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RESEARCH ARTICLE

Time to Positive Blood and Cerebrospinal Fluid Cultures in Febrile Infants ≤60 Days of Age

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ABSTRACT

OBJECTIVES: To determine the time to positivity for bacterial pathogens and contaminants in blood and cerebrospinal fluid (CSF) cultures in a cohort of febrile infants ≤60 days of age.

METHODS: This was a secondary analysis of prospective observational multicenter study of noncritically ill infants ≤60 days of age with temperatures ≥38°C and blood cultures (December 2008 to May 2013). The main outcome was time to positivity for bacterial pathogens and contaminants.

RESULTS: A total of 256 of 303 (84.49%) patients with positive blood cultures, and 73 of 88 (82.95%) with positive CSF cultures met inclusion criteria. Median time (interquartile range [IQR]) to positivity for blood cultures was 16.6 hours (IQR 12.6–21.9) for bacterial pathogens ($n = 74$) and 25.1 hours (IQR 19.8–33.0) for contaminants ($n = 182$); $P < .001$. Time to bacterial pathogen positivity was similar in infants 0 to 28 days of age (15.8 hours [IQR 12.6–21.0]) and 29 to 60 days of age (17.2 [IQR 12.9–24.3]; $P = .328$). Median time to positivity for CSF was 14.0 hours (IQR 1.5–21.0) for bacterial pathogens ($n = 22$) and 40.5 hours (IQR 21.2–62.6) for contaminants ($n = 51$); $P < .001$. A total of 82.4% (95% confidence interval, 71.8–90.3) and 81.8% (95% confidence interval, 59.7%–94.8%) of blood and CSF cultures showed bacterial pathogen positivity within 24 hours.

CONCLUSIONS: Among febrile infants ≤60 days of age, time to blood and CSF positivity was significantly shorter for bacterial pathogens than contaminants. Most blood and CSF cultures for bacterial pathogens were positive within 24 hours. With our findings, there is potential to reduce duration of hospitalization and avoid unnecessary antibiotics.

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Febrile infants ≤60 days of age are at risk for invasive bacterial infections, including bacteremia and bacterial meningitis. To evaluate for the presence of these infections, young febrile infants often undergo blood, cerebrospinal fluid (CSF), and urine testing, including bacterial cultures.[1] Urinalysis findings are immediately available to identify infants at high risk of urinary tract infections and to direct treatment.[2] Although complete blood counts and CSF studies including cell counts and chemistry results can be used as screening tests to help determine presence of bacteremia and bacterial meningitis, their performance is suboptimal. Young febrile infants are frequently hospitalized awaiting the results of blood and CSF cultures to exclude bacteremia and bacterial meningitis. There is substantial variation in the management of young febrile infants, including the recommended duration of hospitalization and treatment with antibiotics pending these culture results.[3,4]

In other groups of patients (eg, older children at risk for occult bacteremia, patients with sickle cell disease), the time to culture positivity in blood and CSF for most pathogenic bacteria has been reported to be within 24 hours.[5–8] Previous studies of the time to positive bacterial cultures in the evaluation of infants ≤60 days of age were conducted at single centers,[9–11] in a neonatal unit,[12] with analysis limited to blood cultures,[13] or were retrospective in case identification.[14] There are few studies on time to positivity for bacterial pathogens in CSF cultures among young febrile infants and none that are prospective, limited to patients in the emergency department (ED), and/or conducted at multiple sites.[14–16] Prospective cohort identification is particularly important to allow for both full and accurate capture of young infants at risk for invasive bacterial infections, including bacteremia and bacterial meningitis. Retrospective diagnostic code identification has been shown to underidentify infants, especially those prone to severe outcomes.[17]

Our objective in the current study was to determine and compare the time to positivity for blood and CSF cultures with pathogenic versus contaminant bacteria in a prospective multicenter observational study of febrile infants ≤60 days of age.

