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Management of the Febrile Young Infant: Update for the 21st Century

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Abstract

Infants ≤90 days of age with fever are frequently evaluated in the pediatric emergency department. Physical exam findings and individual laboratory investigations are not reliable to differentiate benign viral infections from serious bacterial infections in febrile infants. Clinical prediction models were developed over 25 years ago and have high sensitivity but relatively low specificity to identify bacterial infections in febrile infants. Newer laboratory investigations such as C-reactive protein (CRP) and procalcitonin (PCT) have favorable test characteristics compared to traditional laboratory studies such as a white blood cell count. These novel biomarkers have not gained widespread acceptance due to lack of robust prospectively collected data, varying thresholds to define positivity, and differing inclusion criteria across studies. However, CRP and PCT, when combined with other patient characteristics in the Step-by-Step approach have a high sensitivity for detection of serious bacterial infection. RNA biosignatures are a novel biomarker under investigation for detection of bacterial infection in febrile infants.

Keywords

febrile young infant; c-reactive protein; procalcitonin; clinical prediction model; serious bacterial infection

Background

Fever accounts for 10–20% of all pediatric emergency department visits.[1,2] Although viruses account for the majority of infections, up to 8–12.5% of all febrile infants ≤90 days of age will have a serious bacterial infection (SBI).[3] Among these infants, urinary tract infections predominate, however, 1–2% will have an invasive bacterial infection (IBI), i.e. bacteremia and bacterial meningitis. Delayed diagnosis of IBIs is associated with increased morbidity and mortality, although there is a paucity of outcome data for these infections in young infants.[4–7] It is difficult to differentiate benign viral infections from the more serious IBIs in

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febrile infants ≤90 days of age based on symptoms or individual laboratory tests alone.[8,9] Therefore clinical prediction models were developed in the 1980's and early 1990's to help guide the practitioner's medical decision-making regarding the diagnostic workup and therapeutic interventions.[10–12] These models include historical features, physical exam findings, and laboratory data such as white blood cell (WBC) count, absolute band count or band to neutrophil ratio, urinalysis (UA), and cerebrospinal fluid WBC count to risk stratify febrile infants into high-risk and low-risk groups for SBI (Table 1). While there has been ongoing work to examine the reproducibility and validity of these risk stratification algorithms, no single approach is uniformly used.[8]

In the past two decades, incorporation of newer vaccines into the routine immunization schedule for infants in the United States has changed the epidemiology of bacterial infections in infants.[13,14] However, the impact of these vaccines on the diagnostic test performance of the clinical prediction models remain largely unstudied. We must also evaluate new laboratory tools that can be incorporated into these prediction models to improve their diagnostic performance, or that may better serve as stand-alone biomarkers for detection of SBI and IBI.

Epidemiology of fever without a source in the vaccine era

The rate of IBI in previously healthy older infants and children has decreased dramatically since the implementation of routine vaccination for haemophilus influenza type B (HiB) and pneumococcus.[15,16] Among young infants, an inverse relationship between infant age and SBI prevalence has been demonstrated with a decline in SBI from 21.6% in the first week of life to 12.1% in the fourth week of life,[17] with a lower prevalence around 8% after 1 month of age.[18] The prevalence of IBI also has an inverse relationship with age in the vaccine era.[18] Watt et al. reported an IBI prevalence of 5.1% in infants 0–30 day olds, 3.9% in 31–60 day olds, and 0.9% in 61–90 day olds.[13] Additionally, the overall prevalence of bacterial meningitis is low in the ≤90 day old population, at 0.6–0.9%.[4,13]

HiB and pneumococcus were causes of IBI prior to routine vaccination.[11–14,16,19] While HiB is exceedingly rare in the vaccine era, the incidence of pneumococcus has declined due to herd immunity.[20] Now SBIs and IBIs are most commonly caused by *Escherichia coli*, Group B streptococcus (GBS), *Staphylococcus aureus*, Klebsiella sp., and, uncommonly, enterococcus.[4,14,21,22] GBS prevalence has had a recent decline in infants ≤90 days old, likely secondary to routine perinatal prophylaxis.[23,24] Additionally, *Listeria monocytogenes* is now rarely identified as a pathogen in febrile infants with IBI.[21,22,25,26] Therefore, traditionally utilized empiric antibiotic coverage, in particular ampicillin, should be re-assessed in the era of vaccines and perinatal prophylaxis. With a changing epidemiology of SBI/IBI, we must also re-evaluate the diagnostic accuracy of our clinical prediction models.

