Value of Temperature for Predicting Invasive Bacterial Infection in Febrile Infants

A Spanish Pediatric Emergency Research Group (RISeuP-SPERG) Study

Mercedes de la Torre, MD, Borja Gómez, MD,† Roberto Velasco, MD, PhD, MSc,‡ and on behalf of the Group for Study of Febrile Infant of Spanish Pediatric Emergency Research Group (RISeuP-SPERG)*

Objective: This study aimed to analyze the prevalence of invasive bacterial infection (IBI) among infants younger than 90 days with fever without source according to the degree of fever.

Methods: We performed a secondary analysis of a multicenter study with 19 participating Spanish pediatric emergency departments that included 3401 febrile infants 90 days or younger.

Results: Prevalence of IBI was 3.2% (5.3% among infants <29 days old, 2.5% among those 29–60 days old, and 2.2% among those 61–90 days old). Prevalence of bacteremia increased with the degree of fever, meanwhile the prevalence of bacterial meningitis did not. No cutoff point was useful for ruling out an IBI safely. Overall, 46.7% of the IBIs were diagnosed in patients with temperature <38.6° (sensitivity, 53.3%; negative likelihood ratio, 0.81).

Conclusions: Performing blood tests should be recommended in infants 90 days or younger with temperature ≥38°C without source regardless of the degree of fever.

Key Words: bacteremia, febrile infant, meningitis, temperature

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Infants up to 90 days old with fever without source (FWS) are at higher risk of having an invasive bacterial infection (IBI), and a more aggressive management is usually recommended for this population. Some risk factors have been described, including appearance, age, or different biomarkers.[1] Among these risk factors, fever has always been considered as a dichotomous variable, with most guidelines recommend considering all infants with a temperature above 38°C (100.4°F) to be at risk of an IBI.[2] However, some authors recommend a different management depending on the degree of fever. In this way, they consider a temperature ≥38.6°C as an additional risk factor that requires a more aggressive management and even suggest, for instance, a full sepsis evaluation, including performing a lumbar puncture, in any infant 29 to 60 days old with a temperature ≥38.6°C, even if he/she is well appearing and has normal urine and blood test results.[3,4] Other authors have included the degree of temperature as an item in some predictive models to determine the risk of IBI in those patients.[5,6]

Our objective was to analyze the prevalence of IBI among infants younger than 90 days related to the degree of fever. As a secondary objective, we tried to determine the prevalence in the specific group of well-appearing infants 29to 90 days old.

From the *Pediatric Emergency Department, Niño Jesús University Hospital, Madrid; †Pediatric Emergency Department, Cruces University Hospital, Barakaldo; and ‡Pediatric Emergency Department, Rio Hortega Universitary Hospital, Valladolid, Spain.

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Reprints: Roberto Velasco, MD, PhD, MSc, C/ Pisuerga, 7-3° B, Laguna de Duero, Valladolid, Spain, 47140 (e-mail: robertovelascozuniga@gmail.com).

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METHODS

This is a secondary analysis of a prospective multicenter study including febrile infants 90 days or older with FWS.[7] This study was carried out between October 2011 and September 2013 in 19 hospital members of the Spanish Pediatric Emergency Research Group (RISeuP-SPERG) and included infants up to 90 days old who attended in any of the participating emergency departments (EDs) with a complaint of fever. Axillary or rectal temperature ≥38°C at home or in the ED was considered fever. The management of the patients, including the decision of performing a lumbar puncture, was made according to the protocol of each hospital. Approval for the study and for data sharing with the coordinating institution and with the centralized data center was granted by the institutional review board at each participating institution. Informed consent was requested to the parents or the caregivers of the patients before including them in the study. The database used in the original prospective study has been described elsewhere.[7]

Inclusion Criteria

In the original study, we included those infants younger than 90 days with FWS (axillary or rectal temperature ≥38°C at home or in the ED) in whom urine dipstick, urine culture (sample obtained by a sterile method), and blood culture were performed at the pediatric ED.[7]

Exclusion Criteria

We excluded patients meeting any of the following: (*a*) patients in whom the anamnesis and/or the physical examination suggested the source of the fever; (*b*) afebrile patients at arrival at the pediatric ED who had not any measured temperature ≥38°C at home, no matter that parents or caregivers complaint of fever; (*c*) parental refusal to participate; and (*d*) no phone contact to follow up 1 month after their inclusion in the study.

Data Collection

A standardized form with the following data was filled for every patient included in the study: demographics (age, sex), highest temperature measured at home and at arrival to the pediatric ED, time between fever was detected and the arrival to the pediatric ED, appearance of the patient when arrival to the pediatric ED, medical history, physical examination, results of the laboratory and microbiological tests, and the final diagnosis and disposition of the patient. A phone call was made to every patient's parent to check any unnoticed adverse event 1 month after the inclusion in the study. Also, every month each investigator had to send the total number of patients and febrile infants attended in his or her hospital. Data were sent to the main investigator using an online formulary.