METHODS

Patients

We performed a planned secondary analysis of a prospective observational study that enrolled a convenience sample of infants ≤60 days of age. Infants were eligible for the parent study if they had rectal temperatures ≥38°C (measured at home, by the primary care physician, or in the ED) and blood cultures performed as part of clinical care.[18] The study was conducted in the Pediatric Emergency Care Applied Research Network (PECARN) between December 2008 and May 2013. Subject enrollment excluded children with congenital heart disease, prematurity (≤36 weeks' gestation), inherited or acquired immunodeficiency, indwelling devices or catheters, critical illness, or treatment with antibiotics in the preceding 48 hours.[18] This secondary analysis included patients with any blood or CSF culture with bacterial growth noted and with documentation of notification time for a positive culture result and included 24 sites. Institutional review board approval was obtained at each participating site.

End Points

Clinicians completed standardized case report forms to document patient history and physical examination findings in each of the enrolled infants. Laboratory reports of the blood and CSF cultures from the health records of enrolled infants were blinded at the site and uploaded to a central repository. Three study principal investigators (pediatric emergency and pediatric infectious disease physicians) classified all organisms identified in blood and CSF cultures as pathogens or contaminants, as described previously.[18] Time to positivity was determined as the difference between the time of culture collection and the time to earliest notification of positivity reported in hours and 10ths of hours. For blood cultures, time to positivity was defined as the notification of a positive growth from the automated blood culture detection system used at all study sites. For CSF cultures, time to positivity was defined as the earliest notification of either a positive culture, typically performed twice daily by microbiology laboratories at each study site or the time to positive Gram-stain notification defined as the earliest notification of documented communication of Gram-stain positive for bacteria.

Race was categorized as white, Black, and other. Ethnicity was categorized as Hispanic and/or Latino, not Hispanic and/or Latino, or unknown. Time of ED visit was categorized as 24:00 to 7:59, 8:00 to 15:59, and 16:00 to 23:59. Duration of fever was categorized as <12, 12 to 24, or >24 hours before the time of presentation to the ED.

Statistical Analysis

Analyses were conducted at the patient level for both blood and CSF cultures. The time to positivity for blood and CSF cultures was summarized using medians and interquartile ranges (IQRs) overall, by 12-hour categories, by organism, by organism group within the categories of bacterial pathogen or contaminant, and by age (≤28 days vs 29–60 days). Time to positivity was compared between characteristic groups using the Wilcoxon rank test without continuity correction (for 2 categories) or the Kruskal–Wallis test by ranks (for ≥3 categories). Statistical analyses were performed using SAS software version 9.4 (SAS Institute, Inc, Cary, NC). Time to positivity plots for blood and CSF cultures were created, comparing pathogens to contaminants.

RESULTS

Two hundred and fifty-six of 303 (84.49%) patients with positive blood cultures and 73 of 88 (83.0%) patients with positive CSF cultures met inclusion criteria for this planned secondary analysis. The median time to positive blood culture for pathogenic bacteria ($n = 74$) was 16.6 hours (IQR: 12.6–21.9 hours) and for bacteria classified as contaminants ($n = 182$) was 25.1 hours (IQR: 19.8–33.0 hours; $P < .001$; Table 1). Within each blood culture group (pathogenic versus contaminant bacteria), there were no significant differences in the distributions of time to positivity by patient demographic or clinical presentation characteristics (Table 1). Blood cultures with bacterial pathogens from infants 0 to 28 days of age had similar times to positivity (15.8 hours) as those of infants 29 to 60 days of age (17.2 hours; $P = .33$;

TABLE 1 Blood Culture Time to Positivity by Patient Demographics and Clinical Characteristics

