Performance of the Modified Boston and Philadelphia Criteria for Invasive Bacterial Infections

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abstract

BACKGROUND: The ability of the decades-old Boston and Philadelphia criteria to accurately identify infants at low risk for serious bacterial infections has not been recently reevaluated.

METHODS: We assembled a multicenter cohort of infants 29 to 60 days of age who had cerebrospinal fluid (CSF) and blood cultures obtained. We report the performance of the modified Boston criteria (peripheral white blood cell count [WBC] $\geq$20 000 cells per mm^3, CSF WBC $\geq$10 cells per mm^3, and urinalysis with $>$10 WBC per high-power field or positive urine dip result) and modified Philadelphia criteria (peripheral WBC $\geq$15 000 cells per mm^3, CSF WBC $\geq$8 cells per mm^3, positive CSF Gram-stain result, and urinalysis with $>$10 WBC per high-power field or positive urine dip result) for the identification of invasive bacterial infections (IBIs). We defined IBI as bacterial meningitis (growth of pathogenic bacteria from CSF culture) or bacteremia (growth from blood culture).

RESULTS: We applied the modified Boston criteria to 8344 infants and the modified Philadelphia criteria to 8131 infants. The modified Boston criteria identified 133 of the 212 infants with IBI (sensitivity 62.7% [95% confidence interval (CI) 55.9% to 69.3%] and specificity 59.2% [95% CI 58.1% to 60.2%]), and the modified Philadelphia criteria identified 157 of the 219 infants with IBI (sensitivity 71.7% [95% CI 65.2% to 77.6%] and specificity 46.1% [95% CI 45.0% to 47.2%]). The modified Boston and Philadelphia criteria misclassified 17 of 53 (32.1%) and 13 of 56 (23.3%) infants with bacterial meningitis, respectively.

CONCLUSIONS: The modified Boston and Philadelphia criteria misclassified a substantial number of infants 29 to 60 days old with IBI, including those with bacterial meningitis.

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WHAT'S KNOWN ON THIS SUBJECT: The Boston and Philadelphia criteria for febrile infants were developed decades ago, before widespread conjugate vaccine use to identify infants at low risk of serious and invasive bacterial infections. The continued applicability of these tools remains unclear.

WHAT THIS STUDY ADDS: The Boston and Philadelphia criteria misclassified approximately one-third of infants 29 to 60 days old who had invasive bacterial infections as being low risk, including those with bacterial meningitis. Newer tools are needed to stratify infants' risk of bacterial infections.

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Febrile young infants pose a diagnostic challenge for clinicians. Although most febrile young infants have self-limited viral infections,[1,2] even well-appearing infants can have occult bacterial infections.[3–5] Because clinical appearance alone cannot be used to identify infants who have bacteremia or meningitis,[5,6] clinicians frequently obtain blood, urine, and cerebrospinal fluid (CSF) specimens for screening tests and cultures.[7–9] Because bacterial culture results are usually not declared negative until after 48 hours of incubation,[10–13] many infants are treated with parenteral antibiotics and hospitalized for multiple days while awaiting culture results.[14]

Because of these challenges, strategies have been developed to stratify the risk of bacterial infections in young febrile infants.[5,15–18] The Boston and Philadelphia criteria,[16,17] which were derived >2 decades ago, are 2 of the more commonly used tools for stratifying young infants' risk of bacterial infection.[8] Both use peripheral and CSF white blood cell counts (WBCs) and the absence of pyuria to classify an infant as being at low risk of serious bacterial infections (SBIs), including bacteremia, bacterial meningitis, and urinary tract infection (UTI). Although these criteria performed well in their derivation and limited validation cohorts,[19,20] these tools have not been recently validated in a broader patient population. Since their derivation, herd immunity from widespread use of conjugated pneumococcal vaccines as well as maternal antibiotic group B *Streptococcus* (GBS) prophylaxis have changed the epidemiology of invasive bacterial infections (IBIs) in these young infants.[21–26]

To this end, we sought to measure the diagnostic accuracy of the Boston and Philadelphia criteria to identify infants at low risk for IBI in a large multinational, multicenter cohort of infants who underwent evaluation for bacterial infections.

METHODS

Study Setting

We performed a planned secondary analysis of the Pediatric Emergency Medicine Collaborative Research Committee Herpes Simplex Virus Study. The parent study was a retrospective, cross-sectional study of infants evaluated for meningitis at 1 of 23 tertiary-care emergency departments (EDs) located in the United States and Canada from January 2005 to December 2013.[27] The enrollment period varied by study center on the basis of the availability of electronic health record data. The study protocol was approved by the institutional review board of each participating center with agreements for data sharing.

Patients

In our secondary analysis, we include infants 29 to 60 days of age who had a CSF and blood culture obtained within 24 hours of ED arrival. We limited our analysis to infants in the second month of life who could potentially be managed as outpatients if at low risk for bacterial infections.[16,17] We excluded infants who were critically ill (ie, admitted to an ICU) because the Boston and Philadelphia criteria were both developed for the evaluation of well-appearing infants.

