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A Clinical Prediction Rule to Identify Febrile Infants 60 Days and Younger at Low Risk for Serious Bacterial Infections

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IMPORTANCE In young febrile infants, serious bacterial infections (SBIs), including urinary tract infections, bacteremia, and meningitis, may lead to dangerous complications. However, lumbar punctures and hospitalizations involve risks and costs. Clinical prediction rules using biomarkers beyond the white blood cell count (WBC) may accurately identify febrile infants at low risk for SBIs.

OBJECTIVE To derive and validate a prediction rule to identify febrile infants 60 days and younger at low risk for SBIs.

DESIGN, SETTING, AND PARTICIPANTS Prospective, observational study between March 2011 and May 2013 at 26 emergency departments. Convenience sample of previously healthy febrile infants 60 days and younger who were evaluated for SBIs. Data were analyzed between April 2014 and April 2018.

EXPOSURES Clinical and laboratory data (blood and urine) including patient demographics, fever height and duration, clinical appearance, WBC, absolute neutrophil count (ANC), serum procalcitonin, and urinalysis. We derived and validated a prediction rule based on these variables using binary recursive partitioning analysis.

MAIN OUTCOMES AND MEASURES Serious bacterial infection, defined as urinary tract infection, bacteremia, or bacterial meningitis.

RESULTS We derived the prediction rule on a random sample of 908 infants and validated it on 913 infants (mean age was 36 days, 765 were girls [42%], 781 were white and non-Hispanic [43%], 366 were black [20%], and 535 were Hispanic [29%]). Serious bacterial infections were present in 170 of 1821 infants (9.3%), including 26 (1.4%) with bacteremia, 151 (8.3%) with urinary tract infections, and 10 (0.5%) with bacterial meningitis; 16 (0.9%) had concurrent SBIs. The prediction rule identified infants at low risk of SBI using a negative urinalysis result, an ANC of 4090/μL or less (to convert to $\times 10^9$ per liter, multiply by 0.001), and serum procalcitonin of 1.71 ng/mL or less. In the validation cohort, the rule sensitivity was 97.7% (95% CI, 91.3-99.6), specificity was 60.0% (95% CI, 56.6-63.3), negative predictive value was 99.6% (95% CI, 98.4-99.9), and negative likelihood ratio was 0.04 (95% CI, 0.01-0.15). One infant with bacteremia and 2 infants with urinary tract infections were misclassified. No patients with bacterial meningitis were missed by the rule. The rule performance was nearly identical when the outcome was restricted to bacteremia and/or bacterial meningitis, missing the same infant with bacteremia.

CONCLUSIONS AND RELEVANCE We derived and validated an accurate prediction rule to identify febrile infants 60 days and younger at low risk for SBIs using the urinalysis, ANC, and procalcitonin levels. Once further validated on an independent cohort, clinical application of the rule has the potential to decrease unnecessary lumbar punctures, antibiotic administration, and hospitalizations.

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Supplemental content

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Nearly 500 000 febrile infants are evaluated in US emergency departments (EDs) and other outpatient settings annually.[1,2] Among febrile infants 60 days and younger, 8% to 13% have serious bacterial infections (SBIs) including urinary tract infections (UTIs), bacteremia, and bacterial meningitis.[3-5] Because missed SBIs, particularly bacteremia and meningitis, may lead to serious complications,[6,7] the treatment of febrile infants frequently involves lumbar punctures, broad-spectrum antibiotic administration, and hospitalization.

Fever may be the only sign of infection in young infants with SBIs. Clinical observation frequently fails to identify infants with invasive bacterial infections (bacteremia and meningitis),[8,9] and no single laboratory test result reliably identifies all infants with SBIs.[6,10-19] Transcriptome analysis holds promise for earlier diagnosis[20-23]; however, these tests have not been fully evaluated in the clinical setting. The incidence of SBIs in infants has decreased over time,[24] making it imperative to balance the consequences of missed SBIs with risks of hospital-related complications, costs, and potential increases in antimicrobial resistance owing to empirical antibiotic treatment.[6,25]

Clinical prediction rules with decision support can reduce variation in care and limit unnecessary interventions.[26-29] However, many algorithms for the evaluation of febrile infants combine subjective clinical findings and laboratory markers using pre-existing numerical cutoffs rather than statistically derived values[11,12,14,15,17,30] and lack precision and specificity, and validation studies have less than ideal accuracy.[31-33] Biomarkers, such as C-reactive protein and procalcitonin, have been used either alone[16,18,34-36] or combined with other laboratory and clinical findings[32,37,38] to risk stratify febrile infants, but further assessment is necessary to identify optimal thresholds and determine their utility for inclusion in prediction rules. We sought to derive and validate an accurate prediction rule in a large, prospectively enrolled, geographically diverse cohort of febrile infants 60 days and younger to identify those at low risk of SBIs.