Definitions

- Well-appearing: a patient was considered as well appearing when the 3 components of the Pediatric Assessment Triangle were defined as normal in his/her medical report in those centers in which these data are systematically recorded. For the other centers, infants were considered to be not well appearing under the criteria of the attending pediatrics physician.
- FWS: axillary or rectal temperature ≥38°C (100.4°F) measured either at home or at the ED, in an infant in whom, after taking a medical history and conducting a physical examination, it is not possible to identify the source of the fever (patients with no respiratory signs/symptoms or a diarrheal process and a normal physical examination finding including normal chest auscultation and an absence of signs of acute otitis media and bone, joint, and soft tissue infection). For the purpose of this subanalysis, we combined in a unique variable both the maximum temperature registered at home by parents before being attended at the ED and the temperature measured on arrival at the ED, considering only the highest one. In the original study, only rectally or axillary measured temperatures were collected, both at home and at the ED. The decision of using one or another method in the ED was arbitrary.
- IBI: isolation of a single bacteria pathogen from the blood or the cerebrospinal fluid (CSF). Isolation of *Staphylococcus epidermidis*, *Propionibacterium acnes*, *Streptococcus viridans*, or *Diphtheroides* in inmunocompetent patients without cardiac disease, ventriculoperitoneal shunt, central catheters, or another indwelling device were considered contaminants.

Statistical Analysis

Normally distributed data were expressed as mean and SD, nonnormally distributed data were expressed as median and interquartile range, and categorical variables were reported as percentages. For nonnormally distributed data, comparison was performed using the Mann-Whitney U test, and comparison of normally distributed data was performed using an independent-samples *t* test. For categorical data, the χ^2 test was used. The significance level was established at $P < 0.05$.

For the main objective of the study, a bivariate analysis was used, analyzing the association between the degree of temperature, categorized in intervals, and the prevalence of IBI with a χ^2 test. We calculated the sensitivity, specificity, and positive and negative likelihood ratios (LRs) of different temperature cutoff points for identifying IBIs. We made a subanalysis in the specific subgroup of well-appearing infants older than 28 days.

Data were analyzed with Stata 14 (StataCorp, College Station, Tex).

RESULTS

Nineteen hospitals participated in the original study over a 2-year period. A flowchart of the participants is included in Figure 1. Of 4008 episodes from infants younger than 90 days with FWS, 3401 (84.8%) episodes had urine dipstick, urine culture, and blood culture performed and were included in the study. Fever was measured at home axillary in 2724 (80.1%) infants and rectally in 527 (15.5%), and 150 (4.4%) had no temperature registered at home. Characteristics of the analyzed patients are shown in Table 1.

Global prevalence of IBI was 3.2% (107 of 3401). Prevalence of IBI was 5.3% (95% confidence interval [CI], 4.0%–6.7%) among infants younger than 29 days, 2.5% (95% CI, 1.8%–3.4%) among those 29 to 60 days old, and 2.2% (95% CI, 1.5%–3.3%) among those 61 to 90 days old. Bacteria isolated in blood and CSF cultures are shown in Supplemental Table 1, http://links.lww.com/PEC/A922.

Fifty of the 107 IBIs (46.7%) were diagnosed in patients with a temperature <38.6°C. Area under the receiver operating characteristic curve for temperature for predicting an IBI was higher in patients older than 60 days (0.653 [95% CI, 0.623–0.682]) than in younger patients (0.569 [95% CI, 0.549–0.590]). Table 2 and Supplemental Table 2, http://links.lww.com/PEC/A923, show the prevalence of bacteremia and meningitis and the performance of different temperature cutoff points for predicting IBIs. Prevalence of IBI according to temperature in those patients who had fever at the ED and in those who were afebrile is shown in Supplemental Table 3, http://links.lww.com/PEC/A924.

Eighteen patients were diagnosed with meningitis. Eight of them were infants with a temperature <38.6°C (6 of them in well-appearing infants), with a similar prevalence in patients with temperatures <38.6°C and ≥38.6°C (0.41% vs 0.69%, $P = 0.276$).