Do previously developed clinical prediction models have the same predictive accuracy in the vaccine era?

Few studies have evaluated the diagnostic accuracy of previously established clinical prediction models in the post-HiB and post-pneumococcal vaccine era. One study conducted

in the Bronx, NY, performed a reappraisal of the Rochester and Philadelphia criteria. Both criteria demonstrated high sensitivity of 97% (95% confidence interval (CI): 89–100%) for identification of SBI when these previously established clinical prediction models were applied to febrile infants ≤56 days old.[8,27] However, the test characteristics for the identification of IBI were unclear due to the single center design of this study and relatively small numbers of IBI.[8,27]

Critically, these prediction models are primarily designed to have high sensitivity for identification of bacterial infections that have high potential for morbidity and mortality. Therefore, in optimizing sensitivity at the expense of specificity, the prediction models identify most true positive cases of SBI. However, many infants classified as high-risk will not have an SBI. The aforementioned study from the Bronx reported that both the Rochester and Philadelphia criteria had low specificity of 37% (95% CI: 30–44%) with the application of these previously established clinical prediction models in the vaccine era.[8,27]

Are there new diagnostic tools that can be incorporated into clinical prediction models to improve their diagnostic performance?

Novel diagnostic tests with improved sensitivity and specificity for the detection of SBI and IBI have the potential to reduce unnecessary lumbar puncture, hospitalization, antibiotic exposure, and iatrogenic harm among febrile infants. While many studies have evaluated the diagnostic accuracy of C-reactive protein (CRP) and procalcitonin (PCT) for the identification of SBI or IBI in children less than 36 months of age, the following sections will focus on studies that specifically evaluated diagnostic accuracy of CRP, PCT, and RNA biosignatures in infants≤90 days old with fever without source (FWS).

C-Reactive Protein

CRP is an acute phase reactant synthesized in the liver within 4–6 hours after tissue injury and that peaks at 36 hours.[28] Many studies have demonstrated superior, albeit variable, test characteristics of CRP compared to WBC for the detection of bacterial infection (Tables 2 and 3).[29–34] The heterogeneity in the study designs (retrospective vs. prospective), case definitions, prevalence of SBI and IBI, sample sizes, and lack of uniformity of cutoff values has made the interpretation of these findings challenging. However, CRP has consistently demonstrated higher specificity than WBC count for SBI and IBI, often at the expense of a lower sensitivity.[29–34] While Milcent et al. reported the highest sensitivity of 77% (95% CI: 66–86) for detection of SBI with a cutoff value of 20 mg/L,[33] this sensitivity is still low for detection of bacterial infection.

While the specificity of CRP is likely superior to WBC count in detecting SBI/IBI, the summative data from these studies suggests that CRP is likely not sufficient to serve as a stand-alone test in detecting SBI/IBI in infants ≤90 days of age with FWS. However, making formal recommendations based on these studies is difficult due to variability in SBI definition, lack of raw data on IBI, differing inclusion criteria between studies, differing clinical settings between studies, and varying results (Tables 2 and 3).

Procalcitonin

PCT is the protein prohormone of calcitonin which is released by the liver and mononuclear cells 4 hours after tissue injury, and that peaks 6 hours after tissue injury with a sustained peak level for 8–24 hours.[35] Previous studies reported PCT as being more sensitive and specific for SBI and IBI than WBC, although a majority of patients in these studies were older infants and children (up to 36 months of age).[36,37]

