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Prediction of Bacteremia and Bacterial Meningitis Among Febrile Infants Aged 28 Days or Younger

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IMPORTANCE Fever in the first month of life is often the only sign of life-threatening invasive bacterial infection, specifically bacteremia or bacterial meningitis. Most international guidelines recommend routine lumbar punctures for all febrile infants 28 days or younger to rule out bacterial meningitis. Clinical prediction rules may allow for select testing, but limited information exists on their performance to identify infants at low risk for invasive bacterial infections.

OBJECTIVE To evaluate the diagnostic accuracy of the updated Pediatric Emergency Care Applied Research Network (PECARN) prediction rule for identifying febrile infants 28 days or younger with bacteremia or bacterial meningitis.

DESIGN, SETTING, AND PARTICIPANTS This pooled analysis of 4 published prospective cohort studies from pediatric emergency departments across 6 countries within the global Pediatric Emergency Research Network included previously healthy, non–ill-appearing, full-term (≥37 weeks' gestation) infants aged 28 days or younger with a temperature greater than or equal to 38.0 °C who underwent urine, blood, and serum testing.

EXPOSURE Infants were classified as low risk if they had a negative urinalysis/dipstick test result, serum procalcitonin less than or equal to 0.5 ng/mL, and blood absolute neutrophil count less than or equal to 4000/mm^3.

MAIN OUTCOMES AND MEASURES Meta-analytic methods were applied to assess diagnostic accuracy (sensitivity, specificity, and positive and negative predictive values) of the PECARN rule for detection of infants with invasive bacterial infections (bacteremia or bacterial meningitis).

RESULTS Among 1537 infants 28 days or younger (905 male, 1324 hospitalized, 1080 with lumbar punctures), 69 (4.5%) had invasive bacterial infections, including 11 (0.7%) with bacterial meningitis. Overall, 632 (41.1%) met low-risk criteria. The prediction rule had a sensitivity of 94.2% (95% CI, 85.6%-97.8%), specificity of 41.6% (95% CI, 36.7%-46.7%), positive predictive value of 6.9% (95% CI, 4.8%-9.9%), and negative predictive value of 99.4% (95% CI, 98.1%-99.8%) for invasive bacterial infections. In a secondary analysis of 2531 infants from the 2 US-based cohorts from which the rule was originally derived and the 4 validation cohorts, 96 (3.8%) had invasive bacterial infections, 22 (0.9%) had bacterial meningitis, and 1079 (42.6%) were classified as low risk; rule performance was similar. No infants with bacterial meningitis were misclassified in the primary or secondary analyses.

CONCLUSIONS AND RELEVANCE The updated PECARN rule had high sensitivity but lower specificity for identifying febrile infants 28 days or younger with invasive bacterial infections in this study, with no missed cases of bacterial meningitis. These results may support shared decision-making regarding select vs routine use of lumbar puncture among infants classified as being at low risk of invasive bacterial infections.

Editorial

Supplemental content

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Fever among young infants is one of the most common problems in pediatric health care globally. More than 2% of all US full-term infants are evaluated for fever in the first months of life in emergency departments and other outpatient settings.[1] Although most have self-limited viral illnesses, approximately 4% of febrile infants aged 28 days or younger harbor invasive bacterial infections, specifically bacteremia and bacterial meningitis.[2,3] Many febrile young infants with invasive bacterial infections are well-appearing and cannot be reliably identified by history and physical examination alone.[4]

Given that missing young infants with invasive bacterial infections could result in permanent disability or death, efforts to develop safe risk-stratification strategies have spanned more than 4 decades.[5-7] To avoid missing a single infant with bacterial meningitis, most international guidelines currently recommend routine lumbar puncture for cerebrospinal fluid testing, empirical antibiotic treatment, and hospitalization for all febrile infants 21 days or younger[8,9] or younger than 30 days.[10] However, lumbar puncture in infants is invasive and may be stressful for parents,[11,12] and routine empirical antibiotic use and hospitalization is associated with iatrogenic risks[13,14] and substantial resource use.[13,15] Safely reducing unnecessary lumbar punctures for febrile young infants would enhance family-centered, high-value care.

Investigators from the Pediatric Emergency Care Applied Research Network (PECARN) prospectively derived a prediction rule to identify febrile infants 60 days or younger at low risk of urinary tract infections (UTIs), bacteremia, and bacterial meningitis.[16] The prediction rule performed with excellent diagnostic accuracy and was subsequently simplified to use more conservative thresholds of serum procalcitonin less than or equal to 0.5 ng/mL and an absolute neutrophil count (ANC) less than or equal to 4000/mm^3 in combination with a negative urinalysis result.[16] In an external validation study, the updated PECARN rule maintained similar test characteristics for UTIs, bacteremia, and bacterial meningitis.[17] However, UTIs are substantially more prevalent than bacteremia and bacterial meningitis and may distort models that specifically attempt to identify infants with invasive bacterial infections.[8] Therefore, this study evaluated the diagnostic accuracy of the updated PECARN prediction rule for detection of infants 28 days or younger with invasive bacterial infections alone and determined the prevalence of bacterial meningitis among low-risk infants in a large, pooled, international sample.

Key Points

Question How accurately does a clinical prediction rule based on urinalysis, procalcitonin, and absolute neutrophil count identify febrile young infants at low risk for bacteremia and/or bacterial meningitis?

Findings Among 1537 febrile infants 28 days or younger from 4 studies in 6 countries, the prediction rule had a sensitivity of 94.2%, specificity of 41.6%, positive predictive value of 6.9%, and negative predictive value of 99.4% for bacteremia and bacterial meningitis; no infants classified as being at low risk had bacterial meningitis.