Key Points

Question Can clinical features and laboratory tests identify febrile infants 60 days and younger at low risk for serious bacterial infections?

Findings In a cohort of 1821 febrile infants 60 days and younger, 170 (9.3%) had serious bacterial infections, and using recursive partitioning analysis, we derived a low-risk prediction rule involving 3 variables: normal urinalysis, absolute neutrophil count ≤4090/μL, and serum procalcitonin ≤1.71 ng/mL. The rule sensitivity was 97.7%, specificity was 60.0%, and negative predictive value was 99.6%; no infant with bacterial meningitis was missed.

Meaning The urinalysis, absolute neutrophil count, and serum procalcitonin levels may accurately identify febrile infants 60 days and younger at low risk for serious bacterial infections.

Methods

Study Design, Setting, and Population

Febrile infants 60 days and younger were recruited in a prospective observational multicenter study evaluating RNA microarray analysis for detection of bacterial infections.[20,39,40] The parent study has completed 2 grant cycles. The published microarray results include only data obtained during the first grant cycle. The current analytic cohort includes patients enrolled during the first and second grant cycles, between March 2011 and May 2013. Study methods have been previously described[39] but are briefly summarized here. The study received institutional review board approval at each site, with permission for data sharing and material transfer. We obtained written informed consent from the legal guardians of enrolled patients.

Infants from whom blood cultures were obtained for evaluation of SBIs during times when research staff were available were eligible (**Figure 1**). Fever was defined by rectal temperature of at least 38°C in the ED, in a prior health care setting, or at home within 24 hours. We excluded infants who appeared critically ill, had received antibiotics in the preceding 48 hours, had histories of prematurity (≤36 weeks' gestation), preexisting medical conditions, indwelling devices, or soft-tissue infections. Patients were not excluded for otitis media. Clinical care was at the discretion of the treating clinician.

Clinical and Laboratory Evaluation

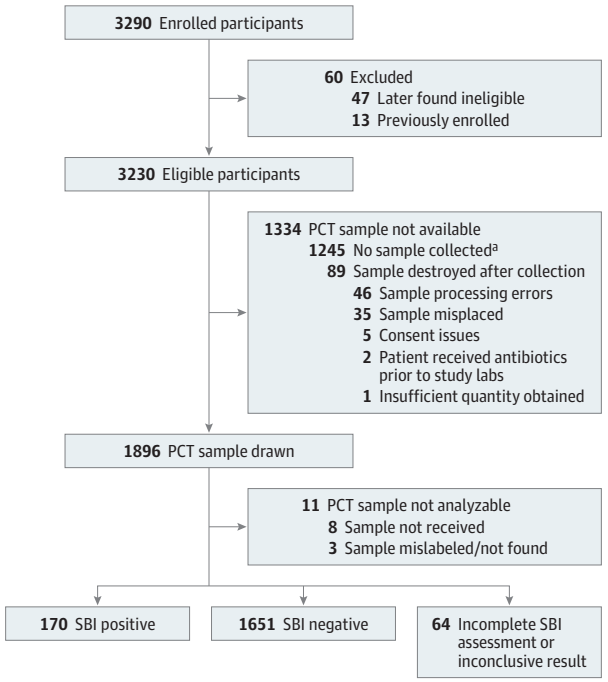
Emergency physicians (faculty or fellows in general or pediatric emergency medicine) performed patient histories and physical examinations, provided assessment of the Yale Observation Scale (YOS) score,[41] and recorded unstructured clinical suspicion of SBI (using 5 risk categories: <1%, 1%-5%, 6%-10%, 11%-50%, or >50%) prior to knowledge of laboratory results. All patients had blood and urine cultures obtained. Cerebrospinal fluid (CSF) testing was performed at the discretion of the treating clinician. To verify that patients discharged from the ED without CSF testing did not have bacterial meningitis, we contacted families of those patients by telephone 8 to 14 days after the ED visit and/or reviewed their medical records. Viral test results were not considered for the prediction rule because these were not typically available for ED decision making, and there was substantial variability among clinicians in their use.[42-45] Band counts were not considered for the prediction rule because they are variably performed across centers[16] and their utility has been questioned.[46]

For procalcitonin measurement, 1 mL of blood was centrifuged and stored at −80°C within 6 hours of the blood draw and shipped to a central laboratory. Procalcitonin results were not available to the treating clinicians.

