Management and Outcomes of Previously Healthy, Full-Term, Febrile Infants Ages 7 to 90 Days

Tara L. Greenhow, MD,[a] Yun-Yi Hung, PhD,[b] Robert H. Pantell, MD[c]

abstract

BACKGROUND: There is considerable variation in the approach to infants presenting to the emergency department and outpatient clinics with fever without a source. We set out to describe the current clinical practice regarding culture acquisition on febrile young infants and review the outcomes of infants with and without cultures obtained.

METHODS: This study analyzed Kaiser Permanente Northern California's electronic medical record to identify all febrile, full term, previously healthy infants born between July 1, 2010, and June 30, 2013, presenting for care between 7 and 90 days of age.

RESULTS: During this 3-year study, 96 156 full-term infants were born at Kaiser Permanente Northern California. A total of 1380 infants presented for care with a fever with an incidence rate of 14.4 (95% confidence interval: 13.6–15.1) per 1000 full term births. Fifty-nine percent of infants 7 to 28 days old had a full evaluation compared with 25% of infants 29 to 60 days old and 5% of infants 61 to 90 days old. Older infants with lower febrile temperatures presenting to an office setting were less likely to have a culture. In the 30 days after fevers, 1% of infants returned with a urinary tract infection. No infants returned with bacteremia or meningitis.

CONCLUSIONS: Fever in a medical setting occurred in 1.4% of infants in this large cohort. Forty-one percent of febrile infants did not have any cultures including 24% less than 28 days. One percent returned in the following month with a urinary tract infection. There was no delayed identification of bacteremia or meningitis.

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[a]*Kaiser Permanente Northern California, San Francisco, California;* [b]*Kaiser Permanente Division of Research, Oakland, California; and* [c]*University of California San Francisco, San Francisco, California*

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Address correspondence to Tara L. Greenhow, MD, Department of Pediatrics, Division of Infectious Diseases, Kaiser Permanente Northern California, 2200 O'Farrell St, San Francisco, CA 94115. E-mail: tara.greenhow@kp.org

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WHAT'S KNOWN ON THIS SUBJECT: There is wide variation in testing and management of the febrile young infant. Controversy exists regarding the appropriateness of testing febrile, well appearing infants.

WHAT THIS STUDY ADDS: Fever in a medical setting occurred in 1.4% of infants in this population-based study. Forty-one percent did not have any cultures obtained including 24% less than 28 days. There was no delayed identification of bacteremia or meningitis.

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It is estimated that 7% to 12.8%[1–17] of febrile infants less than 3 months will have a serious bacterial infection (SBI; includes urinary tract infection [UTI], bacteremia, and/or meningitis); however, there is considerable variation in the approach to infants presenting to the emergency department (ED) and outpatient clinics with fever.[1,18–21] The diagnostic strategy advocated for febrile infants includes urine, blood, and cerebrospinal fluid (CSF) cultures, but depending on age many do not have all 3 cultures or any cultures obtained.[1,19–22] Over 25% of febrile infants less than 3 months do not have any cultures collected[1,19,21] yet have low return rates to EDs[19,21] and outpatient clinics.[1,18]

As bacteremia rates drop,[23] it is unclear if fewer blood cultures are obtained and bacteremia cases are missed. UTIs are the most frequent infections and lead to bacteremia and meningitis in 6.5% to 10%[2,24] and 0.3% to 0.7%,[2,24,25] respectively. Despite current recommendations for urine testing, practitioners may not ever screen those at highest risk for UTIs such as uncircumcised boys and girls.[1,18]

Concomitant confirmed viral infections reduce the probability of SBIs from 12.3% to 4.2% and bacteremia from 2.7% to 1%.[5] However, many continue to recommend bacterial testing for all febrile young infants. It is unclear if the documented selective testing now focuses on those at highest risk.

Despite the extensive literature on febrile infants, to our knowledge there is no current data on the occurrence or evaluation of fever in a large managed care population. Using a population-based approach in a large health care organization in Northern California, the purpose of this study was to (1) determine the incidence rate of fever and underlying SBIs in young infants presenting for medical care, (2) describe the current clinical practice regarding acquisition of blood, urine, and CSF cultures on febrile young infants, (3) review the outcomes of febrile infants with and without bacterial culture evaluations, and (4) document the reasons physicians do not obtain cultures.