Meaning A prediction rule using laboratory tests without lumbar puncture had high sensitivity but more limited specificity for identifying febrile infants 28 days or younger with invasive bacterial infections.

Methods

Study Design, Setting, and Population

This study included 4 prospective cohort studies from 6 countries conducted in pediatric emergency departments within the global Pediatric Emergency Research Network.[18] The Pediatric Emergency Research Network consists of 8 pediatric emergency care networks formed to facilitate international collaborative research, including PECARN in the US, the Pediatric Emergency Research Canada Network, the Paediatric Emergency Research in the UK and Ireland, and Red de Investigación de la Sociedad Española de Urgencias de Pediatría (Spanish Pediatric Emergency Research Group), from which we identified our study cohorts.

We pooled data from 4 international prospective cohorts (2 multicenter and 2 single center),[19-22] which included non-ill-appearing, previously healthy full-term (≥37 weeks' gestation) infants aged 0 to 28 days evaluated for fever and who underwent diagnostic testing with PECARN rule components (serum procalcitonin, ANC, and urinalysis or urine dipstick). In all studies, blood and urine testing were standard, whereas lumbar punctures were performed at the treating physicians' discretion. All studies were conducted between 2008 and 2024, during an era of stable invasive bacterial infection epidemiology owing to widespread group B *Streptococcus* intrapartum antibiotic prophylaxis and *Haemophilus influenzae* type b and pneumococcal conjugate vaccinations.[3] Details of the 4 international cohorts,[19-22] as well as the PECARN derivation[16] and validation[17] cohorts, appear in **Table 1**.

The McGill University Health Centre research ethics board determined that this study did not require ethics approval. All included studies had prior ethics approvals. As this pooled analysis used only deidentified aggregated data, no additional parental/guardian consent was required. The study followed the 2015 Standards for Reporting of Diagnostic Accuracy (STARD) reporting guideline.[23]

Definitions and Outcome Measures

For all included studies, infant invasive bacterial infection status was ascertained by review of medical records and microbiological culture results and/or telephone follow-up more than 7 days after hospital discharge. Follow-up and outcome ascertainment were carried out per each study protocol. Bacteremia was defined by growth of a single bacterial pathogen in blood culture. Bacterial meningitis was defined by detection of a bacterial pathogen in cerebrospinal fluid culture. Growth of bacteria not commonly considered pathogens (eg, diphtheroids or coagulase-negative *Staphylococcus*) were categorized a priori as contaminants (negative for invasive bacterial infection). As in the PECARN derivation and validation cohorts, UTIs were defined in 1 study by the growth of a single

Table 1. Description of Study Cohorts

Characteristic	US[16]	US[17]	Canada[19]	Spain[20]	Europe[21]	UK/Ireland[22]
Study design	Prospective cohort convenience sample	Prospective cohort convenience sample	Prospective consecutive cohort	Prospective consecutive cohort	Prospective consecutive cohort	Prospective cohort convenience sample
Setting and recruitment period	26 Pediatric emergency departments; 2011-2013	21 Pediatric emergency departments; 2016-2019	Single pediatric emergency department; 2020-2024	Single pediatric emergency department; 2008-2021	11 Pediatric emergency departments (8 Spain, 2 Italy, 1 Switzerland); 2012-2014	30 Pediatric emergency departments; 2022-2023
Study population	Infants ≤60 d (N = 1802)	Infants ≤60 d (N = 1363)	Infants ≤60 d (N = 2024)	Infants ≤90 d (n = 1411 ≤60 d)[a]	Infants ≤90 d (n = 1166 ≤60 d)	Infants ≤90 d (n = 262 ≤60 d)
Inclusion criteria	Rectal temperature ≥38.0 °C at home or at emergency department triage	Rectal temperature ≥38.0 °C at home or at emergency department triage	Rectal temperature ≥38.0 °C at home or at emergency department triage	Rectal temperature ≥38.0 °C at home or at emergency department triage; fever without source	Rectal temperature ≥38.0 °C at home or at emergency department triage; fever without source	Temperature ≥38.0 °C at home or at emergency department triage measured by any means
Exclusion criteria	Critically ill, antibiotics in the preceding 48 h, prematurity (≤36 wk gestational age), preexisting medical conditions, indwelling devices, and soft-tissue infections	Critically ill, antibiotics in the preceding 48 h, prematurity (≤36 wk gestational age), preexisting medical conditions, indwelling devices, and soft-tissue infections	Critically ill, antibiotics in the preceding 7 d, prematurity (≤37 wk gestational age), preexisting medical conditions, indwelling devices, soft-tissue infections, and abnormal Pediatric Assessment Triangle result	Viral signs present and parental refusal to participate	Viral signs present and parental refusal to participate	Refusal to participate
Follow-up	Observation in hospital, medical record review, and telephone follow-up of outpatients without lumbar punctures	Observation in hospital, medical record review, and telephone follow-up of outpatients without lumbar punctures	Observation in hospital, medical record review, and telephone follow-up of all infants ≥30 d after discharge	Observation in hospital, telephone follow-up of all infants ≤30 d after discharge, and review of medical record and public health registry for those not reached by telephone	Observation in hospital, telephone follow-up of all infants ≤30 d after discharge, and review of medical record and public health registry for those not reached by telephone	Observation in hospital and medical record review

[a] Excludes infants enrolled in the Umana et al study.[22]

uropathogen in a catheterized specimen with greater than 50 000 colony-forming units per milliliter (cfu/mL) or greater than 10 000 cfu/mL with a positive urinalysis or urine dipstick result (any leukocyte esterase, nitrites, >5 white blood cells per high-power field in a centrifuged sample, or >10 white blood cells per high-power field in an uncentrifuged sample).[19] Two studies defined UTI as urine culture growth of at least 10 000 cfu/mL with associated leukocyturia[20,21] and 1 study defined it as growth of at least 100 000 cfu/mL of a single organism.[22]