Definitions and Outcome Measures

Serious bacterial infection was defined by bacterial meningitis, bacteremia, or UTI. We defined UTIs by the growth of a single urine pathogen with (1) at least 1000 cfu/mL for cultures obtained by suprapubic aspiration, (2) at least 50 000 cfu/mL from catheterized specimens, or (3) 10 000 to 50 000

Figure 1. Patient Flow Diagram



[a] This includes patients for whom procalcitonin (PCT) could not be sampled, regardless of whether an eligible RNA biosignature sample was obtained in the parent study. SBI indicates serious bacterial infection.

cfu/mL from catheterized specimens in association with an abnormal urinalysis, defined by the presence of leukocyte esterase, nitrite, or pyuria (>5 white blood cells per high-power field [WBC/hpf]).[47] This UTI definition was conservatively modified from the American Academy of Pediatrics practice parameter to account for the lower colony counts of bacteria (10 000-50 000 cfu/mL) sometimes present in the urine of young infants with UTIs[48-52] in comparison with older infants.[47] Bacteremia and bacterial meningitis were defined by the growth of a single bacterial pathogen in the blood or CSF, respectively.[20] Growth of bacteria not commonly considered pathogens (eg, diphtheroids or coagulase-negative *Staphylococcus*) were categorized a priori as contaminants, and patients with growth of these organisms (meeting no other criteria for SBI) were categorized in the SBI-negative group.

Statistical Analysis

We compared descriptive statistics from patients enrolled in the parent study before procalcitonin levels were collected to the study cohort to detect any important differences. To create the prediction rule, patients who had procalcitonin levels measured were randomly divided into derivation and validation sets. Random sampling was constrained to provide balanced representation of bacteremia, bacterial meningitis, and UTIs between derivation and validation sets. As predictor variables, we included age group (≤28 days vs >28 days), qualifying temperature, duration of fever, YOS score, unstructured clinician suspicion, urinalysis, WBC count, absolute neutrophil count (ANC), and serum procalcitonin level. We performed univariable analyses for each potential predictor using differences in proportions, with 95% confidence intervals for categorical variables, differences in means with 95% confidence intervals for continuous variables, and medians with interquartile ranges for YOS scores. All *P* values were 2-sided, with *P* values less than .05 considered significant.

Recursive Partitioning Analysis

To identify a low-risk cohort using the derivation set, all potential predictors of SBI were entered into a binary recursive partitioning analysis.[53] The algorithm identifies optimal thresholds for each numerical predictor to generate decision trees. We prioritized the sensitivity of the prediction rule by specifying a relative cost of 100 to 1 for failure to identify an SBI vs incorrectly predicting SBI. The final tree was chosen prior to applying the results to the validation set. In both derivation and validation sets, we calculated the prediction rule's sensitivity, specificity, positive and negative predictive values, and likelihood ratios, with corresponding 95% confidence intervals.

Additional Analyses

We performed exploratory analyses to determine whether procalcitonin results could further subdivide the high-ANC group. In addition, because bacteremia and bacterial meningitis are more invasive infections than UTIs, we performed a subanalysis to evaluate the rule accuracy for identifying patients with those infections (including patients with concurrent UTI and bacteremia or meningitis).

We also performed a sensitivity analysis to account for uncertain diagnoses of UTIs in patients with colony counts of 10 000 to 49 999 cfu/hpf and abnormal urinalysis results. Patients in this category were removed from the data set and the recursive partitioning was repeated.

Finally, we performed a multivariable logistic regression analysis to determine whether this would result in a more accurate model. See the eMethods in the Supplement for details.

Salford Predictive Modeler software, version 8.0, was used for all recursive partitioning analyses (Salford Systems). All other statistical analyses and summaries were performed using SAS software, version 9.4 (SAS Institute Inc).