METHODS

The Kaiser Foundation Research Institute's Institutional Review Board approved this study.

Study Design

This study retrospectively analyzed Kaiser Permanente Northern California's (KPNC's) electronic medical record (EMR) system to identify all febrile (rectal or axillary ≥38°C), full term (≥37 weeks at birth), previously healthy infants born between July 1, 2010, and June 30, 2013, presenting for care between 7 and 90 days of age. A medical setting was defined as a clinician's office, ED, or first 24 hours of hospitalization.

All infants born between July 1, 2010, and June 30, 2013, with a fever between 7 and 90 days in a medical setting were captured. Additionally, to capture infants febrile outside a medical setting, febrile infants born between January 1, 2012, and June 30, 2013, were identified by (1) *International Classification of Diseases, Ninth Revision* (ICD-9) codes of "fever" (780.6, 780.60, 780.61) and (2) call center advice calls, telephone appointments, and ED and clinic visits with chief complaint of fever. These charts were manually reviewed for temperature taken at home and the duration of elevated temperature.

Infants with underlying medical conditions (neuromuscular, cardiovascular, respiratory, gastrointestinal, metabolic, hematologic, immunologic, other congenital or genetic, malignant, or renal abnormalities) were excluded as determined by ICD-9 codes.[26,27] Postoperative fevers were excluded. Fevers in the hospital setting were reviewed to confirm no operative notes in the day before the fever. Data on age, gender, race/ethnicity, circumcision status for boys, laboratory studies (if obtained), ill appearance, antibiotic prescriptions, source of febrile temperature (home, medical setting or both), height, and duration of temperature were either extracted from EMR or obtained from charts. To be included in the "ill" category, 1 of the following terms had to be documented in the medical records: "toxic," "lethargic," "ill," "ill appearing," "irritable," "nonresponsive," or "inconsolable." Standard definitions of bacteremia, UTI, and meningitis have been previously defined.[2,22,28] For all febrile infants, clinic notes of all visits and cultures obtained for the next month were reviewed. Recent immunization was defined as immunization in previous 48 hours to fever presentation.

As of December 2011, Kaiser Permanente had 3.2 million members in Northern California, more than 40 pediatric clinics, 19 EDs, and 10 pediatric hospital wards. At several facilities, a pediatric consult is available for in-person evaluation in the ED. In 2009, 59% of enrolled women of child bearing age were white, 5% were African American, 18% were Asian, 17% were Latino/Hispanic, and 1% were "Other." The mean household income was $86 238 (SE $2366).[29]

Statistical Analysis

Comparisons involving categorical variables were performed by using the χ^2 or Fisher's exact test. Normally distributed continuous variables were compared by using analysis of variance. Comparisons of nonnormally distributed continuous variables were conducted by using the Wilcoxon rank-sum test. All statistical tests were 2-sided, and $P < .05$ was considered statistically

TABLE 1 Incident Rate of Fever in a Medical Setting and SBI per 1000 Full Term Infants

	Incident Rate (CIs)					
	Fever	UTI	Bacteremia	Meningitis	UTI + Bacteremia	UTI + Bacteremia + Meningitis
Age, d						
7–28	3.4 (1.1)	0.5 (0.2)	0.05 (<.01–0.1)	0	0.1 (<.1)	0.01 (<.01)
29–60	6.5 (2.8)	0.8 (0.4)	0.06 (<.01–0.1)	0.01 (<.01–0.1)	0.06 (<.01)	0.01 (<.01)
61–90	4.4 (1.6)	0.4 (0.1)	0	0	0.04 (<.01)	0.01 (<.01)

TABLE 2 Infants (N = 1380) Febrile in a Medical Setting With and Without Cultures

	No Culture Total, N = 442	Culture[a] Total, N = 938	No Culture Versus Culture
	N (%)		P
Age, d			
7–28	78 (18)	252 (27)	<.0001
29–60	177 (40)	448 (48)	
61–90	187 (42)	238 (25)	
Uncircumcised boys	102 (23)	267 (29)	.02
Girls	205 (46)	442 (47)	
Circumcised boys	135 (31)	229 (24)	
Temperature °C			
38–38.3	328 (74)	369 (39)	<.0001
38.4–38.8	92 (21)	352 (38)	
38.9–39.4	17 (4)	164 (17)	
>39.4	5 (1)	53 (6)	
Ill appearance	8 (2)	65 (7)	<.0001
Documentation of fever			
Outpatient clinic	311 (70)	254 (27)	<.0001
ED	111 (25)	429 (46)	
Hospital	20 (5)	255 (27)	

[a] Had at least 1 culture collected.

