The Journal of Emergency Medicine, Vol. 57, No. 3, pp. 306–313, 2019

0736-4679/$ - see front matter

https://doi.org/10.1016/j.jemermed.2019.06.028

Original Contributions

FEVER CHARACTERISTICS AND RISK OF SERIOUS BACTERIAL INFECTION IN FEBRILE INFANTS

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☐ **Abstract—Background: Fever is a common complaint in the pediatric emergency department (ED), but the vast majority of children evaluated with fever do not have a serious bacterial infection (SBI). However, in the neonate, a missed SBI can have devastating consequences. Objectives: To determine the association between various fever characteristics and the risk of SBI in febrile infants. Methods: This is a secondary analysis of the Pediatric Emergency Care Applied Research Network study on febrile infants. Infants with a fever were prospectively enrolled at 26 enrolling EDs between 2008 and 2013. We analyzed association of height of fever, location of where temperature was taken (enrolling ED vs. non-health care location), and duration of fever with SBI. Results: We included 4821 patients who had at least a blood culture completed. Height of fever was significantly associated with risk of SBI, with an odds ratio of 1.5 (95% confidence interval 1.2–1.8). Duration of fever was not associated with risk of SBI, and a fever taken in the enrolling ED vs. at a non-health care facility was minimally associated with risk of SBI (odds ratio 1.3, 95% confidence interval 1.0–1.5). Conclusion: In all analyses, height of fever was associated with all three major types of SBI in febrile infants. Duration and location of fever were less reliably associated with risk of SBI, but there was a small association of risk of SBI and a fever taken at the enrolling ED vs. at a non-health care location.** © **2019 Elsevier Inc. All rights reserved.**

☐ **Keywords—fever; neonatal fever; pediatrics; infectious disease**

Preliminary work from this paper was presented at the 2019 American College of Emergency Physicians Conference in October 2018 in San Diego, CA and the 2019 Society for Academic Emergency Medicine Conference in May 2019 in Las Vegas, NV.

INTRODUCTION

Fever is an exceedingly common complaint in the pediatric emergency department (ED), accounting for nearly 20% of pediatric ED visits (1,2). The vast majority of children evaluated with fever do not have a serious bacterial infection (e.g., bacteremia), and many of them have a viral infection without any evidence of bacterial infection (3–7). One high-risk group of children is the febrile neonate, whose risk of serious bacterial infection can be as high as 10–20% (8–10). Identifying an adequately sensitive clinical tool to identify neonates at low risk of serious bacterial infection has been attempted but has proven difficult (11,12).

"Fever phobia" is a well-documented phenomenon among parents and even health care workers (13,14). Many parents misclassify mild fever as high, and this can lead to an unwarranted fear of brain damage and seizures from fevers (14). Another concern is that children with high fevers must have a serious infection.

Several studies have looked at fever characteristics as a predictor of serious bacterial infections in children and shown mixed results (15–17). Height of fever is generally

RECEIVED: 16 March 2019; FINAL SUBMISSION RECEIVED: 7 June 2019;
ACCEPTED: 15 June 2019

regarded as a poor predictor of risk of bacterial infection, but a recent study in Israel showed a significant correlation between height of fever and risk of bacterial infection in febrile infants (18). The location of whether the fever is documented at home or at the hospital is another area of contention. Nevertheless, neonates with a reported fever and not one documented in the initial evaluation may still have a serious bacterial infection (19).

The purpose of this article is to determine the association between fever characteristics and risk of serious bacterial infection (SBI) in infants < 8 weeks old with a fever.

METHODS

This is a secondary analysis of a large de-identified public use data set from the Pediatric Emergency Care Applied Research Network. The original study has been published elsewhere (20). In brief, the original study was a prospective observational study of infants < 60 days old presenting with a fever to one of the 26 enrolling EDs between December 2008 and May 2013. For this secondary analysis, Institutional Review Board approval was not required.