Results

Patient Population

A total of 1896 febrile infants were enrolled (1821 with procalcitonin data analyzable and complete assessments for SBI; Figure 1). One thousand eight hundred six infants (99.2%) had CBCs, 1775 (97.5%) had urinalyses, and 1399 (76.8%) had lumbar punctures performed (including 871 of 1266 infants aged 29-60 days [68.8%]). Of the 1821 infants, 908 were randomly allocated to the derivation set and 913 to the validation set (**Table 1**); demographic and clinical characteristics were similar between groups. Patients enrolled in the parent study before procalcitonin levels were obtained, and patients from whom procalcitonin levels were not obtained for other

Table 1. Patient Characteristics

Characteristic	Sample, No. (%)		
	Derivation (n = 908)	Validation (n = 913)	Overall (N = 1821)
Age, mean (SD), d	35.9 (14.8)	36.1 (15.0)	36.0 (14.9)
Age ≤28 d	280 (30.8)	275 (30.1)	555 (30.5)
Female	387 (42.6)	378 (41.4)	765 (42.0)
Race/ethnicity			
White, non-Hispanic	397 (43.7)	384 (42.1)	781 (42.9)
Black	183 (20.2)	183 (20.0)	366 (20.1)
Asian	20 (2.2)	34 (3.7)	54 (3.0)
Hispanic	263 (29.0)	272 (29.8)	535 (29.4)
Other/missing	45 (5.0)	40 (4.4)	85 (4.7)
Qualifying temperature, mean (SD), °C	38.5 (0.5)	38.5 (0.4)	38.5 (0.4)
Duration of fever prior to ED visit, h			
<12	569 (62.7)	575 (63.0)	1144 (62.8)
12-24	265 (29.2)	254 (27.8)	519 (28.5)
>24	69 (7.6)	75 (8.2)	144 (7.9)
Unknown	5 (0.6)	9 (1.0)	14 (0.8)
YOS, median (IQR)	6.0 (6.0-8.0)	6.0 (6.0-8.0)	6.0 (6.0-8.0)
Clinician suspicion			
<1%	322 (35.5)	361 (39.5)	683 (37.5)
1%-5%	387 (42.6)	366 (40.1)	753 (41.4)
6%-10%	138 (15.2)	127 (13.9)	265 (14.6)
11%-50%	44 (4.8)	42 (4.6)	86 (4.7)
>50%	10 (1.1)	14 (1.5)	24 (1.3)
Unknown	7 (0.8)	3 (0.3)	10 (0.5)
Urinalysis positive	127 (14.0)	149 (16.3)	276 (15.2)
WBC, mean (SD), /μL	10 300 (4500)	10 500 (4.9)	10 400 (4700)
ANC, mean (SD), /μL	4000 (2800)	4200 (3300)	4100 (3100)
PCT, ng/mL, median (IQR)	0.2 (0.2-0.3)	0.2 (0.2-0.3)	0.2 (0.2-0.3)
SBI positive	82 (9.0)	88 (9.6)	170 (9.3)
UTI alone	65 (7.2)	75 (8.3)	140 (7.7)
Bacteremia alone	8 (0.9)	2 (0.2)	10 (0.5)
Meningitis alone	3 (0.3)	1 (0.1)	4 (0.2)
UTI and bacteremia	3 (0.3)	7 (0.8)	10 (0.5)
Bacteremia and meningitis	2 (0.2)	3 (0.3)	5 (0.3)
UTI and bacteremia and meningitis	1 (0.1)	0	1 (0.1)
SBI positive			
Age ≤28 d[a]	36 (12.9)	36 (13.1)	72 (13.0)
UTI alone	28 (10.0)	29 (10.5)	57 (10.3)
Bacteremia alone	3 (1.1)	1 (0.4)	4 (0.7)
Meningitis alone	2 (0.7)	1 (0.4)	3 (0.5)
UTI and bacteremia	1 (0.4)	3 (1.1)	4 (0.7)
Bacteremia and meningitis	1 (0.4)	2 (0.7)	3 (0.5)
UTI and bacteremia and meningitis	1 (0.4)	0	1 (0.2)
Age >28 d[a]	46 (7.3)	52 (8.2)	98 (7.7)
UTI alone	37 (5.9)	46 (7.2)	83 (6.6)
Bacteremia alone	5 (0.8)	1 (0.2)	6 (0.5)
Meningitis alone	1 (0.2)	0	1 (0.1)
UTI and bacteremia	2 (0.3)	4 (0.6)	6 (0.5)
Bacteremia and meningitis	1 (0.2)	1 (0.2)	2 (0.2)
UTI and bacteremia and meningitis	0	0	0

Abbreviations: ANC, absolute neutrophil count; ED, emergency department; IQR, interquartile range; PCT, procalcitonin; SBI, serious bacterial infection; UTI, urinary tract infection; WBC, white blood cell count; YOS, Yale Observation Scale score.