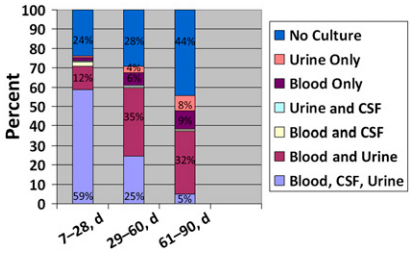

FIGURE 1
Culture acquisition by age.

significant. The statistical program used was SAS 9.3 (SAS Institute, Inc, Cary, NC).

RESULTS

Infants Febrile at Medical Setting

During this 3-year study, 96 156 full-term infants were born at KPNC. A total of 1380 infants received care for fever in a medical setting between 7 and 90 days of age; an incidence rate of 14.4/1000 full term infants (95% confidence interval [CI]: 13.6–15.1). One hundred ninety-five (14%) infants had infections, including 183 infants with a UTI (13.2%), 36 (2.6%) with bacteremia, and 4 (0.3%) with meningitis. Twenty-five infants had multiple sites of infection, including 22 with bacteremia accompanying UTIs and 3 with meningitis and bacteremia accompanying UTIs.

Infections were identified in 18.8% of infants 7 and 28 days old, 13.9% of infants 29 and 60 days old, and 10.8% of infants 61 and 90 days old. The incidence of bacteremia accompanying UTI was highest from 7 to 28 days (Table 1). There was a decrease in the rate of infants seen in a medical setting with an ICD-9 diagnosis of fever (P = .01) over the 3-year study.

Sixty-eight percent (938 of 1380) of infants had at least 1 culture obtained. Older infants with lower febrile temperatures presenting to an office setting were less likely to have a culture. The mean temperature of infants without cultures was lower than those cultured (38.3°C versus 38.6°C, P < .001). Infants evaluated in an ED were 5 times more likely to be cultured than infants in an office setting (P < .0001). Nonill appearing infants were 3 times as likely to be evaluated without a culture (P < .0001; Table 2).

Infants 7 to 28 days were more likely to get a complete sepsis evaluation including urine, blood, and CSF cultures (Fig 1). The average number of cultures obtained in febrile infants 7 to 28, 29 to 60, and 61 to 90 days was 2.05, 1.58, and 0.99, respectively (P < .0001). Fifty-nine percent of infants 7 to 28 days had a full evaluation compared with 25% of infants 29 to 60 days and 5% of infants 61 to 90 days. More infants 29 to 90 days had only a blood culture obtained instead of a urine culture, 15% vs 12%, respectively (Fig 1).

Evaluating the results of urine, blood, and CSF (positive, negative, and not done) by age, infants age 7 to 28 days had the highest percent positive and highest percent tested (Table 3). Ill appearance was infrequent, occurring in 72 infants. More ill appearing infants 7 to 28 days and 29 to 60 days had urine and blood, respectively, collected than those not ill appearing. Similarly, from 29 to 60 days and 61 to 90 days, CSF was obtained more frequently with ill appearance than without (P = .007 and 0.001, respectively; Table 3). Of

TABLE 3 Results of Urine, Blood, and CSF Cultures (Positive, Negative, and Not Tested) by Age and Ill Appearance