Data Collection

We abstracted the following from the medical record: demographics (age, sex, and study site), clinical data (triage temperature, admission status, and length of stay), laboratory results (complete blood count [CBC] and differential, CSF cell counts, CSF Gram-stain, urine dip, and/or urine microscopy), and microbiology results (blood, CSF, and urine cultures).

Outcome Measures

Our primary outcome was IBI, defined as growth of pathogenic bacteria form either a blood or CSF culture. We classified the following bacterial organisms a priori as contaminants: coagulase-negative staphylococci, Viridans group *Streptococcus*, *Lactobacillus* species, *Micrococcus* species, *Bacillus* species (non-*cereus* and non-*anthracis*), *Propionibacterium acnes*, and *Corynebacterium* species.[28] Infants with a positive CSF culture result were defined as having bacterial meningitis regardless of the blood culture results.

Our secondary outcome was SBI, defined as IBI or UTI. We defined UTI as growth of ≥50 000 colony-forming units of pathogenic bacteria from a urine culture or growth of ≥10 000 colony-forming units of pathogenic bacteria from a urine culture in the presence of pyuria (>10 WBC per high-power field [hpf] or positive leukocyte esterase result).[29]

Modified Boston and Philadelphia Criteria

We modified the published Boston and Philadelphia criteria for application to our study cohort (Table 1). The original Philadelphia criteria include spun urine microscopy, including urine Gram-stain. Because most study infants did not have this test performed, we modified the high-risk Philadelphia predictors to include both spun and unspun urine results on the basis of each study site's laboratory.[30] Both criteria required urine microscopy to stratify risk. However, not all infants underwent urine microscopy, including those for whom urine dip screening results were negative. Therefore, if infants had both urine dip leukocyte esterase testing and urine microscopy performed, urine microscopy results were used to categorize the infants as having pyuria. If urine dip leukocyte esterase testing was performed without microscopy, a positive urine leukocyte esterase result (trace to 3+) was classified as a positive result to

TABLE 1 Modified Boston and Philadelphia High-Risk Predictors

Boston	Philadelphia
CBC WBC ≥20 000 per mm^3	CBC WBC ≥15 000 per mm^3
CSF WBCs ≥10 per hpf	CSF WBC ≥8 per hpf
Urine WBCs >10 per hpf[a] or positive urinalysis result (trace to 3+)[b]	Urine WBCs >10 per hpf[a] or positive urinalysis result (trace to 3+)[b]
	Positive CSF Gram-stain result

[a] Modified from ≥10 per hpf in original criteria.

[b] Positive urinalysis result only used if urine microscopy was not available.

maximize each criteria's sensitivity.[31,32] In the parent study, urine microscopy results were coded as follows: 0 to 5 WBC per hpf, 6 to 10 WBC per hpf, 11 to 20 WBC per hpf, and >20 WBC per hpf. For this study, we modified both the Boston and Philadelphia criteria to define pyuria as >10 WBC per hpf.

Application of the Boston and Philadelphia Criteria

We applied the modified Boston and Philadelphia criteria to the study cohort. Infants with any of the high-risk predictors were considered not to be at low risk for IBI. Infants missing data for any of the predictors were excluded unless they had one or more high-risk predictors, in which case they were considered not at low risk.

Analyses

We report the diagnostic accuracy of the modified Boston and Philadelphia criteria to identify infants with IBI and SBI. We report sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio. Comparisons of test characteristics between the modified Boston and Philadelphia criteria were performed by using χ^2 tests. Finally, we describe the infants with IBI who were misclassified as low risk by either the modified Boston or Philadelphia criteria.

Statistical analyses were performed by using SAS software (SAS Institute, Inc, Cary, NC).

RESULTS

Study Population

Of the 11 679 infants 29 to 60 days of age, we included the 10 928 infants (93.6%) who had both blood and CSF cultures obtained (Fig 1). The median age in this study cohort was 42 days (interquartile range [IQR] 35–50 days); 6089 (55.9%) were boys, and 8620 (78.9%) were admitted to the hospital. Overall, 10 286 (94.1%) also had urine cultures obtained and were included in our SBI subanalysis.

IBI

Of the 10 928 study infants, 264 (2.4%) had an IBI, including 71 (0.6%) with bacterial meningitis and 193 (1.8%) with bacteremia. Fifty-one (72.9%) infants with bacterial meningitis had positive CSF culture results alone, and 20 (28.2%) had both a positive CSF and blood culture result. The most commonly identified bacterial pathogen was GBS, followed by *Escherichia coli* and *Staphylococcus aureus* (Table 2).