Eligibility

The original study enrolled a convenience sample of 4821 infants 60 days of age and younger with documented fevers ≥ 38°C and a blood culture completed. It is noteworthy that if the temperature was taken at the enrolling ED, it was taken rectally, but infants were also included if their temperature was taken at another health care facility or at home (which could have been taken by any method). Infants were excluded from the parent study if they had clinical sepsis, a history of prematurity, significant comorbid conditions, or recent systemic antibiotic use. Infants met criteria for this analysis if they were verified to meet original inclusion criteria (i.e., had documented fever, had at least one culture drawn). As results of several bacterial cultures of blood, urine, or cerebrospinal fluid (CSF) were indeterminate or unclear, we included these infants and ran subgroup analyses where these results were excluded and presumed positive. Testing was done at the determination of the treating physician, and not all patients had urine or CSF cultures completed.

Definitions

We define SBI as a positive blood culture, a positive urine culture, or a positive CSF culture for a bacterial pathogen. In the original study, determination of a positive culture was made after review of the results by Pediatric Emergency Care Applied Research Network (PECARN) investigators, who could also adjudicate the results as indeterminate or unclear.

Temperature was recorded in either degrees Centigrade or Fahrenheit, but was converted to Centigrade for this analysis. The location of the temperature was either in the enrolling ED, at another health care facility (i.e., another ED or a primary care office), or at a non-health care facility (i.e., home or day care).

Statistical Analysis

All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC), and statistical significance was set at $p < 0.05$. SBI and positive culture was a dichotomous variable. Analyses were performed with indeterminate results, both included as positive and subsequently excluded. A subgroup analysis of patients with all three tests was performed as a check of validity. Logistic regression was used to look for association between temperature location, fever duration, and temperature in centigrade and the outcome variables. Odds ratios were used to quantify the magnitude and direction of any significant associations. The odds ratio for temperature in centigrade uses a unit increase of 0.5 centigrade.

Results

A total of 5998 patients < 60 days old with a fever were identified (Figure 1). Of these, 4821 (80.4%) infants had at least one culture test completed (44 had one culture type; 1114 had two culture types; and 3663 had all three culture types). Patients included were 56.5% (2724/4821) male with a mean age of 35.9 days (SD 14.8). Patients were 57.3% (n = 2761) white, 24.2% black (n = 1165), 6.8% unknown (n = 327), and 11.8% (n = 568) other. Patients were 68.4% (n = 3299) non-Hispanic, 29.6% (n = 1427) Hispanic, and 2% (n = 95) unknown. Patients who were excluded had similar demographics (Table 1), with a mean age of 35.7 days (SD 15.4) and a median temperature of 38.3°C (interquartile range [IQR] 38.1°–38.7°), and a similar breakdown of gender (48% female), race (56% white), and ethnicity (23.8% Hispanic).

A total of 9.2% (443/4821) of patients had at least one test positive for SBI. Rates of specific types of SBI are in Figure 1. Among the patients who had all three cultures complete (urine, blood, and CSF), the rate of any one of them being positive (SBI) was 10.7% (392/3663). The average age in this group was 33.2 days (SD 14.5). The rates of specific SBI were similar in this group to the group with at least one culture completed (2.0% blood, .6% CSF, and 9.2% urine), noting that some patients had more than one positive culture.