Days	Urine, *N* (%)			*P*		Blood, *N* (%)			*P*		CSF, *N* (%)			*P*	
	UTI	Negative	Not Tested	No Culture Versus SBI	SBI Versus No SBI	Bacteremia	Negative	Not Tested	No Culture Versus SBI	SBI Versus No SBI	Meningitis	Negative	Not Tested	No Culture Versus SBI	SBI Versus No SBI
All infants															
7–28	57 (17)	180 (55)	93 (28)	<.0001	.39	18 (5)	231 (70)	81 (25)	<.0001	.01	1 (0.3)	202 (61.2)	127 (38.5)	.14	.07
29–60	80 (13)	322 (52)	223 (36)			13 (2)	407 (65)	205 (33)			2 (0.3)	164 (26.2)	459 (74.5)		
61–90	46 (11)	149 (35)	230 (54)			5 (1)	198 (47)	222 (52)			1 (0.2)	25 (5.9)	399 (93.9)		
Ill-Appearing Infants															
7–28	4 (19)	16 (76)	1 (5)	.01	.7	3 (14)	18 (86)	0	.02	.43	0	19 (90)	2 (10)	.97	.15
29–60	3 (11)	22 (78)	3 (11)			1 (4)	25 (89)	2 (7)			0	14 (50)	14 (50)		
61–90	1 (4)	12 (52)	10 (44)			1 (4)	14 (61)	8 (35)			1 (4)	5 (22)	17 (74)		

the 65 infants with ill appearance and cultures obtained, there were 3 with UTI alone, 4 with bacteremic UTI, and 1 with UTI, bacteremia, and meningitis. Ill appearance predicted SBI including bacteremic UTIs in infants 7 to 28 days, but not in older infants.

Of the 442 infants with no bacterial cultures obtained, 5 (1%) were diagnosed with a subsequent UTI in the 30 days after a fever in a medical setting. There were no cases of bacteremia or meningitis subsequently detected in these infants.

Infants Febrile Inside and Outside a Medical Setting

Among the 47 550 full term infants born during the final 18 months of the study, 1104 episodes were evaluated for fever. This included 654 febrile in a medical setting (described above) and 408 febrile only at home. Additionally, 42 infants had no documented fever recorded during a medical visit, but had either a chief complaint or final diagnosis of fever. Removing the 42 infants without documented fever, there were 1062 episodes of fever in 1026 infants with an incidence rate of fever of 21.6/1000 full term, previously healthy births (95% CI: 20.3/1000–22.9/1000). Ten (0.9%) were transferred to an outside hospital for further evaluation resulting in 1052 episodes of fever available for further analysis. Additional investigation of this subset revealed infants with prolonged fevers >1 day at time of presentation were more likely to have a SBI (19%) than those with fever ≤1 day (11%; *P* = .0056).

Fifty-nine percent (623 of 1052) had at least 1 culture obtained. The average temperature was 101.3 (median = 38.3°C). Comparing infants with no cultures to those with cultures obtained, infants with no cultures were more likely to be older, nonill appearing, circumcised boys

with lower temperatures and fevers documented outside the medical setting only (Table 4).

In this 18-month cohort, the main reasons cultures were not obtained differed by age (Table 5). In infants 7 to 28 days, the main reason cultures were not obtained (63%) was the provider not believing the elevated temperature (ie, thermometer itself or felt to be due to environmental conditions; 7–28 days versus 29–90 days, $P < .0001$). For older infants, concomitant upper respiratory symptoms and/or bronchiolitis (39%) or recent vaccination (23%) were the most likely reasons (7–28 days versus 29–90 days; $P = .002$ and <.0001, respectively).

Nineteen of 105 (18%) presenting for care with fevers after immunization had cultures; 1 infant had a UTI. Excluding the 105 infants with fever after an immunization, the incidence of fever was 19.4 per 1000 full term previously healthy infants (95% CI: 18.2–20.7).

Use of antibiotics was common. Almost 20% (208 of 1052) received oral antibiotics within the 14 days after the fever episodes, including 35 (17%) infants with no bacterial cultures obtained.

In the 30 days after a fever, 63 febrile infants had subsequent cultures, including 28 with urine cultures and 18 with blood and urine cultures collected. Ten infants returned in the subsequent 30 days with fever and UTI; 5 of the 10 did not have previous cultures obtained. With 1 month of evaluation, return rates for SBIs were 0.97% and there were no cases of bacteremia or meningitis in this group.