There were 2253 well-appearing infants older than 28 days (66.3%). In this subgroup, prevalence of IBI was 1.53% (95%

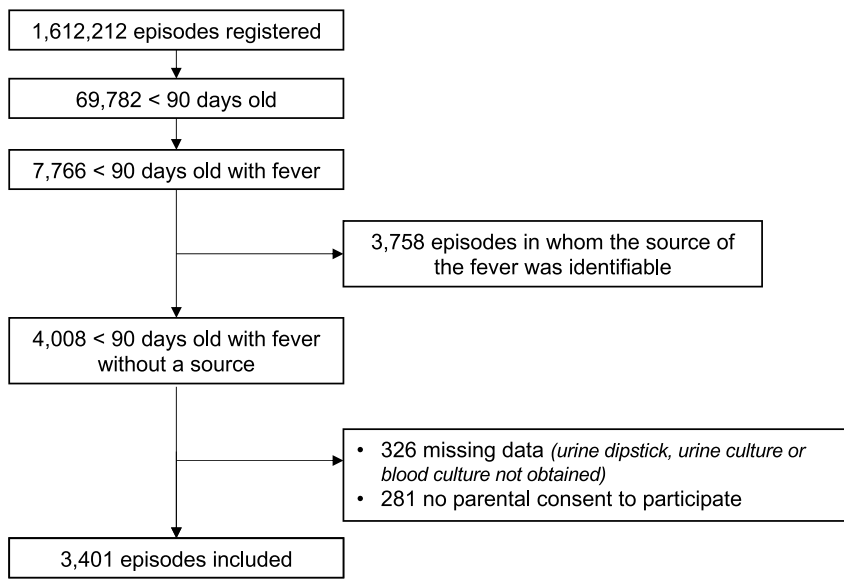

FIGURE 1. Flowchart of the study.

TABLE 1. Characteristics of Analyzed Patients

Age, mean (SD), d	46.6 (23.6)
Male sex	2029 (59.7%)
Well appearing	3034 (89.2%)
Hours of fever, median (P25–P75)	5 (2–12)
Maximum temperature, mean (SD), °C	38.6 (0.46)
38°C–38.5°C	1943 (57.1%)
38.6°C–39°C	1016 (29.9%)
39.1°C–39.5°C	321 (9.4%)
>39.5°C	121 (3.6%)
Lumbar puncture performed	877 (25.8%)
<29 d old	548 (60.1%)
29–60 d old	233 (16.1%)
>60 d old	96 (9.1%)
IBI	107 (3.2%)
Bacteremia	100* (2.94%)
Meningits	18* (0.53%)

*Eleven patients had both bacteremia and meningitis.

CI, 1.6%–4.2%) among patients younger than 29 days, 1.3% (95% CI, 0.7%–2.1%) among infants 29 to 60 days old, and 1.0% (95% CI, 0.5%–2.0%) among infants 61 to 90 days old. Prevalence of IBI was similar in patients with temperature <38.6°C and in those with higher fever, both in patients younger than 28 days (3.3% vs 1.4%; $P = 0.162$), 29 to 60 days old (1.44% vs 0.97%; $P = 0.506$), and 61 to 90 days old (1.05% vs 0.93%; $P = 0.866$).

DISCUSSION

Our results show that the prevalence of IBI in febrile infants younger than 90 days with FWS increases with the temperature. However, we did not find any useful temperature cutoff point for ruling out the presence of an IBI safely. Therefore, urine and blood tests must be performed in infants younger than 90 days with a temperature ≥38°C even if they present a temperature between 38°C and 38.6°C, as it has been showed by prior literature.[8,9]

Febrile infant is one of the most challenging patients in pediatric emergency medicine. Because of its higher risk of IBIs, different new approaches have been proposed in the last few decades. Most of them agree on recommending performing urine and blood tests in any infant with a temperature of 38°C or higher.[1] However, some authors proposed a higher cutoff of 38.2°C to consider that an infant has fever.[10] In our sample, this cutoff point would misdiagnose 12.7% of the IBIs, so we think it would not be safe to raise the most usual 38°C cutoff point to consider fever.

A less aggressive management is proposed for infants who have a temperature lower than 38.6°C by some authors.[4] As it is shown on our results, the prevalence of IBI among infants with fever <38.6°C was 2.4%, and it was 1.35% in the specific group of well-appearing patients 29 days or older. This higher prevalence compared with the one obtained in the study by Pantell et al[4] (0.4%) could be related to the inclusion criteria used in each study. We included only infants presenting with FWS, whereas Pantell et al included any febrile infant, regardless of the patient presenting with additional symptoms. In this way, more than 30% of the included infants in that study were diagnosed with an upper respiratory tract infection or a bronchiolitis. The prevalence of IBI in our sample is similar to those found by other authors in febrile infants with negative viral respiratory test results.[11] In any case, because our study only included infants with FWS, further research might be needed in infants with upper airway symptomatology.