In our primary outcome analysis for IBI, we applied the modified Boston criteria to 8344 (76.4%) infants (Fig 1), of whom 212 (2.5%) had an IBI, and the modified Philadelphia criteria to 8131 (74.4%) infants, of whom 219 (2.7%) had an IBI. The clinical and laboratory characteristics of the infants in the modified Boston and Philadelphia cohorts were similar (Table 3). Overall, 2322 infants (21.2%) did not have sufficient laboratory results to be classified by either criterion. The rate of IBI among the unclassified and classified infants did not differ significantly (44 of 2322 [1.9%] unclassified versus 221 of 8606 [2.6%] classified by at least one set of criteria; $P = .06$).

The modified Boston criteria had lower sensitivity (62.7% Boston versus 71.7% Philadelphia [difference 9.0%; 95% confidence interval (CI) 0.1% to 17.7%]) but higher specificity (59.2% Boston versus 46.1% Philadelphia [difference 13.1%; 95% CI 11.6% to 14.6%]) than the modified Philadelphia criteria for the identification of IBI (Table 4). Of the 79 (0.9%) infants with IBI who were

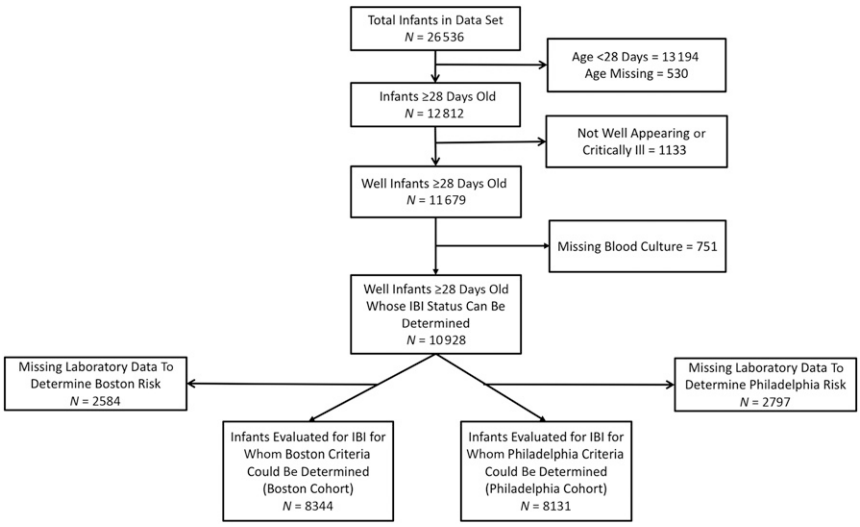

FIGURE 1
Study patients.

TABLE 2 Bacterial Pathogens Identified Among Infants With IBI

	All IBI (*N* = 264), *n* (%)	Bacterial Meningitis (*N* = 70), *n* (%)	Bacteremia (*N* = 194), *n* (%)
GBS *(Streptococcus agalactiae)*	72 (27.3)	17 (24.3)	55 (28.4)
E coli	72 (27.3)	11 (15.7)	61 (31.4)
S aureus	34 (12.9)	12 (17.1)	22 (11.3)
Enterococcus spp	15 (5.7)	7 (10.0)	8 (4.1)
Klebsiella spp	15 (5.7)	5 (7.1)	10 (5.2)
S pneumoniae	13 (4.9)	4 (5.7)	9 (4.6)
Enterobacter spp	11 (4.2)	1 (1.4)	10 (5.2)
Acinetobacter spp	7 (2.7)	3 (4.3)	4 (2.1)
Salmonella spp	4 (1.5)	1 (1.4)	3 (1.5)
Group A *Streptococcus (Streptococcus pyogenes)*	4 (1.5)	1 (1.4)	3 (1.5)
H influenzae	3 (1.1)	1 (1.4)	2 (1.0)
Stenotrophomonas spp	2 (0.8)	0 (0)	2 (1.0)
Neisseria meningitidis	2 (0.8)	2 (2.9)	0 (0)
Pseudomonas spp	2 (0.8)	1 (1.4)	1 (0.5)
Serratia spp	2 (0.8)	2 (2.9)	0 (0)
Moraxella spp	2 (0.8)	1 (1.4)	1 (0.5)
Listeria spp	1 (0.4)	1 (1.4)	0 (0)
Morganella spp	1 (0.4)	0 (0)	1 (0.5)
Proteus mirabilis	1 (0.4)	0 (0)	1 (0.5)
Chryseobacterium meningosepticum	1 (0.4)	0 (0)	1 (0.5)

spp, species.

misclassified by the modified Boston criteria as low risk, 17 (0.2%) had bacterial meningitis and 62 (0.7%) had bacteremia. Of the 62 (0.8%) with IBI misclassified by the modified Philadelphia criteria, 13 (0.2%) had bacterial meningitis and 49 (0.6%) had bacteremia. Both criteria had similar negative predictive value (98.4% Boston versus 98.3% Philadelphia [difference 0.1%; 95% CI −0.4% to 0.7%]). Cases of IBI misclassified by the modified Boston and Philadelphia criteria are summarized in Supplemental Tables 5 and 6, respectively.