TABLE 4 Infants ($N = 1052$) Febrile Inside and Outside a Medical Setting With and Without Cultures

	No Culture Total ($n = 429$), *N* (%)	Culture[a] Total ($n = 623$), *N* (%)	No Culture Versus Culture, *P*
Age, d	56 (13)	172 (28)	<.0001
7–28	182 (42)	294 (47)	
29–60	191 (45)	157 (25)	
61–90			
Uncircumcised boys	96 (22)	191 (31)	.0001
Girls	193 (45)	295 (47)	
Circumcised boys	140 (33)	137 (22)	
Temperature °C			
38–38.3	305 (71)	248 (40)	<.0001
38.4–38.8	97 (23)	238 (38)	
38.9–39.4	17 (4)	102 (16)	
>39.4	10 (2)	35 (6)	
Ill appearance	3 (1)	32 (5)	<.0001
Documentation of fever			
Medical setting only	100 (23)	108 (17)	<.0001
Outside medical setting only	240 (56)	160 (26)	
Both	89 (21)	355 (57)	

[a] Had at least 1 culture collected.

TABLE 5 Reasons Cited for Cultures Not Obtained in 429 Febrile Infants

	Days Old, *N* (%)		
	7–28	29–60	61–90
Reason cultures not obtained			
Other diagnosis (ie, otitis media, pneumonia, etc)	8 (14)	12 (7)	10 (5)
Immunization	0	41 (22)	45 (24)
Upper respiratory symptoms/bronchiolitis	10 (18)	62 (34)	83 (43.5)
Sick contacts appeared well	3 (5)	25 (14)	31 (16)
Did not believe thermometer environmental conditions	35 (63)	35 (19)	15 (8)
Parents decline	0	5 (3)	6 (3)
Laboratory error/unknown	0	2 (1)	1 (0.5)
Total	56	182	191

DISCUSSION

In the 30 years since Dagan et al[15] described a strategy to sort febrile infants to high and low risk categories for SBI, no clinical approach has enabled clinicians to detect every infant with the infections most likely to cause rapid clinical deterioration. Similarly, although urinalysis is sensitive in detecting 87% to 98% of UTIs,[30,31] detecting all UTIs before positive culture results remains elusive. Therefore, although awaiting potentially more accurate testing or prediction rules, it is essential we evaluate emerging strategies and existing approaches in an effort to strike a balance between overtreating and underdiagnosis.

In a large enrolled population of infants from the outpatient setting, ED and first 24 hours of hospitalization, the overall occurrence of fever was 2.2% including 1.4% who were seen and documented to be febrile in a medical setting. The incidence rate of fever encounters in a medical setting was 14.4/1000 full term infants (95% CI: 13.6–15.1). No cultures were obtained in 24%, 28%, and 44% of infants 7 to 28 days, 29 to 60 days, and 61 to 90 days, respectively. Outcomes of febrile infants with and without bacterial culture evaluations were uniformly reassuring with only 1% returning in the following month with a UTI.

Nearly a third of infants seen in a medical setting did not have bacterial cultures, and only 59% of febrile infants younger than 29 days had a complete evaluation. Fourteen percent of infants had a SBI including 36 with bacteremia and 4 with meningitis. Twenty-five infants had multiple sites of infection, including 22 with bacteremia accompanying

UTIs (1.6%) and 3 with meningitis and bacteremia accompanying UTIs (0.2%).

The risk of bad outcome due to delayed recognition of SBI in young infants with fever is certainly influenced by the overall low incidence of truly serious bacterial illness (bacteremia 0.4 [95% CI, 0.1–1.1] and meningitis 0.04 [95% CI, <0.01–0.1] per 1000 full term birth). Even very experienced practitioners with rapidly available diagnostic testing might not identify all seriously infected infants; however, the absence of delayed recognition is noteworthy.

Several studies have documented incomplete culturing and low rates of return for subsequent infections when infants are sent home with incomplete bacterial testing.[19,21] A multicenter ED setting of febrile neonates described low return rates for missed infections as 0.3%.[19] As a closed system, we were able to describe return rates for both the ED and office setting. We confirmed that within 1 month of initial evaluation, return rates were very low with 1% returning in the following month with a febrile UTI with no cases of missed bacteremia or meningitis.