SI conversion factors: To convert ANC to $\times 10^9$ per liter, multiply by 0.001; WBC to $\times 10^9$ per liter, multiply by 0.001.

[a] Percentages are calculated out of all patients in the referenced age category (n = 280 and 275 for 28 days and younger, n = 628 and 638 for older than 28 days).

reasons were similar to those with procalcitonin measurements (eTable 1 in the Supplement). All patients had blood and urine cultures, and 1383 (76%) had CSF cultures obtained. No patients who did not have CSF cultures obtained were later

Table 2. Univariable Analysis of Combined Derivation and Validation Cohorts

Characteristic	SBI Status, No. (%)		Difference (95% CI)
	Positive (n = 170)	Negative (n = 1651)	
Age, mean (SD), d	33.0 (15.1)	36.4 (14.8)	−3.3 (−5.7 to −0.9)
Age ≤ 28 d	72 (42.4)	483 (29.3)	13.1% (5.4 to 20.8)
Qualifying temperature, mean (SD), °C	38.7 (0.5)	38.5 (0.4)	0.2 (0.1 to 0.3)
Duration of fever prior to ED visit, h			
<12	106 (63.5)	1038 (63.3)	0.2% (−7.5 to 7.8)
12-24	49 (29.3)	470 (28.7)	0.7% (−6.6 to 7.9)
>24	12 (7.2)	132 (8.0)	−0.9% (−5.0 to 3.3)
YOS, median (IQR)[a]	6.0 (6.0 to 10.0)	6.0 (6.0 to 8.0)	
Clinician suspicion			
<1%	36 (21.4)	647 (39.4)	−18.0% (−24.6 to −11.3)
1%-5%	75 (44.6)	678 (41.3)	3.4% (−4.5 to 11.3)
6%-10%	27 (16.1)	238 (14.5)	1.6% (−4.2 to 7.4)
11%-50%	20 (11.9)	66 (4.0)	7.9% (2.9 to 12.9)
>50%	10 (6.0)	14 (0.9)	5.1% (1.5 to 8.7)
Urinalysis positive	141 (82.9)	135 (8.2)	74.8% (69.0 to 80.6)
WBC, mean (SD), /μL	14 300 (6100)	10 000 (4300)	4300 (3400 to 5300)
ANC, mean (SD), /μL	7700 (4500)	3700 (2600)	4000 (3300 to 4700)
PCT, ng/mL, median (IQR)	0.7 (0.3 to 3.4)	0.2 (0.2 to 0.3)	0.5 (0.4 to 0.6)

Abbreviations: ANC, absolute neutrophil count; ED, emergency department; IQR, interquartile range; PCT, procalcitonin; SBI, serious bacterial infection; WBC, white blood cell count; YOS, Yale Observation Scale score.

SI conversion factors: To convert ANC to $\times 10^9$ per liter, multiply by 0.001; WBC to $\times 10^9$ per liter, multiply by 0.001.

[a] The *P* value for the associated Wilcoxon rank sum test is 0.0294.

found to have bacterial meningitis. Follow-up information for these patients was based on observation in the hospital (n = 178), telephone follow-up (n = 216), or medical record review (n = 44). Serious bacterial infections were diagnosed in 170 infants (9.3%; 95% CI, 8.1-10.8), including 151 (8.3%; 95% CI, 7.1-9.6) with UTIs, 26 (1.4%; 95% CI, 1.0-2.1) with bacteremia, and 10 (0.5%; 95% CI, 0.3-1.0) with bacterial meningitis; 16 (0.9%; 95% CI, 0.5-1.4) had concurrent bacterial infections (eTable 2 in the Supplement). Of the 16 with multiple infections, 1 had UTI, bacteremia, and meningitis; 5 had bacteremia and meningitis; and 10 had UTI and bacteremia. Four patients had herpes simplex virus infections (all were hospitalized). Three were younger than 28 days (aged 10, 12, and 20 days) and had herpes simplex virus in the CSF; the other was aged 33 days and had herpes simplex virus detected in a nasopharyngeal swab only.

Univariable Analysis

The associations between potential predictors and SBI are shown in **Table 2**. Although the groups with and without SBIs were similar in mean age, infants with SBIs were more likely to be 28 days or younger, have higher temperatures, WBC counts and ANC, and procalcitonin levels. Increased clinician suspicion was also associated with increased SBI risk.