	Pathogens			Contaminants			Pathogen-Contaminant Comparison
	n (%)	Time to Positivity, Median (IQR), h	*P*[a]	*n* (%)	Time to Positivity, Median (IQR), h	*P*[a]	*P*[a]
Total population	74	16.6 (12.6–21.9)	—	182	25.1 (19.8–33.0)	—	<.001
Sex			.787			.856	
Male	39 (52.7)	17.2 (12.5–21.5)	—	123 (67.6)	25.1 (19.8–33.3)	—	<.001
Female	35 (47.3)	15.8 (12.6–24.3)	—	59 (32.4)	25.0 (19.5–32.9)	—	<.001
Age group, d			.328			.251	
0–28	41 (55.4)	15.8 (12.6–21.0)	—	77 (42.3)	24.5 (19.2–31.8)	—	<.001
29–60	33 (44.6)	17.2 (12.9–24.3)	—	105 (57.7)	25.5 (20.6–34.8)	—	<.001
Race category (white, Black, other)[b]			.418			.650	
White	45 (64.3)	14.4 (12.0–21.9)	—	110 (64.3)	25.0 (19.0–33.7)	—	<.001
Black or African American	19 (27.1)	19.3 (13.7–21.0)	—	44 (25.7)	25.2 (21.3–36.1)	—	<.001
Other	6 (8.6)	18.0 (13.6–24.3)	—	17 (9.9)	25.0 (20.6–29.0)	—	.16
Ethnicity			.597			.107	
Hispanic or Latino	18 (24.3)	14.8 (12.4–22.0)	—	55 (30.2)	23.4 (18.5–32.7)	—	.001
Not Hispanic or Latino	56 (75.7)	17.3 (13.0–21.9)	—	122 (67.0)	25.9 (20.6–33.9)	—	<.001
Unknown	0 (0)		—	5 (2.7)	21.8 (20.8–21.9)	—	—
Categories of date and time of ED discharge[c]			.885			.327	
00:00–08:00	13 (17.6)	14.4 (12.4–22.0)	—	48 (26.5)	27.2 (20.6–35.8)	—	.005
08:00–16:00	20 (27.0)	19.4 (13.0–21.9)	—	32 (17.7)	26.2 (20.5–32.7)	—	<.001
16:00–24:00	41 (55.4)	16.1 (12.7–21.5)	—	101 (55.8)	24.2 (19.2–33.7)	—	<.001
Duration of fever before ED visit[d]			.366			.754	
<12 h	37 (68.5)	14.3 (12.0–20.5)	—	99 (67.8)	25.0 (19.8–32.8)	—	<.001
12–24 h	12 (22.2)	19.3 (14.2–23.1)	—	35 (24.0)	23.0 (18.2–36.7)	—	.01
>24 h	5 (9.3)	12.9 (12.5–22.0)	—	12 (8.2)	23.4 (18.8–29.9)	—	.09

—, not applicable.

[a] Kruskal–Wallis test for comparing 3 or more groups. Wilcoxon rank test without continuity correction for comparing 2 groups.

[b] The variable race category had 4 missing values for pathogens and 11 missing values for contaminants.

[c] The variable date and time of ED discharge had 1 missing value for contaminants.

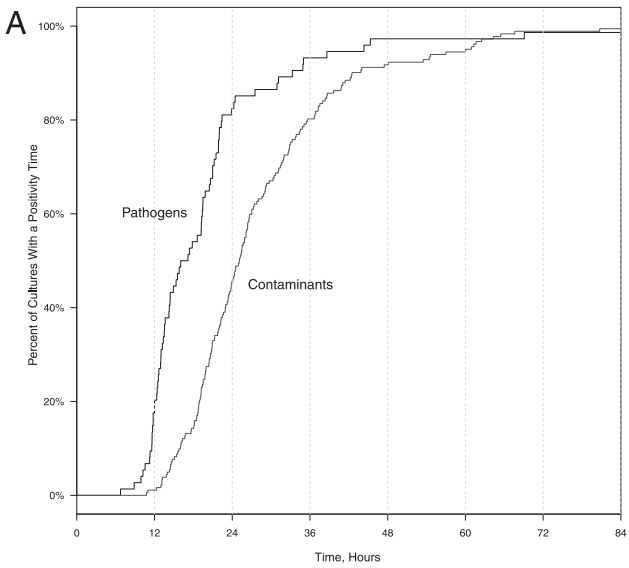
[d] The variable duration of fever had 20 missing values for pathogens and 36 missing values for contaminants.