TABLE 3 Characteristics of Infants Classified by the Boston or Philadelphia Criteria

Characteristic	Boston Cohort (*N* = 8344)	Philadelphia Cohort (*N* = 8131)
Demographics		
Age, d, median (IQR)	42 (35–50)	42 (35–50)
Male sex, *n* (%)	4696 (56.3)	4564 (56.1)
Clinical		
Triage temperature, °F, median (IQR)	100.2 (99.1–101.3)	100.2 (99.1–101.3)
CBC WBC, cells per μL, median (IQR)	9.9 (7.2–13.3)	10.2 (7.4–13.9)
CSF WBC, WBC per mL^3, median (IQR)	4 (2–12)	4 (2–13)
CSF Gram-stain positive, *n* of *N* (%)	19 of 7109 (0.3)	26 of 7276 (0.4)
Positive urine leukocyte esterase test result, *n* of *N* (%)	1200 of 7985 (15.0)	1177 of 7644 (15.4)
Positive urine microscopy result, >10 WBC per hpf, *n* of *N* (%)	882 of 4584 (19.2)	882 of 4455 (19.8)
Hospital management		
Admitted, *n* (%)	6669 (79.9)	6486 (80.9)
Length of stay (admitted patients), d, median (IQR)	2.1 (1.7–2.8)	2.1 (1.7–2.8)
IBIs, *n* (%)	212 (2.5)	219 (2.7)
Bacterial meningitis	53 (0.64)	56 (0.69)
Bacteremia	159 (1.9)	163 (2.0)
SBIs, *n* (%)	975 (11.7)	977 (12.0)
UTI	763 (9.1)	758 (9.3)

SBI

Among the 10 286 infants included in our secondary analysis of the modified Boston and Philadelphia criteria performance for identifying SBI, 1053 (10.2%) infants had an SBI, including 805 (7.8%) with an isolated UTI (ie, without associated bacteremia or bacterial meningitis). Among infants with an isolated UTI, *E coli* was the most common pathogen, accounting for 653 (81.1%) infections. In this cohort, we were able to apply the modified Boston criteria to 7982 (77.6%) infants, of whom 960 (12.0%) had an SBI, and the modified Philadelphia criteria to 7733 infants (75.2%), of whom 963 (12.5%) had an SBI. The modified Boston criteria had lower sensitivity (79.4% Boston versus 86.2% Philadelphia [difference 6.8%; 95% CI 3.4% to 10.2%]) and higher specificity (64.6% Boston versus 51.3% Philadelphia [difference 13.3%; 95% CI 11.7% to 14.9%]) than the modified Philadelphia criteria for the identification of SBI (Table 4).

DISCUSSION

We evaluated the performance of the modified Boston and Philadelphia criteria to identify bacterial infections in a large multinational cohort of infants between 29 and 60 days of age undergoing ED evaluation for meningitis. Approximately one-third of infants with an IBI were misclassified as low risk by both of these fever criteria. Although both criteria had a high negative predictive value (>98%), this was driven largely by the high prevalence of infants without IBI (>97%). Furthermore, only 4% of those infants identified as high risk (potentially leading to hospitalization and parenteral antibiotic exposure) actually had an IBI. Given well-described changes in the epidemiology of IBI as well as practice patterns for the management of febrile infants, new tools to risk

TABLE 4 Test Characteristics of the Boston and Philadelphia Criteria for Identifying IBIs and SBIs

	IBI		SBI	
	Boston Criteria	Philadelphia Criteria	Boston Criteria	Philadelphia Criteria
Sensitivity, % (95% CI)	62.7 (55.9 to 69.3)	71.7 (65.2 to 77.6)	79.4 (76.7 to 81.9)	86.2 (83.9 to 88.3)
Specificity, % (95% CI)	59.2 (58.1 to 60.2)	46.1 (45.0 to 47.2)	64.6 (63.5 to 65.7)	51.3 (50.1 to 52.5)
Negative predictive value, % (95% CI)	98.4 (98.0 to 98.8)	98.3 (97.9 to 98.7)	95.8 (95.2 to 96.4)	96.3 (95.6 to 96.9)
Positive predictive value, % (95% CI)	3.9 (3.2 to 4.6)	3.5 (3.0 to 4.1)	23.5 (22.0 to 25.0)	20.1 (18.9 to 21.4)
Negative likelihood ratio (95% CI)	0.6 (0.5–0.8)	0.6 (0.5–0.8)	0.3 (0.3–0.4)	0.3 (0.2–0.3)
Positive likelihood ratio (95% CI)	1.5 (1.4–1.7)	1.3 (1.2–1.4)	2.2 (2.1–2.4)	1.8 (1.7–1.8)

stratify febrile infants are needed to enable the accurate and rapid identification of infants with IBI without overtesting or treating low-risk infants.