All studies defined fever as a temperature of at least 38.0 °C in the preceding 24 hours; 3 studies required rectal temperature measurement[19-21] and 1 included temperature measurement by any method.[22] The definition of *non-ill-appearing* varied between studies. For this analysis, infants were excluded for critical illness (eg, highest triage acuity level/Canadian Triage Acuity Scale level 1), requiring emergent interventions such as endotracheal intubation or vasopressors, emergency department death,[16,17,19] abnormal appearance, and work of breathing or circulation to skin according to the Pediatric Assessment Triangle[24] tool.[19-21]

Infants were classified as being at low risk for bacteremia and/or bacterial meningitis if they met all 3 updated PECARN prediction rule criteria: a negative urinalysis or urine dipstick result, serum procalcitonin level less than or equal to 0.5 ng/mL, and ANC less than or equal to 4000/mm^3.[16,17]

Statistical Analysis

Lead investigators provided data from the primary studies restricted to infants aged 0 to 28 days. To avoid biasing results by double counting infants, investigators from the Spanish cohort[20] provided data after removing infants included in the European cohort.[21] Patient demographic and clinical characteristics were summarized with frequencies and percentages for dichotomous measures and medians and IQRs for continuous measures.

Diagnostic accuracy of the updated PECARN prediction rule was calculated within each study for sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), with 95% CIs estimated using the exact binomial method.

For the primary analysis, we applied a meta-analytic approach using a random-effects model to produce a pooled estimate of diagnostic accuracy across the 4 international cohorts, accounting for heterogeneity in case mix and invasive bacterial infection prevalence. We used logit transformation with maximum-likelihood estimation of between-study variance. Statistical heterogeneity was assessed using Cochran *Q* and quantified as I^2 with 95% CIs. We also performed a secondary analysis of diagnostic accuracy across all 6 cohorts, pooling the 2 PECARN cohorts with the 4 international cohorts.

We then estimated PPV and NPV across the range of observed and plausible invasive bacterial infection prevalences[3] from 0% to 8% (in 1% increments) using the meta-pooled sensitivity and specificity. To quantify uncertainty, we applied a parametric bootstrap with 10 000 random draws from logit-normal distributions for sensitivity and specificity, parameterized by their meta-pooled estimates and 95% CIs. The resulting distributions were used to derive 95% CIs for PPV and NPV.

The same approach was applied for an analysis of point estimates for bacterial meningitis. However, when estimating 95% CIs for PPV and NPV across a range of meningitis prevalences, all cohorts observed zero false-negative cases (ie, sensitivity of 100%). This boundary condition resulted in meta-pooled sensitivity with a 95% CI spanning 0% to 100%, which prevented use of parametric bootstrapping on the logit scale. To address this, we instead applied a β-posterior simulation based on the aggregated counts of true-positive, false-positive, true-negative, and false-negative results across all 6 cohorts. Using Jeffrey prior (α = .5, β = 0.5), we generated 10 000 random draws for sensitivity and specificity. For each draw, 95% CIs of PPV and NPV were calculated across observed and plausible meningitis prevalences[3] from 0% to 2% (in 0.25% increments) and 95% CIs were defined as the 2.5th and 97.5th percentiles of the simulated distributions. All 95% CIs were 2-sided. Analyses were performed in R version 4.4.1 (R Core Team 2024).

Results

The pooled sample came from 4 studies conducted in pediatric emergency departments in 6 countries (Table 1). Clinical characteristics of infants in each study are shown in **Table 2**. Overall, data were available for 1537 infants aged 0 to 28 days; 69 (4.5%) had invasive bacterial infections, including 58 (3.8%) with bacteremia alone and 11 (0.7%) with bacterial meningitis with or without bacteremia. The prevalence of invasive bacterial infections ranged from 2.5% to 7.3% between the studies. The majority of infants were male (905 [58.9%]), presented within 12 hours of fever (1027 [66.8%]), and were hospitalized (1324 [86.1%]). All infants had blood and urine cultures obtained, and 1080 (70.3%) had cerebrospinal fluid cultures available. No infants without cerebrospinal fluid obtained were later found to have bacterial meningitis.

The **Figure** summarizes the diagnostic accuracy of the PECARN rule. In the 4-cohort primary analysis, 632 infants (41.1%) were classified as being at low risk of invasive bacterial infection. The PECARN rule performed with a sensitivity of 94.2% (95% CI, 85.6%-97.8%), specificity of 41.6% (95% CI, 36.7%-46.7%), PPV of 6.9% (95% CI, 4.8%-9.9%), and NPV of 99.4% (95% CI, 98.1%-99.8%) for invasive bacterial infections. Rule performance was similar in the secondary analysis including the 2 PECARN cohorts (sensitivity, 94.8% [95% CI, 88.1%-97.8%]; specificity, 43.3% [95% CI, 38.7%-48.0%]; PPV, 6.1% [95% CI, 4.5%-8.2%]; NPV, 99.6% [95% CI, 98.7%-99.9%]), with 1079 of 2531 (42.6%) classified as low risk. The pooled sensitivity and specificity were used to estimate PPVs and NPVs for invasive bacterial infection across a range of prevalences (0% to 8%) and are shown in **Table 3.** Confusion matrices of invasive bacterial infection frequencies for all 6 cohorts appear in eTable 1 in Supplement 1.