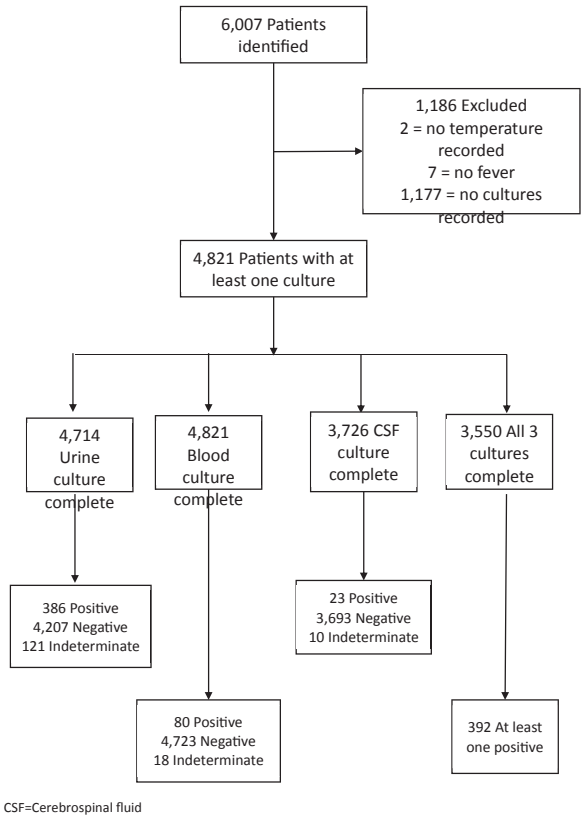

Figure 1. Flow diagram of patients included in a secondary analysis of fever characteristics and risk of serious bacterial infection in febrile infants.

Among patients with at least one test complete, the median temperature was 38.4°C (IQR 38.2°–38.7°; range 38.0°–41.1°), and among patients with all three cultures complete, was also 38.4°C (IQR 38.2-38.8; range, 38.0°–41.1°). Many more patients had lower temperatures, with 4103 temperatures < 39°C. The majority of temperatures were taken in the enrolling ED (61.5%, 2964/4821), with the second most common location being a non-health care facility (29.7%, 1430/4821), and 7.2% (346/4821) at a primary care office and 1.7% (81/4821) at a nonenrolling ED. The duration of fever was most often < 12 h (51.1%, 2463/4821), followed by 12–24 h (22.2%, 1071/4821), and > 24 h (5.7%, 273/4821). Twenty-one percent (1014/4821) had an unknown or uncollected duration of fever.

Height of temperature was significantly associated with risk of SBI (odds ratio [OR] 1.48, 95% confidence interval [CI] 1.35–1.63). This carried over to each of the individual types of SBI and whether indeterminate results were presumed positive or excluded (Tables 2–5). For height of fever, the OR for a positive blood or CSF culture only was 1.49 (95% CI 1.23–1.80). Among patients who had all three tests completed, the OR for risk of SBI was 1.46 (95% CI 1.32–1.62), the OR for temperature location being in enrolling ED vs. non-health care facility was 1.40 (95% CI 1.09–1.79), and for duration of fever > 24 h vs. < 12 h was 1.21 (95% CI .76–1.92). The risk of SBI by height of fever among the patients who had at least one test done (n = 4821) is shown in Figure 2.

Duration of fever by guardian report (< 12 h vs. > 24 h) was not associated with risk of SBI in all analyses. Having the fever recorded in the enrolling ED (vs. at home or a non-health care facility) was associated with risk of SBI (OR 1.4, 95% CI 1.1–1.8), specifically a positive urine culture (OR 1.5, 95% CI 1.2–1.9) when indeterminate results were presumed positive; however, this result decreased to an OR of 1.2 (95% CI 1.0–1.5) for risk of SBI.

DISCUSSION

Our study showed that height of fever is associated with risk of SBI in infants with a fever in a large data set. Other characteristics, such as location of fever and duration of

Table 1. Demographic Characteristics and Risk of Serious Bacterial Infection (SBI) in Febrile Infants

	% of Sample	Rate of SBI	*p* Value (χ^2)	*p* Value (Multivariate Regression)	Average Temperature (°C)
Age				<0.001	
Age < 30 days	33.8%	23.9%	<0.001		38.5
Age 30 days or greater	66.2%	12.2%			38.5
Gender				<0.001	
Male	56.5%	18.6%	<0.001		38.5
Female	43.5%	12.9%			38.5
Race				0.15	
White	57.3%	16.0%	<0.001		38.5
Black	24.2%	13.5%			38.6
Asian	2.8%	30.6%			38.5
Other/unidentified	15.8%	18.1%			38.5
Ethnicity				0.44	
Hispanic	29.6%	18.7%	0.002		38.5
Non-Hispanic	70.4%	15.1%			38.5