The Boston and Philadelphia criteria were developed in the early 1990s to identify young, febrile infants at low risk for SBI who may be safely managed as outpatients.[16,17,33] Because the Boston criteria derivation study only enrolled low-risk infants, the criteria sensitivity cannot be calculated.[17] However, rates of SBI in infants identified as low risk by the Boston criteria have been reported between 3% and 5%, which is similar to our IBI rate.[17,34,35] In the single-center derivation study of 747 infants, the Philadelphia criteria had a sensitivity of 98% (95% CI 92% to 100%) for SBI,[16] and in follow-up studies, rates of SBI in low-risk infants have been reported between 0% and 3%, which is also similar to our findings.[35–37] Although both the original Philadelphia and Boston criteria were designed to identify infants with SBI, we chose IBI as our primary outcome because delays in diagnosis could result in significant morbidity and mortality, whereas infants with UTI could be safely managed as outpatients.[38] Importantly, the Boston and Philadelphia criteria performed similarly for the identification of SBI.

Changes in the microbiology of invasive infections[39] may explain, in part, the modest sensitivity of both fever criteria because the host immune response differs by pathogen[40] and both rely on measures of host immune response. The epidemiology of IBIs in febrile infants has changed over the past few decades, reflecting widespread conjugate vaccination for *Haemophilus influenzae* as well as *Streptococcus pneumoniae* (including introduction of the 13-valent pneumococcal vaccination during our study period). The impact has extended to the youngest infants,[21,41] presumably because of herd immunity.[22] A decrease in the rates of IBI caused by these pathogens was seen in our study: *H influenzae*, 11% to 25% (Boston and Philadelphia derivation studies) versus 1% (current study); *S pneumoniae*, 11% to 15% (derivation studies) versus 5% (current study). Although maternal antibiotic prophylaxis has prevented early-onset GBS, rates of late-onset GBS infections (ie, beyond the first week of life) have remained largely unchanged.[42,43] Consistent with this observation, our observed GBS rates are similar: 22% to 43% (Boston and Philadelphia derivation studies) versus 27% (our study).[16,17,23,25,26,44]

Furthermore, with recent data suggesting that lumbar puncture may be safely avoided in some infants 29 to 60 days old,[45] clinicians may be obtaining CSF only from infants with a higher clinical concern for meningitis, thereby leading to the Boston and Philadelphia criteria being applied to a different patient population from which they were derived. Despite this concern, our observed IBI rates are similar to other recent ED febrile infant cohorts.[2,9,28,39,46–48] Although we cannot apply either the Boston or the Philadelphia criteria to those infants who did not have CSF obtained, newer strategies should focus on methods to identify febrile infants who may safely avoid diagnostic lumbar puncture.

Given the limitations of these febrile infant criteria, more accurate ways to risk stratify infants at risk for IBI are needed. Newer biomarkers, including procalcitonin and C-reactive protein, have shown promise in risk stratifying infants.[5,18,28,49] The Step-By-Step Approach, using leukouria, serum procalcitonin, peripheral WBC, and C-reactive protein, had a sensitivity of 92% and specificity of 46% in a large prospective cohort of infants.[5] The Pediatric Emergency Care Applied Research Network Febrile Illness Working Group recently published a clinical prediction model to identify infants at low risk for SBI using a cohort of 1821 prospectively enrolled infants. Infants with negative urinalysis results, absolute neutrophil count <4090 /mm^3, and a procalcitonin <1.71mg/dL were at very low risk of SBI (sensitivity 97.7% [95% CI 91.3% to 99.6%] and specificity 60.0% [95% CI 56.6% to 63.3%]).[6] Multiplex bacterial polymerase chain reaction panels can be used to identify bacterial pathogens from both blood and CSF with a sufficiently short turnaround time to impact decisions regarding antibiotics and hospital admission.[50–52] Finally, novel RNA expression patterns measuring host response to infection have also shown

promise in identifying infants without acute bacterial infections but require further development before real-time clinical application.[53,54]

Our study had several limitations. First, our sample cohort was limited to those infants who had a CSF culture obtained. Although clinical practice for febrile infants in the second month of life is changing,[7] both of the studied criteria require CSF results for application. Second, we were unable to apply the Boston and Philadelphia criteria to the entire study cohort because of missing data. However, the IBI rates were similar between those we could and could not classify. Third, we were unable to determine infants' clinical appearance, comorbidities, or indication for undergoing evaluation for IBI. We did, however, exclude infants who were admitted to the ICU as a proxy measure for critical illness. In a large prospective cohort of febrile infants, neither unstructured clinical appearance nor structured Yale Observation Scale score is a strong predictor of IBI.[9] Fourth, we could not determine whether each infant had a fever at home or later in the ED course. Therefore, we may have inadvertently applied the criteria to some infants for whom these tools were not derived. However, we used the physician's decision to send CSF and blood cultures as a proxy for concern for IBI. Fifth, we had to modify the criteria because some of the included predictors (ie, urine Gram-stain and peripheral bands) were not routinely performed and urine dipstick without microscopy was performed for some infants, and they may have performed better if these laboratories results could have been included.[55] Sixth, despite our large sample size, bacterial meningitis was uncommon, limiting our confidence in identifying this specific IBI. Finally, these criteria were developed to identify infants who could be safely managed as outpatients. Although our analysis focused on missed cases of IBI, it is not possible to determine if infants with IBI who were misclassified as low risk could have been safely managed as outpatients with appropriate close clinical follow-up.