Four of 69 infants (5.8%) with invasive bacterial infections in the primary analysis, and 5 of 95 (5.3%) in the secondary analysis, were misclassified as low risk. All 5 missed infants with invasive bacterial infections had bacteremia without meningitis, including 1 with blood cultures growing *S aureus* and a urine culture growing *Escherichia coli*, suggesting a possible blood culture contaminant (eTable 2 in Supplement 1).

There were no missed cases of bacterial meningitis among low-risk infants in either the 4-cohort primary analysis (11 cases) or in the 6-cohort secondary analysis (22 cases). Estimated PPVs and NPVs for bacterial meningitis across a range of prevalences (0% to 2%) are shown in Table 3, accounting for the zero observed infants with false-negative results for bacterial meningitis. At the prevalence observed in the primary analysis (0.7%), NPV was estimated to be greater than 99.96% (95% CI, 99.82%-100%) for ruling out bacterial meningitis. Confusion matrices of bacterial meningitis frequencies for all 6 cohorts appear in eTable 3 in Supplement 1.

Discussion

In this analysis of pooled data from 4 international prospective cohort studies, the updated PECARN prediction rule performed with excellent diagnostic accuracy for ruling out invasive bacterial infections among febrile infants 28 days or younger. The updated prediction rule identified 41% of infants as being at low risk of bacteremia and meningitis based on 3 widely available laboratory tests that do not require lumbar punctures. The pooled risk of missing any invasive bacterial infection was approximately 0.6%. Importantly, none of the 11 cases of bacterial meningitis among more than 1500 infants in the primary analysis were misclassified, nor were any of the 22 cases among more than 2500 infants in the secondary analysis.

This is the largest and most geographically diverse study of the updated PECARN prediction rule for invasive bacterial infection among infants 28 days or younger, enabling more precise and generalizable estimates than prior studies. These data are critical to inform risk estimates for shared parent-clinician decision-making and guideline development. Results may be used to support individualized, risk-based treatment that may reduce unnecessary lumbar punctures, hospitalization, and antibiotic exposure while maintaining patient safety, even among the youngest infants. Such an approach would constitute a substantial departure from previous teaching.

Clinicians must balance the risk of missing invasive bacterial infections against the potential harms of invasive testing such as lumbar punctures in infants. In this study's sample, more than 70% of infants had cerebrospinal fluid available, and in 26 US pediatric emergency departments from 2008 to 2013, 93% of 1517 febrile infants aged 0 to 28 days underwent lumbar punctures.[25] Lumbar punctures can be technically challenging and frequently unsuccessful or uninterpretable, lead-

Table 2. Characteristics and Outcomes of Infants Aged 28 Days or Younger From Individual Study Cohorts

	US[16]	US[17]	Canada[19]	Spain[20]	Europe[21]	UK/Ireland[22]
Infants ≤28 d, No.	548	446	571	460	412	94
Age, No. (%), d						
0-7	70 (12.8)	33 (7.4)	75 (13.1)	35 (7.6)	46 (11.2)	3 (3.2)
8-14	128 (23.4)	88 (19.7)	131 (22.9)	104 (22.6)	105 (25.5)	30 (31.9)
15-21	153 (27.9)	145 (32.5)	176 (30.8)	157 (34.1)	134 (32.5)	26 (27.7)
22-28	197 (35.9)	180 (40.4)	189 (33.1)	164 (35.7)	127 (30.8)	35 (37.2)
Male sex, No. (%)	324 (59.1)	263 (59.0)	339 (59.4)	272 (59.1)	243 (59.0)	51 (54.3)
CSF culture available, No. (%)	511 (93.2)	393 (88.1)	466 (81.6)	291 (63.3)	254 (61.6)	69 (73.4)
Fever duration, No. (%), h						
<6			203 (35.6)	261 (56.7)	230 (55.8)	68 (72.3)
6 to <12	378 (69.0)[a]	324 (72.6)[a]	104 (18.2)	71 (15.4)	74 (18.0)	16 (17.0)
12 to <24	132 (24.1)	86 (19.3)	93 (16.3)	49 (10.7)	79 (19.2)	7 (7.4)
≥24	31 (5.7)	29 (6.5)	24 (4.2)	21 (4.6)	9 (2.2)	1 (1.1)
Unknown	7 (1.3)	7 (1.6)	147 (25.7)	58 (12.6)	20 (4.9)	2 (2.1)
CRP, median (IQR), mg/L						
Infants without IBI			2.6 (0.6-9.9)	5.2 (1.1-18.2)	8.0 (3.1-18.3)	5.0 (2.0-14.5)
Infants with IBI			52.0 (47.0-114.9)	28.1 (5.0-147.1)	18.0 (7.0-88.9)	123.0 (66.0-129.0)
ANC, median (IQR), /mm^3						
Infants without IBI	3993 (2546-6265)	3470 (2279-5460)	3170 (2070-4850)	4310 (2795-6700)	4440 (2800-7360)	3920 (2810-5750)
Infants with IBI	8280 (5520-10 039)	8531 (5286-12 096)	7185 (5635-9335)	10 325 (5376-13 500)	6400 (3400-9150)	6410 (3610-7415)
Procalcitonin, median (IQR), ng/mL						
Infants without IBI	0.23 (0.16-0.39)	0.15 (0.10-0.42)	0.17 (0.11-0.33)	0.20 (0.10-0.40)	0.20 (0.11-0.49)	0.16 (0.11-0.32)
Infants with IBI	5.89 (1.17-13.51)	2.24 (1.11-18.60)	7.81 (2.06-19.09)	1.20 (0.20-24.80)	1.28 (0.30-14.59)	12.70 (11.55-22.45)
Hospitalized, No. (%)	532 (97.1)	432 (96.9)	513 (89.8)	353 (76.7)	368 (89.3)	90 (95.8)
Bacterial infection, No. (%)						
UTI alone	57 (10.4)	30 (6.7)	52 (9.1)	67 (14.7)	70 (17.0)	10 (10.6)
Bacteremia alone	4 (0.7)	1 (0.2)	2 (0.4)	9 (2.0)	12 (2.9)	3 (3.2)
Bacterial meningitis alone	3 (0.5)	1 (0.2)	1 (0.2)	2 (0.4)	0	0
Bacteremia and bacterial meningitis	3 (0.5)	3 (0.7)	0	0	5 (1.2)	0
UTI and bacteremia	4 (0.7)	7 (1.6)	10 (1.8)	9 (2.0)	13 (3.1)	0
UTI and bacterial meningitis	0	0	1 (0.2)	1 (0.2)	0	0
UTI, bacteremia, and bacterial meningitis	1 (0.2)	0	0	1 (0.2)	0	0
Any IBI, No. (%)	15 (2.7)	12 (2.7)	14 (2.5)	22 (4.8)	30 (7.3)	3 (3.2)
Aged 0-7 d	1 (1.4)	1 (3.0)	0	2 (5.7)	5 (10.9)	0
Aged 8-14 d	5 (3.9)	3 (3.4)	3 (2.3)	8 (7.7)	10 (9.5)	1 (3.3)
Aged 15-21 d	6 (3.9)	6 (4.1)	4 (2.3)	7 (4.5)	7 (5.2)	1 (3.8)
Aged 22-28 d	3 (1.5)	2 (1.1)	7 (3.7)	5 (3.0)	8 (6.3)	1 (2.9)

