (3.9)
Klebsiella spp., *n* = 14	13 (92.9)	1 (7.1)	0
Other Gram-negative,[d] *n* = 11	4 (36.4)	3 (27.3)	4 (36.4)
Enterobacter spp., *n* = 10	9 (90.0)	1 (10.0)	0
Group A *Streptococcus*, *n* = 9	8 (88.9)	0	1 (11.1)
Other Gram-positive,[e] *n* = 8	7 (87.5)	0	1 (12.5)
Streptococcus pneumoniae, *n* = 4	4 (100)	0	0
Salmonella spp., *n* = 3	3 (100)	0	0
Listeria monocytogenes, *n* = 2	2 (100)	0	0

SPP, several species.
[a] Some cultures grew >1 organism.
[b] Blood and/or CSF.
[c] *n* (%) of the total *N* within each row.
[d] *Neisseria meningitidis* (2), *Haemophilus influenzae* nontypeable (2), *Haemophilus parainfluenzae* (1), *Citrobacter* spp. (1), *Moraxella* spp. (1), *Proteus* spp. (1), *Serratia* spp. (1), *Pasteurella* spp. (1), *Acinetobacter* spp. (1).
[e] *Streptococcus bovis* (4), *Streptococcus gallolyticus* (3), *Paenibacillus* spp. (1).

DISCUSSION

In our multicenter study of infants ≤60 days of age with IBI, 88% of pathogens were detected on blood cultures and 89% were detected on CSF Gram-stain or cultures within 24 hours. However, among infants who were not ill-appearing, only 85% of blood pathogens were detected within 24 hours.

Our results are similar to those of Biondi et al[5] who reported that 91% of pathogens were detected in blood culture within 24 hours for febrile infants ≤90 days of age. However, in our study, we expand on this previous investigation by determining the time to positivity on the basis of an infant's clinical appearance. Because of a higher prevalence of IBI,[14] ill-appearing infants are less likely than non–ill-appearing infants to be discharged from the hospital at 24 hours. Although the median time to blood culture positivity was only slightly longer for infants who were not ill-appearing, 15% of these bacteremic infants had a negative blood culture result at 24 hours compared with 7% of ill-appearing infants. Because well-appearing infants are the most likely candidates for early hospital discharge,[14] clinicians may consider using additional laboratory parameters to assist with disposition decisions for these infants. The absolute number was small among non–ill-appearing infants with normal urinalysis, peripheral WBC count, and CSF WBC count (10 infants). Although normal urine, blood, and CSF laboratory values may therefore be used in the decision to discharge a non–ill-appearing infant from the hospital, most infants with delayed pathogen detection (beyond 24 hours) did not have a concomitant UTI.

Although some pathogens may be identified >36 hours after specimen collection, 95% of both blood and CSF pathogens were detected within 36 hours. This information may help clinicians make informed decisions about hospital discharge for infants with negative results for bacterial

TABLE 3 Clinical Appearance and Laboratory Values of Infants With Delayed Detection of Pathogens in Blood and/or CSF culture

	>24 h (*n* = 50), *n* (%)	>36 h (*n* = 19), *n* (%)
Ill-appearing or any abnormal laboratory	40 (80.0)	14 (73.7)
Ill-appearing	13 (26.0)	6 (31.6)
Abnormal urinalysis[a]	17 (34.0)	5 (26.3)
Abnormal peripheral WBC[b]	22 (44.0)	7 (36.8)
CSF pleocytosis[c]	14 (28.0)	6 (31.6)
Non–ill-appearing and normal laboratories	10 (20.0)	5 (26.3)

[a] Positive nitrite or leukocyte esterase or >5 WBC per high-powered field.
[b] WBC count of <5000/μL or >15 000/μL.
[c] CSF WBC count of ≥20 cells per mm^3 for infants ≤28 d and ≥10 cells per mm^3 for infants 29–60 d.

culture at 24 and 36 hours. Given the higher percentage of infants with bacteremia and bacterial meningitis who have negative culture results at 24 hours, particularly non–ill-appearing infants with bacteremia, clinicians must consider the full clinical and laboratory picture and weigh the risk of discharging an infant with IBI at 24 hours with the relative rarity of these infections.[2] Specifically, although 15% of non–ill-appearing infants with IBI did not have a pathogen detected at 24 hours, the prevalence of IBI in non–ill-appearing febrile infants overall is only ~2%.[14] Therefore, of all non–ill-appearing febrile infants, only 0.3%, or 1 in 333, will have a pathogen detected after 24 hours. Further investigation is needed to evaluate clinical outcomes of infants with IBI who are discharged from the hospital before pathogen detection.

The most common pathogen identified >36 hours after specimen collection was *S aureus*, although there were rare delayed detections of Group B *Streptococcus* and *Escherichia coli*. Bacteria detected on blood culture after >36 hours are more likely to be contaminants.[15] In our study, only 1 of the 7 infants with *S aureus* that was detected after >36 hours had a skin or soft tissue infection, which raises the possibility that some of these delayed detections were contaminants rather than pathogens. As varying definitions have been used to define pathogens and contaminants in febrile infants, and the number of infants with *S aureus* in our study is higher than in other investigations,[5,15] additional study is needed to standardize this definition and to determine the true prevalence of delayed pathogen detection in the blood and/or CSF.

Our study has several limitations. First, time to pathogen detection was determined as the time from collection to the time of notification as documented in the medical record, which may lack accuracy. Second, CSF cultures are often examined once daily; time to positivity may therefore differ on the basis of the time of day of specimen collection for infants with a negative Gram-stain result. Third, although we determined ill appearance on the basis of an established definition with high interrater reliability for febrile children with sickle cell disease,[8] this definition may not accurately reflect clinical appearance for febrile infants. Fourth, we do not know the total number of febrile infants evaluated during the study period, and so we cannot determine the proportion of positive culture results in the overall population of febrile infants. Lastly, we do not know the volume of blood or CSF obtained for culture, which may affect the time to positivity and overall yield of pathogen detection.[16]

CONCLUSIONS

Among infants ≤60 days old with bacteremia and/or bacterial meningitis, most pathogens were identified within 24 hours. However, because 15% of blood pathogens were detected after >24 hours among non–ill-appearing infants with IBI, clinicians must weigh the potential for missed bacteremia in infants discharged within 24 hours against the overall low prevalence of infection.

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