In any case, higher temperature seems to be associated with a higher prevalence of IBI. In our sample, we might observe how the prevalence of bacteremia was 2- and 5-fold when temperature was higher than 39°C and 39.5°C, respectively. This might have clinical relevance. Most of the predictive models in the recent literature tried to rule out IBI. Based on our results, we think that temperature is not useful in this way. Some other clinical models have included temperature as a factor useful for ruling in a serious bacterial infection, for instance, when the temperature is higher than 39.5°C.[5] This approach seems to be more reasonable because

TABLE 2. Performance of Different Maximum Temperature (Measured Either at Home or at the ED) Cutoff Points for Identifying Bacterial Infections

	IBI*	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	+LR (95% CI)	−LR (95% CI)
Whole sample							
≤38.5°C vs >38.5°C	**2.6% vs 3.9%**	0.53 (0.44–0.62)	0.57 (0.54–0.58)	0.04 (0.03–0.05)	0.97 (0.97–0.98)	1.25 (1.04–1.50)	0.81 (0.66–1.00)
≤39°C vs >39°C	**2.7% vs 5.9%**	0.24 (0.17–0.33)	0.87 (0.86–0.88)	0.06 (0.04–0.08)	0.97 (0.97–0.98)	1.92 (1.36–2.72)	0.87 (0.78–0.97)
≤39.5°C vs >39.5°C	**3.0% vs 8.3%**	0.09 (0.05–0.16)	0.97 (0.96–0.97)	0.08 (0.05–0.15)	0.97 (0.96–0.98)	2.78 (1.50–5.14)	0.94 (0.88–1.00)
Well appearing 29–90 d old							
≤38.5°C vs >38.5°C	**1.4% vs 2.6%**	0.60 (0.46–0.74)	0.56 (0.54–0.58)	0.03 (0.02–0.04)	0.99 (0.98–0.99)	1.38 (1.08–1.77)	0.70 (0.49–1.02)
≤39°C vs >39°C	**1.5% vs 4.3%**	0.30 (0.19–0.45)	0.87 (0.85–0.88)	0.04 (0.03–0.07)	0.98 (0.98–0.99)	2.31 (1.45–3.69)	0.80 (0.66–0.98)
≤39.5°C vs >39.5°C	**1.7% vs 7.6%**	0.16 (0.08–0.30)	0.96 (0.95–0.97)	0.08 (0.04–0.15)	0.98 (0.98–0.99)	4.23 (2.08–8.60)	0.87 (0.76–0.99)

Sensitivity, specificity, and LR values are for the diagnosis of an IBI.

*In bold format if $P < 0.05$.

NPV indicates negative predictive value; PPV, positive predictive value.

our results show that its positive LR clearly increases with the degree of fever, mainly in well-appearing patients.

Unlike bacteremia, the prevalence of meningitis did not increase with a higher degree of fever. According to our results, although the prevalence of IBI increased with the degree of fever, that degree of fever should not be used as the sole data point on which to base decisions. For example, deciding to perform a lumbar puncture only because the patient had high temperature does not seem appropriate. Instead, age and blood biomarkers should determine the need for this test being performed.[1] In this sense, it might be interesting to analyze in further studies the performance of febrile infant approaches, like the Step-by-Step approach, depending on the temperature of the patient.[9]

There is some controversy about the management of well-appearing patients older than 60 days with a normal urine test result.[3,8] In our sample, the prevalence of bacteremia was similar among patients 29 to 60 days old and among patients 61 to 90 days old, so the same management should be made, and blood tests should be obtained in both age subgroups, as has being recently suggested by Bonilla et al.[8]

Some clinicians might doubt how to manage those patients who are afebrile when arriving at the ED whose caregivers refer fever at home.[12] We did a sensitivity analysis by evaluating the prevalence of IBI according to temperature in those patients who had fever at the ED and in those who were afebrile, and in both groups, patients with a measured temperature between 38°C and 38.6°C (in home or in the ED) had a significant risk of IBI. This is consistent with prior research.[12,13]

Our study has several limitations. First of all, this was a secondary analysis of another study, so sample size was not specifically calculated for our objective; hence, the study was underpowered to find differences in IBI prevalence within age groups and in the prevalence of meningitis at different temperature cutoff values. Also, because home temperature was included, there is an absence of data on whether antipyretics were given before ED arrival, which could affect the temperature values. Despite that, we think that the number of patients included allows us to obtain conclusions reliable enough. Also, only 25.8% had a CSF culture obtained. Because the management of the patients was based on each hospital's protocol, it was each patient's attending physician who decided whether perform a lumbar puncture or not. However, a follow-up phone call was made to identify any possible complication related to the febrile episode, so the risk of misdiagnosing a bacterial meningitis is very low.

CONCLUSIONS

There is not a useful temperature cutoff point to rule out an IBI in febrile infants younger than 90 days, so performing blood and urine tests should be recommended in those with temperature ≥38°C without source.

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