Diagnostic Performance of AAP-Recommended Inflammatory Markers in Febrile Infants Aged 60 Days or Younger

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INTRODUCTION

Approximately 2% of febrile infants aged 60 days or younger have invasive bacterial infections (IBIs).[1] To risk stratify well-appearing febrile infants aged 22 to 60 days, the 2021 American Academy of Pediatrics (AAP) clinical practice guideline (CPG) recommends 2 inflammatory marker (IM)–based strategies based on availability of procalcitonin (PCT): (1) PCT and absolute neutrophil count (ANC) or (2) maximum temperature (Tmax), ANC, and C-reactive protein (CRP).[2] However, these combinations of IMs have not been directly compared in a multicenter study. We aimed to validate and compare the performance characteristics of the AAP CPG recommended risk stratification strategies for detecting IBI.

METHODS

We conducted a secondary analysis of the dataset from the Reducing Excessive Variability in Infant Sepsis Evaluation II (REVISE II), a quality improvement initiative that included infants aged 8 to 60 days with temperature of at least 38 °C who were evaluated at one of 106 sites from November 1, 2020, to October 31, 2022.[3] Sites included freestanding (n = 35) and non-freestanding children's hospitals (n = 37) and general hospitals (n = 34). For inclusion in this analysis, infants required a documented temperature and performance of a blood culture.[4] Exclusion criteria mirrored those in the CPG,[2,3] including ill appearance, which was based on emergency department physical examination documentation.[5] Infants were classified as having IBI if an a priori defined pathogen was identified in blood culture (bacteremia) and/or in cerebrospinal fluid culture (bacterial meningitis) with a treatment course for IBI. We classified indeterminate organisms by consensus. Additional details are described in the parent study.[3]

The data collection form listed normal and abnormal IM values per the AAP CPG; participating sites chose the appropriate option. We calculated the sensitivity, specificity, negative predictive value (NPV), and negative likelihood ratio (LR) for identification of IBI, stratified by AAP CPG age group, in 2 combinations: PCT + ANC and Tmax + ANC + CRP. As an exploratory analysis, we also assessed PCT+ANC+CRP. If all IMs in the combination were obtained, or at least 1 IM in the combination was abnormal (regardless of other IMs obtained), infants were included in that group. Infants could be included in more than 1 IM combination. Performance characteristics were calculated using Stata version 18.0 (StataCorp, Inc, College Station, TX). The study was deemed exempt by the AAP institutional review board.

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Dr Yankova contributed to design of the study, performed data management, conducted the data analysis, interpreted the data, drafted the initial manuscript, critically reviewed and revised the manuscript, and approved the final manuscript as submitted; Dr McDaniel contributed to the conceptualization and design of the study, supervised the REVISE II QI Collaborative, contributed to data management, interpreted the data, critically reviewed and revised the manuscript, and approved the final manuscript as submitted; Dr Kerns performed data management for the REVISE II QI Collaborative, interpreted the data, critically reviewed and revised the manuscript, and approved the final manuscript as submitted; Dr Shine interpreted the data, critically reviewed and revised the manuscript, and approved the final manuscript as submitted; Dr Ruiz contributed to drafting the initial manuscript, contributed to interpretation of the data, critically reviewed and revised the manuscript, and approved the final manuscript as submitted; Ms. Caruso contributed to drafting the initial manuscript, contributed to interpretation of the data, critically reviewed and revised the manuscript, and approved the final manuscript as submitted; (Continued)

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RESULTS

Of 13 262 infants who met eligibility criteria, 12 846 (96.9%) had blood cultures and were included, 292 (2.3%) of whom had IBIs. Characteristics of included infants are described in Supplemental Table 1. For identification of IBI in infants aged 22 to 60 days, both risk stratification strategies had high sensitivity (≥95%) and NPV (≥99.8%) and low negative LRs (≤0.12), though the sensitivity varied by age group (Table 1). Specificity was highest for PCT + ANC (63.2% in infants 22–60 days). Most false negatives were for bacteremia (Supplemental Table 2). When limited to infants who had all IMs obtained in the combination, the specificity of both combinations was slightly higher (Supplemental Table 3). Addition of CRP to PCT + ANC reduced specificity (Supplemental Table 4). Two infants with meningitis aged 22 to 60 days would have been misclassified as low risk by either PCT+ANC (1 infant) or Tmax + ANC + CRP (1 infant); both infants were hospitalized (Table 2).

DISCUSSION

This multicenter study validates the use of the AAP-recommended risk stratification strategies for well-appearing febrile infants aged 22 to 60 days and increases the generalizability of prior studies[4,6] by inclusion of infants evaluated at both children's and general hospitals. Both AAP CPG recommended risk stratification strategies have high sensitivity for identifying febrile infants with IBIs. PCT + ANC had the highest specificity, with fewer infants being classified as non–low risk potentially resulting in fewer lumbar punctures and hospitalizations. Although 2 infants aged 22 to 60 days with meningitis would have been misclassified as low risk (1 by PCT+ANC and 1 by Tmax+ANC+CRP), both were hospitalized which may indicate that other factors raised the suspicion of meningitis (eg, clinical appearance). Further investigation is needed to assess outcomes of the rare infants with IBIs misclassified as low risk and to further evaluate the use of these strategies in infants aged 8 to 21 days.