CONCLUSIONS

The Boston and Philadelphia criteria misclassified a substantial number of infants with bacterial infections, including approximately one-third of infants with bacteremia and bacterial meningitis. Better risk-stratification tools, likely including novel biomarkers, are needed to enable the rapid and accurate identification of infants at low risk of IBI who may be safely managed as outpatients.

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ABBREVIATIONS

CBC: complete blood count
CI: confidence interval
CSF: cerebrospinal fluid
ED: emergency department
GBS: group B *Streptococcus*
hpf: high-power field
IBI: invasive bacterial infection
IQR: interquartile range
SBI: serious bacterial infection
UTI: urinary tract infection
WBC: white blood cell count

Drs Lyons and Nigrovic conceptualized and designed the study, contributed to data collection, performed data analyses, and drafted the initial manuscript; Drs Cruz, Garro, and Freedman conceptualized and designed the study and contributed to data collection and analysis; Drs Okada, Mahajan, Balamuth, Thompson, Kulik, Uspal, and Arms contributed to data collection and analysis; and all authors reviewed and revised the manuscript, approved the final manuscript as submitted, and agree to be accountable for all aspects of the work.

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REFERENCES

1. Byington CL, Enriquez FR, Hoff C, et al. Serious bacterial infections in febrile infants 1 to 90 days old with and without viral infections. *Pediatrics*. 2004;113(6):1662–1666
2. Blaschke AJ, Korgenski EK, Wilkes J, et al. Rhinovirus in febrile infants and risk of bacterial infection. *Pediatrics*. 2018;141(2):e20172384
3. Baker MD, Avner JR, Bell LM. Failure of infant observation scales in detecting serious illness in febrile, 4- to 8-week-old infants. *Pediatrics*. 1990;85(6):1040–1043
4. Gómez B, Mintegi S, Benito J, Egireun A, Garcia D, Astobiza E. Blood culture and bacteremia predictors in infants less than three months of age with fever without source. *Pediatr Infect Dis J*. 2010;29(1):43–47
5. Gomez B, Mintegi S, Bressan S, Da Dalt L, Gervaix A, Lacroix L; European Group for Validation of the Step-by-Step Approach. Validation of the "Step-by-Step" Approach in the management of young febrile infants. *Pediatrics*. 2016;138(2):e20154381
6. Kuppermann N, Dayan PS, Levine DA, et al; Febrile Infant Working Group of the Pediatric Emergency Care Applied Research Network (PECARN). A clinical prediction rule to identify febrile infants 60 days and younger at low risk for serious bacterial infections. *JAMA Pediatr*. 2019;173(4):342–351
7. Aronson PL, Thurm C, Alpern ER, et al; Febrile Young Infant Research Collaborative. Variation in care of the febrile young infant <90 days in US pediatric emergency departments. *Pediatrics*. 2014;134(4):667–677
8. Meehan WP III, Fleegler E, Bachur RG. Adherence to guidelines for managing the well-appearing febrile infant: assessment using a case-based, interactive survey. *Pediatr Emerg Care*. 2010;26(12):875–880
9. Nigrovic LE, Mahajan PV, Blumberg SM, et al; Febrile Infant Working Group of the Pediatric Emergency Care Applied Research Network (PECARN). The Yale observation scale score and the risk of serious bacterial infections in febrile infants. *Pediatrics*. 2017;140(1):e20170695
10. Biondi EA, Mischler M, Jerardi KE, et al; Pediatric Research in Inpatient Settings (PRIS) Network. Blood culture time to positivity in febrile infants with bacteremia. *JAMA Pediatr*. 2014;168(9):844–849
11. Lefebvre CE, Renaud C, Chartrand C. Time to positivity of blood cultures in infants 0 to 90 days old presenting to the emergency department: is 36 hours enough? *J Pediatric Infect Dis Soc*. 2017;6(1):28–32
12. Leazer R, Erickson N, Paulson J, et al. Epidemiology of cerebrospinal fluid cultures and time to detection in term infants. *Pediatrics*. 2017;139(5):e20163268
13. Alpern ER, Kuppermann N, Blumberg S, et al. Time to positive blood and cerebrospinal fluid cultures in febrile infants < 60 days old. *Pediatrics*. 2018;142(1):104
14. Byington CL, Reynolds CC, Korgenski K, et al. Costs and infant outcomes after implementation of a care process model for febrile infants. *Pediatrics*. 2012;130(1). Available at: www.pediatrics.org/cgi/content/full/130/1/e16
15. Bachur RG, Harper MB. Predictive model for serious bacterial infections among infants younger than 3 months of age. *Pediatrics*. 2001;108(2):311–316
16. Baker MD, Bell LM, Avner JR. Outpatient management without antibiotics of fever in selected infants. *N Engl J Med*. 1993;329(20):1437–1441
17. Baskin MN, O'Rourke EJ, Fleisher GR. Outpatient treatment of febrile infants 28 to 89 days of age with intramuscular administration of ceftriaxone. *J Pediatr*. 1992;120(1):22–27
18. Woll C, Neuman MI, Aronson PL. Management of the febrile young infant: update for the 21st century. *Pediatr Emerg Care*. 2017;33(11):748–753
19. Garra G, Cunningham SJ, Crain EF. Reappraisal of criteria used to predict serious bacterial illness in febrile infants less than 8 weeks of age. *Acad Emerg Med*. 2005;12(10):921–925
20. Irwin AD, Wickenden J, Le Doare K, Ladhani S, Sharland M. Supporting decisions to increase the safe discharge of children with febrile illness from the emergency department: a systematic review and meta-analysis. *Arch Dis Child*. 2016;101(3):259–266
21. Poehling KA, Talbot TR, Griffin MR, et al. Invasive pneumococcal disease among infants before and after introduction of pneumococcal conjugate vaccine. *JAMA*. 2006;295(14):1668–1674
22. Olarte L, Ampofo K, Stockmann C, et al. Invasive pneumococcal disease in infants younger than 90 days before and after introduction of PCV7. *Pediatrics*. 2013;132(1). Available at: www.pediatrics.org/cgi/content/full/132/1/e17
23. Centers for Disease Control and Prevention (CDC). Progress toward eliminating Haemophilus influenzae type b disease among infants and children–United States, 1987-1997.