Recursive Partitioning Analysis

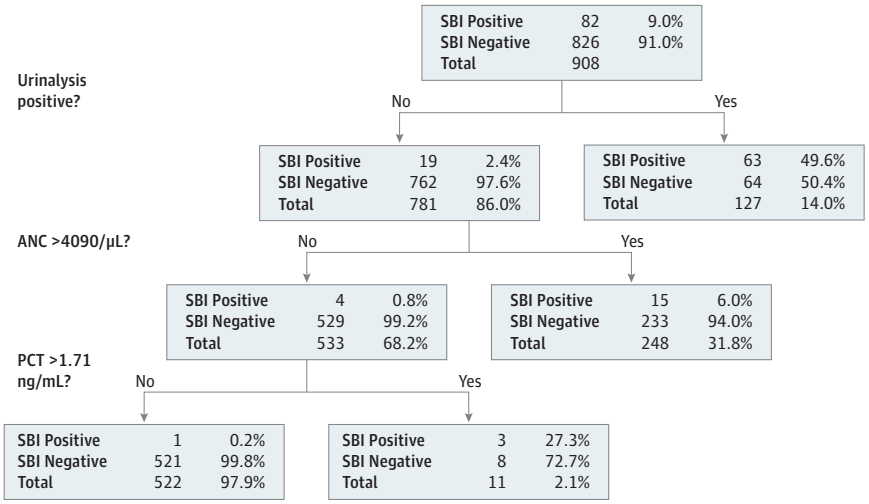
The decision tree retained 3 variables, urinalysis, ANC, and procalcitonin, that together identified a group of infants at low risk of SBI (**Figure 2**). In the derivation set of 908 infants with a rate of SBI of 9.0%, a negative urinalysis, ANC of 4090/μL or lower (to convert to $\times 10^9$ per liter, multiply by 0.001), and a serum procalcitonin level of 1.71 ng/mL or lower identified a low-risk group of 522 infants, with an SBI risk of 0.2% (1 infant). The sensitivity of the decision rule in the derivation set was 98.8% (95% CI, 92.5%-99.9%). In the validation set, the rule identified a low-risk group of 497 infants with an SBI risk of 0.4% (2 infants), yielding a sensitivity of 97.7% (95% CI, 91.3%-99.6%). Other model test characteristics are reported in Figure 2. The types of SBIs in each risk category (ie, each cell of the decision tree) are shown in eFigures 1 and 2 in the Supplement. One patient in the derivation set (with *Enterobacter cloacae* bacteremia) and 2 patients in the validation set (with UTIs with negative urinalyses) with SBIs were misclassified by the prediction rule (**Table 3**). In eFigure 3 in the Supplement, we rounded the ANC to 4000/μL and serum procalcitonin to 1.7 ng/mL; in eFigure 4 in the Supplement, we rounded the ANC to 4000/μL and serum procalcitonin to a commonly accepted cutoff value of 0.5 ng/mL. With these easier-to-apply cutoffs, the model sensitivities and negative predictive values were nearly identical to the empirically derived rule, but specificities were slightly lower.

Of 1266 infants aged 29 to 60 days, 776 (61.3%) were at low risk for the prediction rule, and 523 of these 776 (67.4%) had lumbar punctures performed. This number represents potential lumbar punctures spared in this age group for low-risk patients.

Additional Analyses

To determine whether we could further identify a low-risk cohort among patients with negative urinalyses but with ANC counts greater than the threshold (4090/μL), we explored that branch of the tree in the full cohort using recursive partitioning (eFigure 5 in the Supplement). Among the 500 infants in that risk category, there were 153 (30.6%) with procalcitonin levels of 0.18 ng/mL or lower. Only 1 of 153 (0.7%; 95% CI, 0.1%-3.6%) had an SBI (*S aureus* bacteremia).

Figure 2. Recursive Partitioning Analysis



	Derivation, No.			Validation, No.		
	SBI	No SBI	Total	SBI	No SBI	Total
SBI per rule	81	305	386	86	330	416
No SBI per rule	1	521	522	2	495	497
Total	82	826	908	88	825	913

	Derivation, No.	Validation, No.
Prediction rule sensitivity (95% CI), %	98.8 (92.5-99.9)	97.7 (91.3-99.6)
Prediction rule specificity (95% CI), %	63.1 (59.7-66.4)	60.0 (56.6-63.3)
Negative predictive value (95% CI), %	99.8 (98.8-100.0)	99.6 (98.4-99.9)
Positive predictive value (95% CI), %	21.0 (17.1-25.5)	20.7 (16.9-25.0)
Negative likelihood ratio (95% CI)	0.02 (0.003-0.14)	0.04 (0.01-0.15)
Positive likelihood ratio (95% CI)	2.68 (2.44 - 2.93)	2.44 (2.23-2.67)

Only the derivation cohort is shown in the tree portion of the figure. Overall classification counts and characteristics are shown for both the derivation and validation cohorts below the classification tree. SI conversion factor: To convert absolute neutrophil count (ANC) to $\times 10^9$ per liter, multiply by 0.001. PCT indicates procalcitonin; SBI, serious bacterial infection.