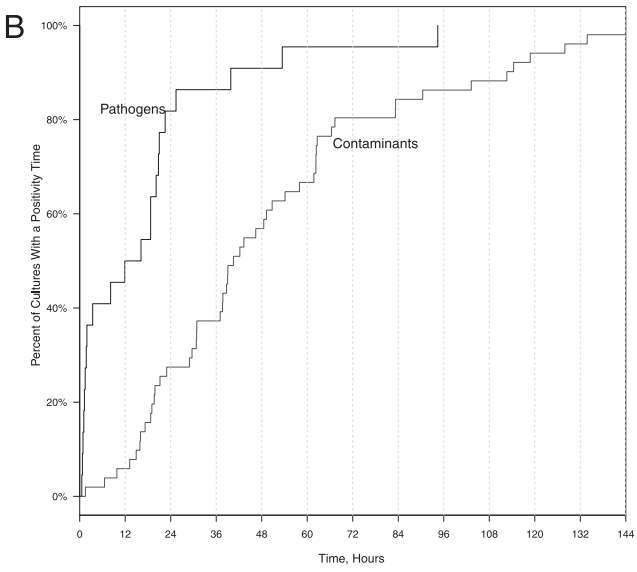
TABLE 2 CSF Culture Time to Positivity by Demographics and Clinical Characteristics

	Pathogens			Contaminants			Pathogen-Contaminant Comparison
	n (%)	Time to Positivity, Median (IQR), h	*P*[a]	*n* (%)	Time to Positivity, Median (IQR)	*P*[a]	*P*[a]
Total population	22	14.0 (1.5–21.0)	—	51	40.5 (21.2–62.6)	—	<.001
Sex			.071			.435	
Male	11 (50.0)	21.0 (1.5–39.8)	—	37 (72.5)	39.1 (21.2–62.3)	—	0.034
Female	11 (50.0)	8.2 (1.3–18.7)	—	14 (27.5)	52.0 (29.6–83.3)	—	<.001
Age group, d			.481			.027	
0–28	17 (77.3)	8.2 (1.3–20.8)	—	18 (35.3)	24.7 (17.3–50.8)	—	.021
29–60	5 (22.7)	18.7 (11.9–21.0)	—	33 (64.7)	46.4 (37.0–67.3)	—	.002
Race category (white, Black, other)			.787			.506	
White	8 (40.0)	9.0 (1.0–30.3)	—	30 (61.2)	38.9 (28.9–54.2)	—	.013
Black or African American	9 (45.0)	3.4 (1.5–22.5)	—	12 (24.5)	62.0 (25.3–97.9)	—	.002
Other	3 (15.0)	18.7 (11.9–20.2)	—	7 (14.3)	58.0 (9.8–90.5)	—	.569
Ethnicity			.592			.120	
Hispanic or Latino	6 (30.0)	17.4 (8.2–21.0)	—	16 (32.7)	38.9 (19.2–47.5)	—	.090
Not Hispanic or Latino	14 (70.0)	7.7 (1.3–20.8)	—	33 (67.3)	50.8 (22.9–67.3)	—	<.001
Categories of date and time of ED discharge			.285			.165	
00:00–08:00	5 (22.7)	1.9 (1.1–8.2)	—	13 (25.5)	62.6 (30.9–103.3)	—	.005
08:00–16:00	6 (27.3)	10.8 (0.7–21.0)	—	11 (21.6)	43.3 (28.9–58.0)	—	.004
16:00–24:00	11 (50.0)	18.7 (3.4–39.8)	—	27 (52.9)	38.7 (19.7–61.8)	—	.055
Duration of fever before ED visit			.255			.420	
<12 h	10 (58.8)	12.2 (1.5–20.8)	—	26 (63.4)	47.5 (28.9–83.3)	—	.001
12–24 h	4 (23.5)	19.4 (9.6–22.8)	—	14 (34.1)	38.2 (19.0–42.2)	—	.089
>24 h	3 (17.6)	0.9 (0.7–11.9)	—	1 (2.4)	66.4 (66.4–66.4)	—	.180

The variable race category had 2 missing values for pathogens and 2 missing values for contaminants. The variable ethnicity had 2 missing values for pathogens and 2 missing values for contaminants. The variable duration of fever had 5 missing values for pathogens and 10 missing values for contaminants. —, not applicable.

[a] Kruskal–Wallis test for comparing ≥3 groups. Wilcoxon rank test without continuity correction for comparing 2 groups.