MMWR Morb Mortal Wkly Rep. 1998; 47(46):993–998

24. Centers for Disease Control and Prevention (CDC). Perinatal group B streptococcal disease after universal screening recommendations–United States, 2003-2005. *MMWR Morb Mortal Wkly Rep*. 2007;56(28):701–705
25. Phares CR, Lynfield R, Farley MM, et al; Active Bacterial Core surveillance/ Emerging Infections Program Network. Epidemiology of invasive group B streptococcal disease in the United States, 1999-2005. *JAMA*. 2008;299(17): 2056–2065
26. Centers for Disease Control and Prevention (CDC). Early-onset and late-onset neonatal group B streptococcal disease–United States, 1996-2004. *MMWR Morb Mortal Wkly Rep*. 2005; 54(47):1205–1208
27. Cruz AT, Freedman SB, Kulik DM, et al; HSV Study Group of the Pediatric Emergency Medicine Collaborative Research Committee. Herpes simplex virus infection in infants undergoing meningitis evaluation. *Pediatrics*. 2018; 141(2):e20171688
28. Cruz AT, Mahajan P, Bonsu BK, et al; Febrile Infant Working Group of the Pediatric Emergency Care Applied Research Network. Accuracy of complete blood cell counts to identify febrile infants 60 days or younger with invasive bacterial infections. *JAMA Pediatr*. 2017;171(11):e172927
29. Primack W, Bukowski T, Sutherland R, Gravens-Mueller L, Carpenter M. What urinary colony count indicates a urinary tract infection in children? *J Pediatr*. 2017;191(4, pt 2):259–261.e1
30. Hoberman A, Wald ER, Penchansky L, Reynolds EA, Young S. Enhanced urinalysis as a screening test for urinary tract infection. *Pediatrics*. 1993; 91(6):1196–1199
31. Schnadower D, Kuppermann N, Macias CG, et al; American Academy of Pediatrics Pediatric Emergency Medicine Collaborative Research Committee. Febrile infants with urinary tract infections at very low risk for adverse events and bacteremia. *Pediatrics*. 2010;126(6):1074–1083
32. Glissmeyer EW, Korgenski EK, Wilkes J, et al. Dipstick screening for urinary tract infection in febrile infants. *Pediatrics*. 2014;133(5). Available at: www.pediatrics.org/cgi/content/full/ 133/5/e1121
33. Dagan R, Powell KR, Hall CB, Menegus MA. Identification of infants unlikely to have serious bacterial infection although hospitalized for suspected sepsis. *J Pediatr*. 1985;107(6):855–860
34. Huppler AR, Eickhoff JC, Wald ER. Performance of low-risk criteria in the evaluation of young infants with fever: review of the literature. *Pediatrics*. 2010;125(2):228–233
35. Kadish HA, Loveridge B, Tobey J, Bolte RG, Corneli HM. Applying outpatient protocols in febrile infants 1-28 days of age: can the threshold be lowered? *Clin Pediatr (Phila)*. 2000;39(2):81–88
36. Baker MD, Bell LM, Avner JR. The efficacy of routine outpatient management without antibiotics of fever in selected infants. *Pediatrics*. 1999;103(3):627–631
37. Brik R, Hamissah R, Shehada N, Berant M. Evaluation of febrile infants under 3 months of age: is routine lumbar puncture warranted? *Isr J Med Sci*. 1997;33(2):93–97
38. Schnadower D, Kuppermann N, Macias CG, et al; American Academy of Pediatrics Pediatric Emergency Medicine Collaborative Research Committee UTI Study Group. Outpatient management of young febrile infants with urinary tract infections. *Pediatr Emerg Care*. 2014;30(9):591–597
39. Woll C, Neuman MI, Pruitt CM, et al; Febrile Young Infant Research Collaborative. Epidemiology and etiology of invasive bacterial infection in infants ≤60 Days old treated in emergency departments. *J Pediatr*. 2018;200(11):210–217.e1
40. Medzhitov R. Recognition of microorganisms and activation of the immune response. *Nature*. 2007; 449(7164):819–826