Table 3. Misclassified Patients With SBIs[a]

Age, d	Qualifying Temperature, °C	YOS	Clinician Suspicion, %	Disposition of Infant After ED Visit	Urinalysis	WBC, /μL	ANC, /μL	Bands, %	PCT, ng/mL	CSF	SBI
30	38.1	6	6-10	Admitted	Negative	6700	2700	0 (B:N 0)	0.14	Negative	*Enterobacter cloacae* bacteremia
55	38.4	8	1-5	Discharged	Negative	3800	2200	3 (B:N 0.05)	0.20	Negative	*Escherichia coli* UTI
36	38.5	6	1-5	Admitted	Negative	2300	900	12 (B:N 0.3)	0.16	Negative	*Pseudomonas aeruginosa* UTI

Abbreviations: ANC, absolute neutrophil count; B:N, band-to-neutrophil ratio; CSF, cerebrospinal fluid; ED, emergency department; PCT, procalcitonin; SBI, serious bacterial infection; UTI, urinary tract infection; WBC, white blood cell count; YOS, Yale Observation Scale score.

[a] The first patient had *Enterobacter cloacae* bacteremia and was in the derivation data set. This patient was admitted to an observation unit for poor feeding without antibiotic treatment. After notification of the positive blood culture at 17 hours, a repeated blood culture was obtained, and the patient started receiving parenteral antibiotics. The repeated blood culture (prior to antibiotics) was negative and the patient was treated for 7 days with antibiotics, had an uneventful clinical course, and had a final diagnosis of transient bacteremia. The other 2 patients with SBIs who were misclassified were in the validation data set and had positive urine cultures with normal urinalyses (one with *Escherichia coli* growing 55 000 cfu/mL and the other with *Pseudomonas aeruginosa* growing >100 000 cfu/mL). Both were treated with uneventful courses.

When patients with UTIs alone were removed from the cohort, the prediction rule performed with similar accuracy for identifying patients with bacteremia and bacterial meningitis (eFigure 6 in the Supplement). In that analysis, the sensitivity of the rule was 96.7% (95% CI, 83.3-99.4) and specificity was 61.5% (95% CI, 59.2-63.9).

In a sensitivity analysis, we reclassified 17 patients with urine culture colony counts of less than 50 000 cfu/mL as SBI-negative. When applied to the new analytic cohort, the recursive partitioning analysis selected the same variables and numerical cutoffs, and the model had similar test accuracies (data not shown).

When we compared multivariable logistic regression analysis with the recursive partitioning analysis, we found inferior test characteristics in the former. For details, see the eResults in the Supplement.

Discussion

In this large, prospective, multicenter study, we derived and validated a highly accurate prediction rule to identify febrile infants 60 days and younger at low risk of SBIs using 3 laboratory test results: the urinalysis, ANC, and serum procalcitonin levels. Neither clinician suspicion nor the YOS added significantly to the rule, as we and others have previously demonstrated.[8,9] The prediction rule had high sensitivity for identifying infants with SBIs and high negative predictive value while maintaining moderately high specificity. The lower end of the 95% confidence interval of the negative predictive value in the validation set was 98.4%, leaving a small potential false-negative rate. Importantly, the rule does not require CSF data, potentially obviating the need for routine lumbar punctures for many young febrile infants provided that further external validation confirms accuracy. Furthermore, the rule is straightforward and uses objective variables, simplifying implementation. Rounding the numerical thresholds of the ANC and serum procalcitonin to easier-to-apply numbers resulted in nearly identical model test characteristics.