Overall, in studies limited to febrile infants ≤90 days old with FWS, PCT has demonstrated favorable test characteristics compared to WBC and CRP for detection of both SBI and IBI (Tables 2 and 3).[29–31,33,34,38,39] However, in addition to the heterogeneity of the design of these studies and the prevalence of SBI and IBI, the biggest challenge to interpretation is the varying performance characteristics of PCT based on the threshold used to define positivity. Maniaci et al. demonstrated the highest sensitivity of PCT in detection of SBI at a level of 0.13 ng/mL. However, the specificity at this level was low (Table 2).[38] The most consistent cutoff value used has been 0.5 ng/mL, which has high specificity but inadequate sensitivity for the detection of SBI. In the largest prospective study to date, Milcent et al. reported a sensitivity of 60% (95% CI: 48–72) for SBI and 85% (95% CI: 62–97) for IBI at a cutoff value of 0.5 ng/mL, with a specificity of 85% for both SBI and IBI. A lower threshold value to 0.3 ng/mL improved the sensitivity with only marginal reduction in specificity (Tables 2 and 3). However, the small number of IBIs in this study resulted in wide confidence limits around the point estimate for sensitivity.[33]

In aggregate, these studies suggest that PCT is superior to CRP and WBC for the detection of SBI and IBI, but the exact threshold value to maximize the combination of sensitivity and specificity remains uncertain (Tables 2 and 3).

New prediction models that incorporate CRP and PCT

These studies demonstrate that a single laboratory test alone cannot reliably identify or exclude the diagnosis of SBI or IBI among febrile infants ≤90 days of age. However, recent investigations have incorporated the use of these newer diagnostic tests into clinical algorithms to optimize the identification of SBI and IBI among febrile infants in the vaccine era. The “Lab score” assigns points based upon results of the results of urine dipstick, PCT, and CRP. A score of ≥3 points defines a population at higher risk of bacterial infection (Table 4).[40] In the original validation of the score, a sensitivity of 94% (95% CI: 74%–99%) and specificity of 78% (95% CI: 64%–87%) was observed for the detection of SBI in children ≤36 months old.[40] However, external validation studies focusing on well-appearing infants <3 months of age using this prediction model have reported high specificity but low sensitivity for detection of SBI and IBI (Tables 2 and 3).[41,42] Most recently, Gomez et al. validated the “Step-by-Step” approach for risk stratification of infants ≤90 days old with FWS.[47] This approach uses age, clinical appearance, urine dipstick, PCT, CRP, and absolute neutrophil count (ANC) in a stepwise fashion to determine which infants are high-, intermediate-, and low-risk for SBI and IBI (Table 4). Gomez et al. prospectively compared the “Step-by-Step” approach, “Lab Score” and Rochester criteria in infants ≤90 days old with FWS, and reported that the “Step-by-Step” approach had the highest sensitivity for detection of IBI (92.0% [95% CI: 84.3%–96.0%]), though similar to the low-risk criteria, the

specificity was low (Table 3). In comparison, “Lab score” was very specific but its low sensitivity limits its use as a screening test for IBI (Table 3).[42]

RNA biosignatures

This novel diagnostic tool has been gaining interest as a more precise method to differentiate viral infections from bacterial infections by analyzing the transcriptional biosignatures of RNA in host leukocytes in response to a clinically undifferentiated infection (Figure 1).[43] Initial research in hospitalized children (14 days–16 years old) reported that RNA biosignatures could differentiate bacterial infections from viral infections with up to 95% accuracy in the inpatient setting.[44] Mahajan et al. demonstrated that RNA biosignatures could also distinguish bacterial from viral infections in infants ≤60 days of age with a sensitivity of 87% (95% CI: 73%–95%) and a specificity of 89% (95% CI: 81%–93%).[45] While these initial results are promising, the wide confidence limits related to the small sample size and lack of a rapid turn-around time may limit their widespread use. Future translational research should seek to validate the initial studies in a large enough sample to reliably evaluate the performance of this testing in a generalizable fashion. Additionally, the logistics of sample collection, storage, and processing time warrants further investigation prior to widespread clinical implementation.