Limitations include those inherent in retrospective data collection, including potential infant misclassification as well appearing. Laboratory results were collected in a binary manner of normal vs abnormal, limiting additional analyses to assess different cutoff values. Additionally, we used ANC of greater than 4000/mm^3 as our cutoff for the Tmax + ANC + CRP group. It is possible that

TABLE 1. Performance Characteristics of AAP CPG–Recommended Risk Stratification Strategies

	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Negative Predictive Value, % (95% CI)	Negative Likelihood Ratio (95% CI)
PCT + ANC[a]				
All ages (N = 10 293; IBI = 262)	95.8 (92.6–97.9)	58.7 (57.7–59.6)	99.8 (99.7–99.9)	0.07 (0.04–0.13)
8–21 d (N = 2079; IBI = 104)	97.1 (91.8–99.4)	40.1 (37.9–42.3)	99.6 (98.9–99.9)	0.07 (0.02–0.22)
22–28 d (N = 1444; IBI = 53)	100.0 (93.3–100.0)	62.3 (59.7–64.9)	100.0 (99.6–100.0)	0.00
29–60 d (N = 6770; IBI = 105)	92.4 (85.5–96.7)	63.4 (62.2–64.5)	99.8 (99.6–99.9)	0.12 (0.06–0.23)
22–60 d (N = 8214; IBI = 158)	94.9 (90.3–97.8)	63.2 (62.1–64.3)	99.8 (99.7–99.9)	0.08 (0.04–0.16)
Tmax + ANC + CRP[b]				
All ages (N = 11 008; IBI = 285)	96.8 (94.1–98.5)	35.3 (34.4–36.2)	99.8 (99.6–99.9)	0.09 (0.05–0.17)
8–21 d (N = 2221; IBI = 110)	99.1 (95.0–100.0)	26.5 (24.6–28.4)	99.8 (99.0–100.0)	0.03 (0.00–0.24)
22–28 d (N = 1538; IBI = 57)	94.7 (85.4–98.9)	41.2 (38.7–43.7)	99.5 (98.6–99.9)	0.13 (0.04–0.39)
29–60 d (N = 7249; IBI = 118)	95.8 (90.4–98.6)	36.7 (35.6–37.8)	99.8 (99.6–99.9)	0.12 (0.05–0.27)
22–60 d (N = 8787; IBI = 175)	95.4 (91.2–98.0)	37.5 (36.4–38.5)	99.8 (99.5–99.9)	0.12 (0.06–0.24)

Abbreviations: ANC, absolute neutrophil count; CRP, C-reactive protein; IBI, invasive bacterial infection; PCT, procalcitonin; Tmax, maximum temperature.
[a] Infant classified as non–low risk if PCT > 0.5 ng/dL and/or ANC > 4000/mm^3.
[b] Infant classified as non–low risk if Tmax ≥ 38.6°C, ANC > 4000/mm^3, and/or CRP ≥ 20 mg/L (≥2 mg/dL).

TABLE 2. Inflammatory Markers and Culture Results of Infants With Bacterial Meningitis Who Would Have Been Misclassified as Low Risk

Age (Days)	Inflammatory Markers[a] (Tmax + ANC + CRP) and (ANC + PCT)				Urinalysis	Urine Culture	Blood Culture	CSF Culture	Disposition
	Tmax[b]	CRP	ANC	PCT					
13	Normal	Normal	Normal	Not obtained	Normal	No growth	GBS	GBS	Admitted
14	Abnormal	Not obtained	Normal	Normal	Normal	*E coli*	No growth	*E coli*	Admitted
34	Normal	Abnormal	Normal	Normal	Abnormal	*E coli*	No growth	*Haemophilus* spp.	Admitted
38	Normal	Normal	Normal	Not obtained	Normal	*Enterococcus* spp.	*E coli*	*E coli*	Admitted

Abbreviations: ANC, absolute neutrophil count; CRP, C-reactive protein; CSF, cerebrospinal fluid; GBS, Group B *Streptococcus*; PCT, procalcitonin; Tmax, maximum temperature.
[a] Inflammatory markers considered abnormal at the following values: Tmax ≥ 38.6°C; CRP ≥ 20 mg/L (≥2 mg/dL); ANC > 4,000/mm^3; and PCT > 0.5 ng/dL.
[b] Tmax defined as the highest temperature documented in the emergency department, at home, or in an outpatient clinic within 24 hours prior to presentation.

sensitivity would be lower and specificity higher if 5200/mm^3 was used, as is recommended when PCT is unavailable.[5]

In conclusion, the AAP-recommended risk stratification strategies for febrile infants are excellent at ruling out IBI. Clinicians can have confidence in not obtaining lumbar punctures in low-risk infants. With higher specificity, use of PCT + ANC can potentially result in less resource utilization and harm.

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ABBREVIATIONS

AAP: American Academy of Pediatrics
ANC: absolute neutrophil count
CPG: clinical Practice Guideline
CRP: C-reactive protein
IBI: invasive bacterial infection
IM: inflammatory marker
LR: likelihood ratio
NPV: negative predictive value
PCT: procalcitonin
REVISE II: Reducing Excessive Variability in Infant Sepsis Evaluation II
Tmax: maximum temperature

Dr Aronson conceptualized and designed the study, supervised the REVISE II QI Collaborative, contributed to data management, interpreted the data, critically reviewed and revised the manuscript, and approved the final manuscript as submitted. All authors agree to be accountable for all aspects of the work.

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