Table 2. Predictors of Bacteremia in Infants with a Fever

Characteristic	Negative/Indeterm.	Positive	Odds Ratio*	*p*-Value*
Height of fever	38.5 ± 0.5 mean (SD)	38.7 ± 0.5 mean (SD)	1.42 (1.18–1.71) (95% CI, per 0.5 °C)	<0.001
Location				
Home	1406 (98.3)	24 (1.7)	Reference	N/A
PECARN ED	2898 (97.8)	66 (2.2)	1.33 (0.83–2.14)	0.231
PCP or other	341 (98.6)	5 (1.5)	0.86 (0.33–2.27)	0.759
Other ED	78 (96.3)	3 (3.7)	2.25 (0.66–7.65)	0.192
Duration of fever				
< 12 h	2412 (97.9)	51 (2.1)	Reference	N/A
12–24 h	1053 (98.3)	18 (1.7)	0.81 (0.47–1.39)	0.442
> 24 h	268 (98.2)	5 (1.8)	0.88 (0.35–2.23)	0.791

Indeterm = indeterminate; PECARN = Pediatric Emergency Care Applied Research Network; ED = emergency department; PCP = primary care physician.
* Odds ratios and *p*-values from unadjusted logistic regression modeling positive culture.

fever, were unreliably associated with risk of SBI. The association between height of fever and SBI carried across all three types of major SBI and regardless of whether indeterminate results were included or excluded. This provides data to support the notion that height of fever in this population can be used to predict SBI.

The data on height of fever and risk of bacterial infection in older age groups are indeterminate, making height of fever an unreliable predictor in those populations (21,22). However, the risk of bacterial infection in those age groups, particularly SBI, is quite low compared with the infant age group. The risk of SBI in the defined cohort was nearly 10%, consistent with previous rates (8–10). This means that what is normally possibly a small association becomes more pronounced when there are more "positive" events. Our analysis is in line with a recent study of Israeli infants, which did show an association between risk of SBI and height of fever in high-risk (but not low-risk) infants (18).

In our study, there was no association with duration of fever and risk of SBI. There was a small association between risk of SBI and fever taken in enrolling ED vs. at home. This risk was mostly contributed by risk of urinary infection. Perhaps this is due to the method of determining temperature at home, though rectal and other temperatures would presumably be higher than other methods. Perhaps this is due to misinterpretation of definition of fever by some parents, but again, these patients should have not been enrolled without a documented fever. Regardless, the association is small and unreliable and is unlikely to have any clinical relevance.

Unfortunately, in infants this young, there is a low threshold to miss SBI. The relative lack of immunity, risk of dire consequences, and rapidity of decline in this age group makes a missed SBI markedly detrimental. Historically, every child < 12 weeks old with a fever obtained blood, urine, and CSF cultures. More recently, clinical criteria to identify low-risk infants who may not need invasive testing have been developed (i.e., Rochester, Boston, and Philadelphia criteria) (8,9,23). These tests are quite sensitive, but apply only to older children in these age groups. In our data set, approximately 20% of children had no culture testing complete, and only 59% had all three cultures completed. This may

Table 3. Predictors of Urinary Infection in Infants with a Fever

Characteristic	Negative/Indeterm.	Positive	Odds Ratio*	*p*-Value*
Height of fever	38.5 ± 0.4 Mean (SD)	38.6 ± 0.5 Mean (SD)	1.39 (1.27–1.52) (95% CI, per .5 °C)	<0.001
Location				
Home	1269 (90.5)	134 (9.5)	Reference	N/A
PECARN ED	2565 (88.4)	336 (11.6)	1.24 (1.0–1.53)	0.046
PCP or other	306 (91.1)	30 (8.9)	0.93 (0.61–1.41)	0.726
Other ED	67 (90.5)	7 (9.5)	0.99 (0.45–2.20)	0.979
Duration of fever				
< 12 h	2155 (89.2)	260 (10.8)	Reference	N/A
12–24 h	925 (88.4)	122 (11.7)	1.09 (0.87–1.37)	0.445
> 24 h	229 (87.4)	33 (12.6)	1.19 (0.81–1.76)	0.368

Indeterm = indeterminate; PECARN = Pediatric Emergency Care Applied Research Network; ED = Emergency Department; PCP = primary care physician.
* Odds ratios and *p*-values from unadjusted logistic regression modeling positive culture.