Abbreviations: ANC, absolute neutrophil count; CRP, C-reactive protein; CSF, cerebrospinal fluid; IBI, invasive bacterial infection; UTI, urinary tract infection.

[a] Fever duration categorized as <12 hours.

ing to downstream harms including repeat lumbar punctures, prolonged hospitalizations,[26] and adverse events.[13,14] Parents and physicians have fundamental differences in values for diagnostic testing, diagnostic error, and short- and long-term morbidity.[27,28] Moreover, parents have identified lumbar punctures as one of the most stressful aspects in the management of febrile infants.[11]

The current analysis found a sensitivity of 94.2% and NPV of 99.4% for any invasive bacterial infection. For uncommon diseases, NPVs are high due to disease prevalence being low, and their clinical interpretation depends on risk tolerance. A clinician may consider a 1% risk of meningitis sufficient to warrant a lumbar puncture, whereas a parent may have a higher risk threshold.[8] This study estimated NPVs for both invasive bacterial infection and bacterial meningitis across a range of prevalences. For bacterial meningitis, even if the pretest prevalence was 2%, more than twice that observed in this study, the prediction rule NPV would be 99.9% (95% CI, 99.5%-100.0%). The observed PPV (approximately 7%) was similar to the derivation cohort (approximately 5%)[17]; PPVs in this

Figure. Sensitivity, Specificity, and Positive and Negative Predictive Values of the Updated PECARN Prediction Rule for Invasive Bacterial Infections

A Sensitivity

Study	No. of infants: True-positive result	No. of infants: True-positive and false-negative results	Sensitivity (95% CI), %
Derivation/validation			
Kuppermann et al,[16] 2019	15	15	100 (78.2-100)
Kuppermann et al,[17] 2021	11	12	91.7 (61.5-99.8)
Random-effects model		27	96.3 (77.9-99.5)
Heterogeneity: I^2 = 0%			
Primary analysis			
Marom et al,[19] 2025	14	14	100 (76.8-100)
Velasco et al,[20] 2024	20	22	90.9 (70.8-98.9)
Gomez et al,[21] 2016	28	30	93.3 (77.9-99.2)
Umana et al,[22] 2023	3	3	100 (29.2-100)
Random-effects model		69	94.2 (85.6-97.8)
Heterogeneity: I^2 = 0% (95% CI, 0%-84.7%)			
Secondary analysis			
Random-effects model		96	94.8 (88.1-97.8)
Heterogeneity: I^2 = 0% (95% CI, 0%-74.6%)			

B Specificity

Study	No. of infants: True-positive result	No. of infants: True-positive and false-negative results	Specificity (95% CI), %
Derivation/validation			
Kuppermann et al,[16] 2019	218	533	40.9 (36.7-45.2)
Kuppermann et al,[17] 2021	228	434	52.5 (47.7-57.3)
Random-effects model		967	46.6 (38.6-54.7)
Heterogeneity: I^2 = 92.3% (95% CI, 73.7%-97.7%)			
Primary analysis			
Marom et al,[19] 2025	272	557	48.8 (44.6-53.1)
Velasco et al,[20] 2024	176	438	40.2 (35.6-44.9)
Gomez et al,[21] 2016	148	382	38.7 (33.8-43.8)
Umana et al,[22] 2023	32	91	35.2 (25.4-45.9)
Random-effects model		1468	41.6 (36.7-46.7)
Heterogeneity: I^2 = 78.8% (95% CI, 43.3%-92.1%)			
Secondary analysis			
Random-effects model		2435	43.3 (38.7-48.0)
Heterogeneity: I^2 = 83.2% (95% CI, 64.7%-92.0%)			

C Positive predictive value (PPV)