The better test characteristics of the current prediction rule compared with many previously proposed likely reflects the prospective study design, use of large derivation and validation cohorts, objective laboratory variables at statistically identified thresholds, inclusion of serum procalcitonin, and multivariable statistical modeling to derive and validate the rule. Among commonly used rules not involving newer biomarkers (mainly developed during an era of higher prevalence of SBIs in febrile infants), several, including the Philadelphia, Rochester, Boston, and Pittsburgh criteria,[11,15,17,54] were not statistically derived and therefore lacked optimal balance between test sensitivity (avoiding missed SBIs) and specificity (preventing overtesting and overtreating patients without SBIs). These models included WBC counts at standard thresholds (5000/mL, 15 000/mL, and 20 000/mL [to convert to $\times 10^9$ per liter, multiply by 0.001]), rather than thresholds determined statistically, limiting diagnostic accuracy.[13,16,55] Furthermore, several previous rules include data from lumbar punctures, an invasive procedure that is not required in our rule. Nonetheless, the sensitivity of our rule is as least as high, and the specificity is higher than several previous rules.[11,15,56,57] Our data contribute important information to the decades-long debate about the necessity of lumbar punctures and hospitalizations in young febrile infants.[3,58,59] Our data also contribute important information to guide initiatives aimed at decreasing variability in the approach to young febrile infants and minimizing unnecessary testing and hospitalizations.[60]

Prediction rules for young febrile infants developed in the past decade include newer blood tests that are more sensitive and/or specific for SBI than the WBC count.[16,18,38,61-63] The "Step-by-Step" rule combined both clinical factors (patient appearance) and laboratory factors (leukocyturia and procalcitonin, C-reactive protein, and ANC levels) in febrile infants aged 22 to 90 days.[32,38,64] That model had a sensitivity of 98.9% to detect all SBIs and a sensitivity of 92.0% to detect invasive bacterial infections (bacteremia or bacterial meningitis).[38] In contrast, our model was derived on a different age group (0-60 days) and does not exclude infants with symptoms or signs of respiratory infections. Our multivariable approach identified ANC and procalcitonin thresholds that maximize test accuracy.

Procalcitonin is particularly sensitive for detecting bacteremia and bacterial meningitis in young febrile infants[16,18] and is widely available for clinical use, requiring only 200 µL of serum and having a turnaround time of 30 to 120 minutes.[65] Not only is the test accuracy of procalcitonin substantially better than the WBC and ANC, but it also surpasses that of C-reactive protein.[19,66] The better test characteristics of procalcitonin vs C-reactive protein is perhaps owing to the earlier rise in procalcitonin in response to systemic infection.[66] Our data add to this information by demonstrating ideal thresholds for procalcitonin interpretation in conjunction with other laboratory measurements used in practice.

Similar to previous evaluations of prediction rules, our rule misclassified a few patients with SBIs. One patient classified as low risk had *Enterobacter cloacae* bacteremia. However, a repeated blood culture prior to antibiotic administration was negative, and the patient was treated with antibiotics with an uneventful course. The 2 patients with UTIs who were misclassified had negative urinalysis results possibly indicating asymptomatic bacteriuria.[67]

Limitations

Our study has limitations. We enrolled patients based on research coordinator availability; however, rates of specific SBIs were similar to prior studies in similar populations,[3-5] suggesting that the enrolled sample was representative. In addition, we did not study biomarkers other than procalcitonin. However, previous literature strongly suggests that procalcitonin has superior test characteristics for bacteremia and bacterial meningitis than C-reactive protein and other biomarkers.[16,18,19] Additionally, we did not evaluate viral testing in the prediction rule because these tests were not part of the protocol nor uniformly performed at the study sites. However, prior literature has shown that identification of viral pathogens diminishes but does not eliminate the risk of SBI in young febrile infants,[5,16,43,68,69] and those results are often unavailable for ED decision making. Furthermore, although our sample included 170 patients with SBIs, only 30 had bacteremia or bacterial meningitis, reflecting the current epidemiology of SBIs in this age group. Therefore, validation of our findings on cohorts with greater numbers of invasive infections is desirable before implementation. Finally, until further validation of the prediction rule, clinicians must remain most cautious with infants younger than 28 days, in whom the risks of bacteremia and bacterial meningitis as well as herpes encephalitis[70] are the greatest. In our sample, similar to previous reports,[70] 0.2% had herpes simplex infections. All 3 infants with herpes encephalitis were in the first month of life, further highlighting the need for caution in this age group.

Conclusions

We derived and validated an accurate prediction rule to identify febrile infants 60 days and younger at low risk for SBIs using 3 easily obtainable, objective variables: the urinalysis, the ANC, and serum procalcitonin. Once further validated, implementation of the rule has the potential to substantially decrease the use of lumbar punctures, broad-spectrum antibiotics, and hospitalization for many febrile infants 60 days and younger.

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