Table 4. Predictors of Bacterial Meningitis in Infants with a Fever

Characteristic	Negative/Indeterm.	Positive	Odds Ratio*	*p*-Value*
Height of fever	38.5 ± 0.5 Mean (SD)	38.7 ± 0.6 Mean (SD)	1.50 (1.12–2.03) (95% CI, per .5 °C)	0.008
Location				
Home	1037 (99.1)	9 (0.9)	Reference	N/A
PECARN ED	2349 (99.1)	22 (0.9)	1.08 (0.50–2.35)	0.848
PCP or other	243 (99.2)	2 (0.8)	0.95 (0.20–4.42)	0.946
Other ED	64 (100.0)	0 (0.0)	N/A	N/A
Duration of fever				
< 12 h	1941 (99.3)	14 (0.7)	Reference	N/A
12–24 h	789 (98.8)	10 (1.2)	1.76 (0.78–3.97)	0.176
> 24 h	188 (98.4)	3 (1.6)	2.21 (0.63–7.77)	0.215

Indeterm = indeterminate; PECARN = Pediatric Emergency Care Applied Research Network; ED = emergency department; PCP = primary care physician.
* Odds ratios and *p*-values from unadjusted logistic regression modelling positive culture.

indicate an increased use of these decision rules, but the expected difference in age between groups with no testing was not seen.

Our analyses suggest that perhaps height of fever could be investigated in future clinical decision rules; however, it should be noted that height of fever alone was not sufficiently sensitive to rule out SBI, as even children with a temperature < 39°C still had a 9.1% risk of SBI. Among children with a fever > 39°C, though, the risk of SBI doubled to 20.4%.

Limitations

Our study has several limitations. Namely, it is a secondary analysis and is retrospective in nature. We are limited by the data as they were collected. For example, certain data, such as route of temperature taken at home, were not collected. Also, only one enrolling temperature was included. It is possible that a higher temperature occurred during the ED stay. The data set contained a significant number of indeterminate cultures, but we ran analyses

Table 5. Logistic Regression for Risk of Serious Bacterial Infection (SBI) in Infants < 60 Days Old Presenting to the Emergency Department with a Fever

	Type of SBI	Odds Ratio	95% CI	*p* Value
Indeterminate culture results presumed positive				
Height of fever (0.5°C)	Blood	1.4	1.2–1.7	<0.001
	Urine	1.4	1.3–1.5	<0.001
	CSF	1.5	1.1–2.0	0.008
	Any SBI	1.4	1.3–1.5	<0.001
Location of fever (enrolling emergency department vs. other)	Blood	1.3	.83–2.1	NS
	Urine	1.3	1.0–1.5	NS
	CSF	1.1	.50–2.4	NS
	Any SBI	1.2	1.0–1.5	NS
Duration of fever (> 24 h compared with < 12 h)	Blood	0.88	.35–2.2	NS
	Urine	1.2	.81–1.8	NS
	CSF	2.2	.63–7.8	NS
	Any SBI	1.2	.80–1.7	NS
Indeterminate culture results excluded				
Height of fever (0.5°C)	Blood	1.5	1.2–1.8	<0.001
	Urine	1.5	1.3–1.6	<0.001
	CSF	1.7	1.2–2.0	0.002
	Any SBI	1.5	1.4–1.6	<0.001
Location of fever (enrolling Emergency Department vs. other)	Blood	1.2	.83–2.4	NS
	Urine	1.5	1.2–1.9	0.01
	CSF	0.77	.32–1.85	NS
	Any SBI	1.4	1.1–1.8	0.01
Duration of fever (> 24 h compared with < 12 h)	Blood	1.2	.45–3.0	NS
	Urine	1.1	.72–1.8	NS
	CSF	3.1	.85–11.4	NS
	Any SBI	1.1	.75–1.7	NS

SBI = serious bacterial infection; 95% CI = 95% confidence interval; CSF = cerebrospinal fluid.