Study	No. of infants: True-positive result	No. of infants: True-positive and false-negative results	PPV (95% CI), %
Derivation/validation			
Kuppermann et al,[16] 2019	15	330	4.5 (2.6-7.4)
Kuppermann et al,[17] 2021	11	217	5.1 (2.6-8.9)
Random-effects model		547	4.8 (3.3-6.9)
Heterogeneity: I^2 = 0%			
Primary analysis			
Marom et al,[19] 2025	14	299	4.7 (2.6-7.7)
Velasco et al,[20] 2024	20	282	7.1 (4.4-10.7)
Gomez et al,[21] 2016	28	262	10.7 (7.2-15.1)
Umana et al,[22] 2023	3	62	4.8 (1.0-13.5)
Random-effects model		905	6.9 (4.8-9.9)
Heterogeneity: I^2 = 61.6% (95% CI, 0%-87.1%)			
Secondary analysis			
Random-effects model		1452	6.1 (4.5-8.2)
Heterogeneity: I^2 = 58.9% (95% CI, 0%-83.3%)			

D Negative predictive value (NPV)

Study	No. of infants: True-positive result	No. of infants: True-positive and false-negative results	NPV (95% CI), %
Derivation/validation			
Kuppermann et al,[16] 2019	218	218	100 (98.3-100)
Kuppermann et al,[17] 2021	228	229	99.6 (97.6-100)
Random-effects model		447	99.8 (98.4-100)
Heterogeneity: I^2 = 0%			
Primary analysis			
Marom et al,[19] 2025	272	272	100 (98.7-100)
Velasco et al,[20] 2024	176	178	98.9 (96.0-99.9)
Gomez et al,[21] 2016	148	150	98.7 (95.3-99.8)
Umana et al,[22] 2023	32	32	100 (89.1-100)
Random-effects model		632	99.4 (98.1-99.8)
Heterogeneity: I^2 = 0% (95% CI, 0%-84.7%)			
Secondary analysis			
Random-effects model		1079	99.6 (98.7-99.9)
Heterogeneity: I^2 = 0% (95% CI, 0%-74.6%)			

The updated Pediatric Emergency Care Applied Research Network (PECARN) prediction rule specifies serum procalcitonin ≤0.5 ng/mL, absolute neutrophil count ≤4000/mm^3, and negative urinalysis or urine dipstick test result.

Table 3. Positive and Negative Predictive Values

Prevalence	PPV (95% CI), %	NPV (95% CI), %
Prevalence of invasive bacterial infections[a]		
0.0	0 (0-0)	100 (100-100)
1.0	1.60 (1.42-1.77)	99.86 (99.64-99.95)
2.0	3.19 (2.82-3.51)	99.72 (99.28-99.89)
3.0	4.75 (4.22-5.23)	99.57 (98.91-99.84)
4.0	6.30 (5.60-6.92)	99.42 (98.54-99.78)
5.0	7.83 (6.97-8.58)	99.27 (98.16-99.72)
6.0	9.33 (8.33-10.22)	99.12 (97.78-99.66)
7.0	10.83 (9.68-11.83)	98.96 (97.40-99.60)
8.0	12.30 (11.02-13.42)	98.80 (97.00-99.54)
Prevalence of bacterial meningitis[b]		
0.0	0 (0-0)	100 (100-100)
0.25	0.44 (0.40-0.46)	99.99 (99.94-100)
0.50	0.87 (0.79-0.92)	99.98 (99.88-100)
0.75	1.31 (1.19-1.37)	99.96 (99.82-100)
1.00	1.74 (1.58-1.82)	99.95 (99.76-100)
1.25	2.17 (1.98-2.28)	99.94 (99.70-100)
1.50	2.60 (2.37-2.73)	99.92 (99.64-100)
1.75	3.02 (2.76-3.17)	99.91 (99.57-100)
2.00	3.45 (3.15-3.62)	99.90 (99.51-100)

Abbreviations: NPV, negative predictive value; PPV, positive predictive value.

[a] Estimated PPVs and NPVs with 95% CIs for invasive bacterial infections across a range of prevalences (0%-8%), with assumed prediction rule sensitivity of 94.2% (95% CI, 85.6%-97.8%) and specificity of 41.6% (95% CI, 36.7%-46.7%).

[b] Estimated PPVs and NPVs with 95% CIs for bacterial meningitis across a range of prevalences (0%-2%), with assumed prediction rule sensitivity of 97.8% (95% CI, 89.4%-100%) and specificity of 44.1% (95% CI, 42.1%-46.1%).

range would be expected for a prediction model derived to rule out an uncommon disease. Infants not classified as being low risk would merit lumbar punctures given the gravity of bacterial meningitis. Specificity is the percentage of infants without invasive bacterial infection correctly classified as being at low risk. The observed specificity was relatively low (approximately 42%), but would identify a large minority of low-risk infants and enable clinicians and parents to avoid lumbar punctures if desired.

Guidelines that historically recommended routine lumbar punctures for febrile infants 28 days or younger were based on small studies using subjective clinical findings and traditional laboratory markers at preexisting cutoffs rather than accurate serum biomarkers at statistically derived thresholds.[7] The updated PECARN rule incorporates newer biomarkers, and infant age did not add predictive value.[16] Infants 28 days and younger are excluded from recent World Health Organization guidelines on meningitis.[29] Many current guidelines, including those from the National Institute for Health and Care Excellence[10] used in the UK and Europe,[30] the American Academy of Pediatrics,[8] and the Sociedad Española de Urgencias de Pediatría[9] all recommend routine lumbar punctures for febrile infants aged 30 days or younger[10] or 21 days or younger.[8,9] In contrast, a Canadian guideline[31] and a US-based network-wide care process model[32] recommend shared decision-making with parents for low-risk infants aged 28 days or younger, although both advise lumbar puncture if initiating antibiotics. For hospitalized low-risk infants under observation, automated continuous blood culture detection can facilitate prompt lumbar puncture if true bacteremia is later identified.