Result Times	Blood Cultures	
	Pathogen Proportion Positive (95% CI)[1,2]	Contaminant Proportion Positive (95% CI)[1,3]
12 h	20.3% (11.8%–31.2%)	1.1% (0.1%–3.9%)
18 h	54.1% (42.1%–65.7%)	14.3% (9.5%–20.2%)
24 h	82.4% (71.8%–90.3%)	45.6% (38.2%–53.1%)
36 h	93.2% (84.9%–97.8%)	80.2% (73.7%–85.7%)
48 h	97.3% (90.6%–99.7%)	91.8% (86.8%–95.3%)

Result Times	CSF Cultures	
	Pathogen Proportion Positive (95% CI)[1,4]	Contaminant Proportion Positive (95% CI)[1,5]
12 hrs	50.0% (28.2%–71.8%)	5.9% (1.2%–16.2%)
18 hrs	54.5% (32.2%–75.6%)	15.7% (7.0%–28.6%)
24 hrs	81.8% (59.7%–94.8%)	27.5% (15.9%–41.7%)
36 hrs	86.4% (65.1%–97.1%)	37.3% (24.1%–51.9%)
48 hrs	90.9% (70.8%–98.9%)	56.9% (42.2%–70.7%)

FIGURE 1 Time to positivity of pathogens and contaminants in (A) blood cultures and (B) CSF cultures. A, Time to positivity for blood cultures. B, Time to positivity for CSF cultures. CI, confidence interval. [a]Exact binomial confidence interval. [b]Pathogen $n = 74$. [c]Contaminant $n = 182$. [d]Pathogen $n = 22$. [e]Contaminant $n = 51$.

Table 1). However, blood cultures growing bacterial pathogens had shorter times to positivity than cultures with contaminants across all patient characteristics, including for both infant age groups (0–28 days of age and 29–60 days of age; Table 1).

CSF with pathogenic bacteria ($n = 22$) had shorter times to positivity (median: 14.0 hours, IQR: 1.5–21.0 hours) than CSF with contaminant bacteria ($n = 51$; median: 40.5 hours, IQR: 21.2–62.6 hours; $P < .001$, Table 2). Of note, 50% of CSF pathogens were positive within 12 hours (Fig 1). When stratified by age, time to CSF positivity was shorter for pathogens than contaminants in infants 0 to 28 days (8.2 hours vs 24.7 hours; $P = .021$; Table 2). Of the CSF with pathogenic bacteria, 10 of 22 had minimum time to positivity determined by initial Gram-stain notification (8 group B *Streptococcus*, 2 other organisms) and 12 of 22 determined by culture notification.

By 24 hours, 82.4% of blood and 81.8% of CSF cultures growing bacterial pathogens were positive. By 36 hours, 93.2% of blood and 86.4% of CSF cultures growing bacterial pathogens were positive. The differences in times to positive cultures between pathogenic and contaminant bacteria isolated in blood and CSF and the proportions of each that became positive in 12-hour increments is presented graphically in Fig 1 A and B, respectively. Of the 4 CSF pathogenic cultures positive after 24 hours (Table 3), 1 had a CSF pleocytosis (CSF white blood count >4000), 2 had 0 to 2 white blood count on CSF studies, and 1 did not have CSF cell counts obtained.

Median time to positivity for blood and CSF varied by type of bacteria isolated (Table 3, Supplemental Fig 2). For example, *Escherichia coli*, the most common pathogenic bacteria isolated in blood cultures, had a median time to positivity of 13.6 hours (IQR: 12.0–20.6 hours; Table 3). Non-aureus staphylococcal species was the most common contaminant bacterium isolated from blood cultures and had a median time to positivity of 26.2 hours (IQR: 22.1–32.8 hours). Group B *Streptococcus*, the most frequent pathogenic bacterium identified in the CSF, had a median time to positivity of 1.7 hours (IQR: 1.1–3.4 hours; Table 3), with 88.9% of Group B *Streptococcus* visits positive in 12 hours and all positive within 24 hours. Of the other CSF pathogenic species (*E coli*, *Enterobacter cloacae*, *Enterococcus faecalis*, *Klebsiella oxytoca*, *Listeria monocytogenes*, *Neisseria meningitidis*, and *Streptococcus pneumoniae*), 75% were also positive within 24 hours, and the single staphylococcal species considered to be a pathogen was not positive until >72 hours (Table 3). Staphylococcal species categorized as contaminants in the CSF had a median time to positivity of 49.6 hours (IQR: 19.7–62.5 hours).