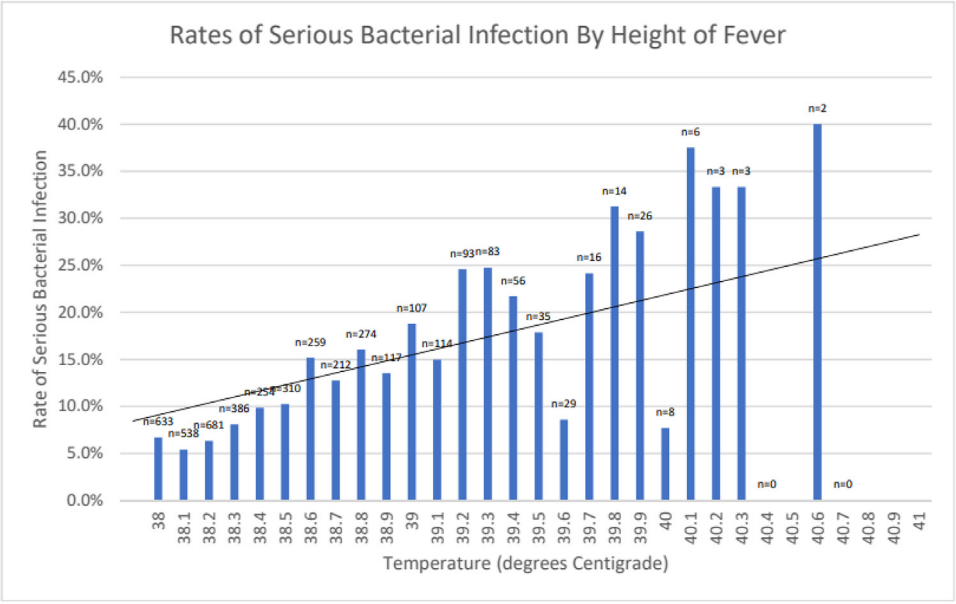

Figure 2. Rates of serious bacterial infection by height of fever in a secondary analysis of febrile infants.

with these both included as positive and excluded with similar results in both analyses.

CONCLUSION

In febrile infants, a higher fever is associated with a higher risk of all three types of major SBI. Other fever characteristics, such as location of fever and duration of fever were less reliably associated with risk of SBI. Future research may help determine if height of fever can be part of decision rules to identify febrile infants at low risk of SBI.

Acknowledgments—This manuscript was prepared using the PECARN "Biosignatures" data set obtained from the PECARN Data Coordinating Center, University of Utah, and does not necessarily reflect the opinions or views of the PECARN biosignatures investigators or the Health Resources Services Administration (HRSA), Maternal Child Health Bureau (MCHB), and Emergency Medical Services for Children (EMSC). The PECARN study was funded by the HRSA/MCHB/EMSC, United States.

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ARTICLE SUMMARY

1. Why is this topic important?

Fever is a common presentation in the emergency department, and febrile neonates require extensive work-up to evaluate for serious bacterial infections.

2. What does this study attempt to show?

This study attempts to show fever characteristics that are associated with an increased risk of serious bacterial infections (SBI) in febrile infants.

3. What are the key findings?

Despite common teaching to the contrary, height of fever is associated with an increased risk of SBI. This was not true of duration of fever nor where the fever was documented.

4. How is patient care impacted?

In the future, clinicians may have a higher level of suspicion for an SBI in infants presenting with a higher temperature.