The updated PECARN rule is intended for use among febrile infants who do not appear unwell, because unwell appearance is an important predictor of invasive bacterial infection.[21] However, the assessment of febrile young infants can be challenging,[4] and the studies included in this analysis used varying approaches. Two studies classified infants as *unwell* using the Pediatric Assessment Triangle tool.[20,21] One excluded both critically ill infants and those with abnormal Pediatric Assessment Triangle results.[19] The smallest study[22] (94 infants; 3.7% of total pooled study sample) included unwell infants. However, if this had any effect on the results, it would have lowered the diagnostic accuracy because these infants would be expected to have a higher rate of invasive bacterial infection.

There were additional differences between study cohorts. Two of the studies[20,21] excluded infants with symptoms of viral illnesses. This likely contributed to the range of invasive bacterial infection prevalences observed between the studies. The same 2 studies also used urine dipstick, but these test results have comparable diagnostic accuracy to urinalysis[33,34] and likely had minimal impact on the rule performance in the pooled sample.

Limitations

This study has limitations. First, all primary studies were conducted in pediatric emergency departments, and results may not be generalizable to other settings. However, the prevalence of serious bacterial illness is often lower in general emergency departments than pediatric emergency departments, which would be expected to further improve NPV. Second, generalizability is limited to settings where procalcitonin results are rapidly available.[35] Third, the definitive risk of bacterial meningitis among low-risk infants 28 days or younger would best be established by a single large prospective study. However, this analysis is likely the largest sample of prospective data on this topic available to date. Fourth, although international data were pooled, low- to middle-income countries were not represented.

Fifth, among all 6 cohorts, 1 of 5 infants classified as having a missed invasive bacterial infection had blood cultures suggestive of contaminant growth rather than true bacteremia. However, this would have led to underestimating the NPV and sensitivity reported. Sixth, C-reactive protein was not collected in all studies, and therefore it was not possible to evaluate risk-stratification strategies requiring that biomarker.[21] Seventh, due to zero false-negative results observed for bacterial meningitis, pooled-count β posterior simulation was used to estimate predictive values and 95% CIs. This method treats data as arising from a single combined population and does not explicitly account for between-study heterogeneity. Therefore, the pooled predictive value estimates may not fully reflect variability in diagnostic performance for bacterial meningitis across settings. Eighth, this study did not assess the risk of herpes simplex virus infections, which affect an estimated 0.17% of in-

fants in this age group,[36] because the PECARN rule is meant to identify infants with serious bacterial rather than viral infections.

Conclusions

In this large, international sample of febrile infants 28 days or younger evaluated in emergency departments, the updated PECARN prediction rule performed with high sensitivity and more limited but clinically acceptable specificity for ruling out invasive bacterial infections. Importantly, there were no missed cases of bacterial meningitis among low-risk infants, challenging decades of practice and current guidelines recommending routine lumbar punctures for febrile infants 28 days or younger. These findings provide evidence to help balance risks of missing invasive bacterial infections vs unnecessary testing. Furthermore, these data should inform guidelines and shared decision-making for low-risk febrile infants 28 days or younger.

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REFERENCES

1. Greenhow TL, Hung YY, Pantell RH. Management and outcomes of previously healthy, full-term, febrile infants ages 7 to 90 days. *Pediatrics*. 2016;138(6):e20160270-e20160270. doi:10.1542/peds.2016-0270

2. McCulloh RJ, McDaniel LM, Kerns E, Biondi EA. Prevalence of invasive bacterial infections in well-appearing, febrile infants. *Hosp Pediatr*. 2021;11(9):e184-e188. doi:10.1542/hpeds.2020-002147

3. Biondi EA, Lee B, Ralston SL, et al. Prevalence of bacteremia and bacterial meningitis in febrile neonates and infants in the second month of life: a systematic review and meta-analysis. *JAMA Netw Open*. 2019;2(3):e190874. doi:10.1001/jamanetworkopen.2019.0874

4. 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. doi:10.1542/peds.2017-0695

5. 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. doi:10.1016/S0022-3476(85)80175-X

6. Jaskiewicz JA, McCarthy CA, Richardson AC, et al; Febrile Infant Collaborative Study Group. Febrile infants at low risk for serious bacterial infection: an appraisal of the Rochester criteria and implications for management. *Pediatrics*. 1994;94(3):390-396. doi:10.1542/peds.94.3.390

7. Baraff LJ, Bass JW, Fleisher GR, et al; Agency for Health Care Policy and Research. Practice guideline for the management of infants and children 0 to 36 months of age with fever without source. *Ann Emerg Med*. 1993;22(7):1198-1210. doi:10.1016/S0196-0644(05)80991-6

8. Pantell RH, Roberts KB, Adams WG, et al; SUBCOMMITTEE ON FEBRILE INFANTS. Evaluation and management of well-appearing febrile infants 8 to 60 days old. *Pediatrics*. 2021;148(2):e2021052228. doi:10.1542/peds.2021-052228

9. Sociedad Española de Urgencias de Pediatría. Fiebre sin focalidad en paciente de 0-24 meses de edad previamente sano. Published 2022. Accessed January 1, 2025. https://seup.org/algoritmo-lactante-febril/

10. National Institute for Health and Care Excellence. Fever in under 5s: assessment and initial management. Published 2021. Accessed November 1, 2024. https://www.nice.org.uk/guidance/ng143

11. Sylvestre P, Aronson PL, Yannopoulos A, Poirier C, Gaucher N, Burstein B. Parental preferences and shared decision-making for the management of febrile young infants. *Pediatrics*. 2024;154(4):e2024066420. doi:10.1542/peds.2024-066420

12. Paxton RD, Byington CL. An examination of the unintended consequences of the rule-out sepsis evaluation: a parental perspective. *Clin Pediatr (Phila)*. 2001;40(2):71-77. doi:10.1177/000992280104000202