DISCUSSION

In this multicenter study in a cohort of febrile infants ≤60 days of age, we documented that bacterial pathogens in CSF grow faster in culture than bacterial contaminants and reaffirm previous findings that the time to culture positivity in blood is shorter for pathogens than for

TABLE 3 Blood and CSF Culture Organism and Time to Positivity

	Overall, *n* (%)	Time to Positivity, Median (IQR), h	Time to Positivity Categories, *n* (%)						
			≤12 h	>12–≤24 h	>24–≤36 h	>36–≤48 h	>48–≤60 h	>60–≤72 h	>72 h
Blood culture time to positivity									
Pathogens, category of blood organism									
E coli	29 (39.2)	13.6 (12.0–20.6)	8 (27.6)	14 (48.3)	5 (17.2)	1 (3.4)	0 (0)	1 (3.4)	0 (0.0)
Enterobacter	4 (5.4)	13.7 (12.7–15.8)	0 (0.0)	4 (100.0)	0 (0.0)	0 (0.0)	0 (0)	0 (0.0)	0 (0.0)
GBS	17 (23.0)	14.3 (12.6–20.5)	4 (23.5)	12 (70.6)	1 (5.9)	0 (0.0)	0 (0)	0 (0.0)	0 (0.0)
Klebsiella	2 (2.7)	17.3 (12.7–22.0)	0 (0.0)	2 (100.0)	0 (0.0)	0 (0.0)	0 (0)	0 (0.0)	0 (0.0)
Staph aureus	9 (12.2)	19.4 (19.2–21.0)	0 (0.0)	9 (100.0)	0 (0.0)	0 (0.0)	0 (0)	0 (0.0)	0 (0.0)
Mixed	1 (1.4)	22.3 (22.3–22.3)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0)	0 (0.0)	0 (0.0)
Other	12 (16.2)	21.9 (12.9–38.8)	3 (25.0)	4 (33.3)	2 (16.7)	2 (16.7)	0 (0)	0 (0.0)	1 (8.3)
Contaminants, category of blood organism									
Staphylococcus species	104 (57.1)	26.2 (22.1–32.8)	0 (0.0)	39 (37.5)	44 (42.3)	12 (11.5)	2 (1.9)	6 (5.8)	1 (1.0)
Streptococcus species	22 (12.1)	19.7 (16.0–27.8)	1 (4.5)	14 (63.6)	6 (27.3)	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)
Mixed	32 (17.6)	20.6 (15.3–25.2)	1 (3.1)	20 (62.5)	7 (21.9)	2 (6.3)	1 (3.1)	1 (3.1)	0 (0.0)
Other	24 (13.2)	34.1 (21.2–43.1)	0 (0.0)	8 (33.3)	6 (25.0)	6 (25.0)	2 (8.3)	1 (4.2)	1 (4.2)
CSF time to positivity (earliest notification of Gram-stain or Culture)[a]									
Pathogens, category of CSF organism									
GBS[b]	9 (40.9)	1.7 (1.1–3.4)	8 (88.9)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0)	0 (0.0)
Staphylococcus species[c]	1 (4.5)	94.4 (94.4–94.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0)	1 (100.0)
Other[d]	12 (54.5)	20.5 (14.0–24.0)	3 (25.0)	6 (50.0)	1 (8.3)	1 (8.3)	1 (8.3)	0 (0)	0 (0.0)
Contaminants, category of CSF organism									
Staphylococcus species[e]	24 (47.1)	49.6 (19.7–62.5)	1 (4.2)	6 (25.0)	1 (4.2)	3 (12.5)	4 (16.7)	5 (20.8)	4 (16.7)
Streptococcus species[f]	8 (15.7)	30.8 (17.2–34.0)	1 (12.5)	2 (25.0)	3 (37.5)	1 (12.5)	0 (0.0)	1 (12.5)	0 (0.0)
Other[g]	19 (37.3)	43.3 (28.9–90.5)	1 (5.3)	3 (15.8)	1 (5.3)	6 (31.6)	1 (5.3)	1 (5.3)	6 (31.6)
CSF positivity reflecting Gram-stain only									
Pathogens, category of CSF organism									
GBS	8 (80.0)	1.6 (1.0–2.7)	8 (100.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Staphylococcus species	0 (0.0)		0 (0.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other	2 (20.0)	1.0 (0.7–1.3)	2 (100.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Contaminants, category of CSF organism									
Staphylococcus species	1 (50.0)	6.6 (6.6–6.6)	1 (100.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Streptococcus species	1 (50.0)	1.5 (1.5–1.5)	1 (100.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other	0 (0.0)		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
CSF positivity reflecting culture only									
Pathogens, category of CSF organism									