Our study had some limitations. This was a retrospective study that relied on physician documentation. Some temperatures at home were not recorded. It is likely a small proportion of infants in the excluded group had true fevers that would have raised the incidence rate slightly. Not all temperatures at home and in a medical setting were measured rectally. There is wide variation across studies between temperature readings at the axilla and rectum.[32] We included only documented temperatures ≥38°C to be a fever.[33] As such, some febrile infants with fevers <38°C axillary may have had rectal temperatures that qualified them for inclusion. The descriptors used to categorize infants in the ill category were chosen from a prepopulated drop down menu in the EMR. Although it is possible that some physicians may have typed in other synonyms of ill and these cases were missed, this is unlikely as most chose to use terms already in the EMR. Although the vast majority of KPNC members receive all their care from a KPNC facility, a small proportion of infants may have been seen elsewhere. If an infant had a serious illness, the infant would likely return to a KPNC facility for follow-up. It is also possible that some of the infants who received antibiotics without having cultures obtained had a UTI or bacteremia; however, it seems unlikely a case of meningitis was missed. KPNC members are very similar to the insured population and general population in Northern California with regard to sociodemographic and health characteristics, but differ in several ways from a population that includes those with Medi-Cal coverage and the uninsured.[29] Despite these limitations, given the large population base, it is likely that our study accurately reported incident rates and the approach to fevers in the general population in our region.

Although older practice-based studies[1] and recent studies from EDs[19,21] indicate many of the youngest infants are not receiving the traditional complete evaluation, our analysis provides both a picture of regional care and physician explanations as to why the "standard" is not being followed. The reasons given for the majority of infants not cultured included not believing the elevated temperature, concomitant upper respiratory symptoms, and/or bronchiolitis or recent immunization. The risk of SBIs are substantially reduced if bronchiolitis is diagnosed or in the presence of positive viral tests.[5,34] With the increasing availability of rapid testing for viral respiratory pathogens and the potential for RNA transcriptional analysis in the next decade,[35,36] it is likely that clinicians may order even fewer bacterial cultures. Although viral infections may be considered a source and the risk of SBI less likely, it is unclear which bacterial cultures are then appropriate. The second most common reason cultures were not obtained in febrile infants 29 to 90 days was recent immunization (23%). As many infants will develop a fever in the 48 hours after immunization, this is not a surprising strategy on the part of clinicians. Furthermore, of those presenting for care after an immunization, 1% had a UTI (5% of those tested) and none were subsequently detected to have bacteremia or meningitis.

Nonill appearing infants comprised 95% of our sample. Of those with no cultures, only 1% were ill appearing. Ill infants without cultures had significant respiratory distress due to bronchiolitis and other presumed viral respiratory tract illness. Ill appearance was a predictor of culturing and positivity. Clinicians should continue to investigate the cause of fever in young infants who are ill appearing.

Although younger age and ill appearance predicted which infants had cultures obtained, there was a disconnect in risk-based culturing. Given the tenfold risk of UTIs in uncircumcised boys, it was surprising 28% did not have urine cultures. Despite their low risk, 63% of circumcised boys did have urine cultures.

Whereas 55% of infants seen in an outpatient clinic had no cultures, only 21% of infants seen in EDs did not have any cultures obtained. Although it is possible that the acuity of infants seen in the ED is higher than the outpatient clinic, it is also possible that pediatricians ordered fewer cultures than nonpediatric emergency medicine

physicians staffing the EDs, the pace and structure in the EDs promotes additional testing, and the pediatricians evaluating infants seen in clinic settings were more familiar with the families.

CONCLUSIONS

Fever is a common symptom in infants 7 to 90 days with an overall occurrence of fever of 2.2% including 1.4% who were febrile in a medical setting. Physicians are using selective strategies in deciding which febrile infants will have blood, urine, and CSF cultures obtained. Forty-one percent of febrile infants did not have any cultures obtained including 24% less than 28 days. One percent returned in the following month with a UTI. There was no delayed identification of bacteremia or meningitis.

ABBREVIATIONS

CI: confidence interval
CSF: cerebrospinal fluid
ED: emergency department
EMR: electronic medical record
ICD-9: *International Classification of Diseases, Ninth Revision*
KPNC: Kaiser Permanente Northern California
SBI: serious bacterial infection
UTI: urinary tract infection

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