13. DeAngelis C, Joffe A, Wilson M, Willis E. Iatrogenic risks and financial costs of hospitalizing febrile infants. *AJDC*. 1983;137(12):1146-1149. doi:10.1001/archpedi.1983.02140380006003

14. Aleem S, Greenberg RG. When to include a lumbar puncture in the evaluation for neonatal sepsis. *Neoreviews*. 2019;20(3):e124-e134. doi:10.1542/neo.20-3-e124

15. Dionisopoulos Z, Strumpf E, Anderson G, Guigui A, Burstein B. Cost modelling incorporating procalcitonin for the risk stratification of febrile infants ≤60 days old. *Paediatr Child Health*. 2022;28(2):84-90. doi:10.1093/pch/pxac083

16. 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. doi:10.1001/jamapediatrics.2018.5501

17. Kuppermann N, Dayan PS, Atabaki S, et al. Validation of a prediction rule for serious bacterial infections (SBIs) in febrile infants <60 days in a multicenter network. *Pediatrics*. 2021;147(3_meetingabstract):513-515. doi:10.1542/peds.147.3MA5.513

18. Klassen TP, Dalziel SR, Babl FE, et al. The Pediatric Emergency Research Network (PERN): a decade of global research cooperation in paediatric emergency care. *Emerg Med Australas*. 2021;33(5):900-910. doi:10.1111/1742-6723.13801

19. Marom A, Yannopoulos A, Dionne KA, Burstein B. Procalcitonin and other inflammatory markers in febrile infants aged 60 days or younger. *Pediatrics*. 2025;155(4):e2024069507. doi:10.1542/peds.2024-069507

20. Velasco R, Gomez B, Labiano I, et al. Performance of febrile infant algorithms by duration of fever. *Pediatrics*. 2024;153(5):e2023064342. doi:10.1542/peds.2023-064342

21. 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. doi:10.1542/peds.2015-4381

22. Umana E, Mills C, Norman-Bruce H, et al. Applying clinical decision aids for the assessment and management of febrile infants presenting to emergency care in the UK and Ireland: Febrile Infant Diagnostic Assessment and Outcome (FIDO) Study protocol. *BMJ Open*. 2023;13(9):e075823. doi:10.1136/bmjopen-2023-075823

23. Bossuyt PM, Cohen JF, Gatsonis CA, Korevaar DA; STARD group. STARD 2015: updated reporting guidelines for all diagnostic accuracy studies. *Ann Transl Med*. 2016;4(4):85.

24. Dieckmann RA, Brownstein D, Gausche-Hill M. The pediatric assessment triangle: a novel approach for the rapid evaluation of children. *Pediatr Emerg Care*. 2010;26(4):312-315. doi:10.1097/PEC.0b013e3181d6db37

25. Rogers AJ, Kuppermann N, Anders J, et al; Febrile Infant Working Group of the Pediatric Emergency Care Applied Research Network (PECARN). Practice variation in the evaluation and disposition of febrile infants ≤60 days of age. *J Emerg Med*. 2019;56(6):583-591. doi:10.1016/j.jemermed.2019.03.003

26. Nigrovic LE, Kuppermann N, Neuman MI. Risk factors for traumatic or unsuccessful lumbar punctures in children. *Ann Emerg Med*. 2007;49(6):762-771. doi:10.1016/j.annemergmed.2006.10.018

27. Kramer MS, Etezadi-Amoli J, Ciampi A, et al. Parents' versus physicians' values for clinical outcomes in young febrile children. *Pediatrics*. 1994;93(5):697-702. doi:10.1542/peds.93.5.697

28. Kramer MS, MacLellan AM, Ciampi A, Etezadi-Amoli J, Leduc DG. Parents' vs physicians' utilities (values) for clinical outcomes in potentially bacteremic children. *J Clin Epidemiol*. 1990;43(12):1319-1325. doi:10.1016/0895-4356(90)90098-A

29. World Health Organization. WHO guidelines on meningitis diagnosis, treatment and care. April 10, 2025. Accessed September 15, 2025. https://www.who.int/publications/i/item/9789240108042

30. Tan CD, van der Walle EEPL, Vermont CL, et al; PERFORM consortium (Personalised Risk assessment in febrile children to optimize Real-life Management across the European Union). Guideline adherence in febrile children below 3 months visiting European emergency departments: an observational multicenter study. *Eur J Pediatr*. 2022;181(12):4199-4209. doi:10.1007/s00431-022-04606-5

31. Burstein B, Lirette MP, Beck C, Chauvin-Kimoff L, Chan K. Management of well-appearing febrile young infants aged ≤90 days. *Paediatr Child Health*. 2024;29(1):50-66. doi:10.1093/pch/pxad085

32. Intermountain Health. Risk assessment and management of febrile infants (3-60 days). April 2025. Accessed November 3, 2025. https://intermountainhealthcare.org/ckr-ext/Dcmnt?ncid=525940008

33. Velasco R, Benito H, Mozun R, et al; Group for the Study of Febrile Infant of the RiSEUP-SPERG Network. Using a urine dipstick to identify a positive urine culture in young febrile infants is as effective as in older patients. *Acta Paediatr*. 2015;104(1):e39-e44. doi:10.1111/apa.12789

34. Glissmeyer EW, Korgenski EK, Wilkes J, et al. Dipstick screening for urinary tract infection in febrile infants. *Pediatrics*. 2014;133(5):e1121-e1127. doi:10.1542/peds.2013-3291

35. Marom A, Papenburg J, Burstein B. The critical lens: it is time to start using the right test for febrile young infants. *Paediatr Child Health*. 2024;29(7):419-421. doi:10.1093/pch/pxae069

36. 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. doi:10.1542/peds.2017-1688