41. Pilishvili T, Lexau C, Farley MM, et al; Active Bacterial Core Surveillance/ Emerging Infections Program Network. Sustained reductions in invasive pneumococcal disease in the era of conjugate vaccine. *J Infect Dis*. 2010; 201(1):32–41
42. Centers for Disease Control and Prevention. *Active Bacterial Core Surveillanc (ABCs) Report, Group B Streptococcus*. Washington, DC: Centers for Disease Control and Prevention; 2016
43. Nanduri SA, Petit S, Smelser C, et al. Epidemiology of invasive early-onset and late-onset group B streptococcal disease in the United States, 2006 to 2015: multistate laboratory and population-based surveillance. *JAMA Pediatr*. 2019;173(3):224–233
44. Kaplan SL, Mason EO Jr., Wald ER, et al. Decrease of invasive pneumococcal infections in children among 8 children's hospitals in the United States after the introduction of the 7-valent pneumococcal conjugate vaccine. *Pediatrics*. 2004;113(3, pt 1):443–449
45. Scarfone R, Murray A, Gala P, Balamuth F. Lumbar puncture for all febrile infants 29-56 days old: a retrospective cohort reassessment study. *J Pediatr*. 2017;187:200–205.e1
46. Aronson PL, McCulloh RJ, Tieder JS, et al; Febrile Young Infant Research Collaborative. Application of the Rochester criteria to identify febrile infants with bacteremia and meningitis. *Pediatr Emerg Care*. 2019;35(1):22–27
47. Tzimenatos L, Mahajan P, Dayan PS, et al; Pediatric Emergency Care Applied Research Network (PECARN). Accuracy of the urinalysis for urinary tract infections in febrile infants 60 days and younger. *Pediatrics*. 2018;141(2): e20173068
48. Powell EC, Mahajan PV, Roosevelt G, et al; Febrile Infant Working Group of the Pediatric Emergency Care Applied Research Network (PECARN). Epidemiology of bacteremia in febrile infants aged 60 days and younger. *Ann Emerg Med*. 2018;71(2):211–216
49. Lyons TW, Cruz AT, Freedman SB, et al; Pediatric Emergency Medicine Clinical Research Network (PEM CRC) Herpes Simplex Virus Study Group. Interpretation of cerebrospinal fluid white blood cell counts in young infants with a traumatic lumbar puncture. *Ann Emerg Med*. 2017;69(5):622–631
50. Lucignano B, Ranno S, Liesenfeld O, et al. Multiplex PCR allows rapid and accurate diagnosis of bloodstream infections in newborns and children

with suspected sepsis. *J Clin Microbiol*. 2011;49(6):2252–2258

51. van den Brand M, van den Dungen FAM, Bos MP, et al. Evaluation of a real-time PCR assay for detection and quantification of bacterial DNA directly in blood of preterm neonates with suspected late-onset sepsis. *Crit Care*. 2018;22(1):105
52. Wagner K, Springer B, Pires VP, Keller PM. Pathogen identification by multiplex LightMix real-time PCR assay in patients with meningitis and culture-negative cerebrospinal fluid specimens. *J Clin Microbiol*. 2018;56(2): e01492-17
53. Mahajan P, Kuppermann N, Mejias A, et al. Association of RNA biosignatures with bacterial infections in febrile infants aged 60 days or younger. *JAMA*. 316(8):846–857
54. Mahajan P, Kuppermann N, Suarez N, et al; Febrile Infant Working Group for the Pediatric Emergency Care Applied Research Network (PECARN). RNA transcriptional biosignature analysis for identifying febrile infants with serious bacterial infections in the emergency department: a feasibility study. *Pediatr Emerg Care*. 2015;31(1):1–5
55. Cantey JB, Gaviria-Agudelo C, McElvania TeKippe E, Doern CD. Lack of clinical utility of urine gram stain for suspected urinary tract infection in pediatric patients. *J Clin Microbiol*. 2015;53(4): 1282–1285

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