TABLE 3 Continued

	Overall, *n* (%)	Time to Positivity, Median (IQR), h	Time to Positivity Categories, *n* (%)						
			≤12 h	>12–≤24 h	>24–≤36 h	>36–≤48 h	>48–≤60 h	>60–≤72 h	>72 h
GBS	4 (25.0)	17.6 (15.2–22.5)	0 (0.0)	3 (75.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0)	0 (0.0)
Staphylococcus species	1 (6.3)	94.4 (94.4–94.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0)	1 (100.0)
Other	11 (68.8)	21.0 (18.7–39.8)	1 (9.1)	6 (54.5)	1 (9.1)	2 (18.2)	1 (9.1)	0 (0)	0 (0.0)
Contaminants, category of CSF organism									
Staphylococcus species	23 (46.9)	50.8 (19.8–62.6)	0 (0.0)	6 (26.1)	1 (4.3)	3 (13.0)	4 (17.4)	5 (21.7)	4 (17.4)
Streptococcus species	7 (14.3)	30.8 (21.2–37.0)	0 (0.0)	2 (28.6)	3 (42.9)	1 (14.3)	0 (0.0)	1 (14.3)	0 (0.0)
Other	19 (38.8)	43.3 (28.9–90.5)	1 (5.3)	3 (15.8)	1 (5.3)	6 (31.6)	1 (5.3)	1 (5.3)	6 (31.6)

GBS, group B *Streptococcus*.

[a] This reflects the minimum time to positivity time defined as the earliest notification of either a positive culture or the earliest notification of documented communication of Gram-stain positive for bacteria.

[b] Category contains GBS.

[c] Category contains Staphylococcus aureus.

[d] Category contains *E coli*, *E cloacae*, *E faecalis*, *K oxytoca*, *Klebsiella pneumoniae*, moderate *L Monocytogenes*, *Neisseria meningitidis*, *Streptococcus pneumoniae*.

[e] Category contains Staphylococcus coagulase negative, Staphylococcus epidermidis, Staphylococcus non-aureus.

[f] Category contains α-hemolytic *Streptococcus*, nonhemolytic *Streptococcus*, Streptococcus mitis, Streptococcus viridans, *Streptococcus anginosus*, *Streptococcus parasanguinis*.

[g] Category contains *Acinetobacter* species, aerobic Gram-positive rod, α-hemolytic *Streptococcus*, diphtheroids, α-hemolytic *Streptococcus*, mixed, multiple flora, organisms, α-hemolytic *Streptococcus*, *Neisseria* meningitidis, *Haemophilus* parainfluenzae, *Bacillus* species, Corynebacteria, *Micrococcus*, *Peptostreptococcus*, Propionibacteria, Staphylococcus aureus, *Klebsiella pneumoniae*, *Alcaligenes* species, bifidobacterium species from subculture only, Gram-positive coccobacilli, rare *Streptococcus* species (2 CFUs only),α-hemolytic *Streptococcus*, coryneform Gram-positive rods isolated from broth media only, *Staphylococcus* capitis subsp. capitis,*Staphylococcus* haemolyticus.

contaminants. We found that within a 24-hour observation period, >82% of the blood cultures growing pathogenic bacteria were identified. Our findings are similar to those of Biondi et al,[13] who used data from the Pediatric Research in Inpatient Setting Network to report that 91% of infants 90 days of age and younger whose blood cultures were growing pathogenic bacteria were identified within 24 hours. In our cohort, we did not find a difference in time to positivity of pathogens in blood culture based on patient age group (younger or older than 28 days of age). This is similar to Aronson et al,[14] who, in a retrospectively identified group of both ill and well appearing infants, found 88% of pathogenic bacteria positive within 24 hours without differences in time to positive culture for those <28 or >28 days of age.

To our knowledge, this is the first study of time to positivity for CSF pathogens in this age group and limited to prospectively identified ED patients. Retrospective cohort identification has been shown to underidentify young febrile infants, particularly those prone to serious outcomes such as bacteremia and bacterial meningitis.[17] Although analysis of CSF cultures typically requires manual monitoring, as opposed to automated blood culture systems, with our data, including culture and Gram-stain identification, we suggest that most pathogens are identifiable within 24 hours. Gram-stain identification, included in this study, is an important component of usual care and strengthens the results of our study.

We found that time to positivity for blood and CSF cultures varied by bacterial species. The pathogenic bacteria and time to positivity for blood cultures in our study closely resemble the organisms and times reported previously, with *E coli* and group B *Streptococcus* accounting for most cases.[13]

Our study has several limitations. First, we were only able to include cultures with earliest notification culture results documented. However, we do not have reason to believe that there was systematic bias in notification of documentation by bacterial species. Although we used an a priori categorization of pathogenic or contaminant organisms, there is controversy in the published literature as to these determinations.[19] In addition, temporal changes of the epidemiology of pathogens should always be considered.[20] We measured times from culture collection to positive culture result and were unable to account for the time it took from culture collection to laboratory arrival or processing. We did not standardize the procedure for obtaining blood or CSF cultures, the amount of blood inoculated or CSF provided, or the laboratory processes at each site. The manual assessment of CSF cultures can impact the precision of assessing time to positivity (eg, cultures may have been positive before the scheduled assessment time); however, our data reveal that most CSF pathogens were identified within 24 hours despite this limitation. This "real life" determination of time to positivity within the study reflects current practice within hospitals.

Reduced variation in patient care, often accomplished with implementation of clinical care guidelines, can improve the quality of that care. The American Academy of Pediatrics' Quality Improvement Innovation Networks and Value in Inpatient Pediatrics Network are currently undertaking a multicenter improvement project, Reduce Excessive Variability in Infant Sepsis Evaluations, which has a goal of reducing hospitalization length of stay.[21] Our findings have direct implications for development of clinical care guidelines that address the goals to reduce duration of hospitalization and provide antimicrobial stewardship while providing safe care for febrile infants. From our data, any observation period of hospitalized febrile infants <24 hours would miss ≤18% of patients with bacteremia or bacterial meningitis. Furthermore, if febrile infants are discharged before 24 hours, we believe adequate follow-up should be ensured within 24 hours. Our data can help inform an evidence-based approach to determining the duration of inpatient hospitalizations and empirical antibiotic treatment in young febrile infants. For instance, restriction of empirical antibiotics to 24 hours instead of 48 hours is expected to improve antimicrobial stewardship and likely improve cost effectiveness without compromising patient safety.

Among febrile infants ≤60 days of age who had positive blood and/or CSF cultures, the time to positivity was significantly shorter for bacterial pathogens than contaminants. Among blood cultures, >80% were positive within 24 hours. Our findings have direct implications for duration of hospitalization and antibiotic therapy for febrile infants in the ED.

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Dr Alpern conceived and designed the study, supervised patient enrollment and data abstraction, contributed to data analysis, and drafted the initial manuscript; Dr Kuppermann conceived and designed the study, obtained funding, supervised patient enrollment and data abstraction, contributed to data analysis, and revised the manuscript; Drs Blumberg, Roosevelt, Cruz, Nigrovic, and Browne supervised patient enrollment and data abstraction, contributed to study design, and revised the manuscript; Dr Van Buren 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 and revised the manuscript; Dr Ramilo conceived and designed the study, obtained funding, and revised the manuscript; and Dr Mahajan conceived and designed the study, obtained funding, supervised patient enrollment and data abstraction, contributed to data analysis, and revised the manuscript; and all authors approved the final manuscript as submitted.

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