Conclusions

While the epidemiology and prevalence of SBI and IBI in infants ≤90 days of age has changed in the vaccine era, previously developed clinical prediction models have retained their high sensitivity for detection of bacterial infection though specificity remains low. Advances in technology have allowed novel laboratory biomarkers to be incorporated into clinical prediction models to improve their diagnostic performance. While neither CRP nor PCT have adequate diagnostic test characteristics to be used as a stand-alone test to identify bacterial infection in febrile infants, they offer promise when combined with other clinical and laboratory findings in the “Step-by-Step” approach. Large prospective studies are needed to evaluate the performance, cost, feasibility, and outcomes of using these newer approaches in the management of the febrile infant. Additionally, future studies that evaluate the use of RNA biosignatures for the identification of bacterial infections among febrile infants are warranted.

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Abbreviations

ANC	absolute neutrophil count
CBC	complete blood count

CI	confidence interval
CRP	C-reactive protein
CSF	cerebrospinal fluid
FWS	fever without source
IBI	invasive bacterial infection
PCT	procalcitonin
SBI	serious bacterial infection
UA	urinalysis
WBC	white blood cell

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Target audience

This continuing medical education activity is intended for physicians, physician assistants, and nurse practitioners who care for pediatric patients in the outpatient, emergency department, or inpatient settings.

Learning objectives

- Summarize the changing epidemiology of serious bacterial infections and invasive bacterial infections in febrile infants ≤90 days of age in the vaccine era.
- Discuss the strengths and weaknesses of previously established clinical prediction models for febrile infants in the vaccine era.
- Describe the current literature on novel biomarkers including C-reactive protein, procalcitonin, and RNA biosignatures for identification of bacterial infection in febrile infants.

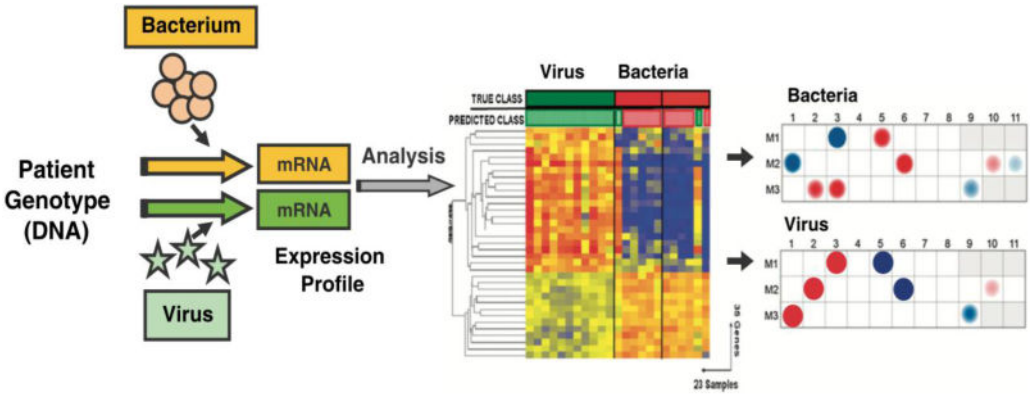

Figure 1.

Micro-array showing the difference in transcriptional profiles of host leukocytes in response to different pathogens. Heat maps (middle diagram) show over-expressed genes labeled in red and under-expressed genes labeled in blue. Alternatively, modular analysis (right diagram) shows genes with similar function being grouped together and are labeled red for over-expressed or blue for under-expressed. From Mahajan et al, Pediatr Emerg Care. 2015.[43]

Table 1

Low-risk definition in classic clinical prediction models. Adapted from Hui et al.[8]

Model	Rochester Criteria	Philadelphia Criteria	Boston Criteria
Age (d)	≤60	29–56	28–89
Fever definition (°C)	≥38.0	≥38.2[1]	≥38.0
History	Gestation ≥37w0d No perinatal antibiotics Previously healthy Birth hospitalization not longer than mother	N/A	No immunizations 48 hours prior to arrival No antibiotics 48 hours prior to arrival No dehydration Normal vital signs
Physical Exam	Well-appearing No AOM, SSTI, osteomyelitis or septic arthritis	Well-appearing Unremarkable physical exam	Well-appearing No AOM, SSTI, osteomyelitis or septic arthritis
Labs	WBC >5,000 and <15,000/mm^3 Absolute band count <1500 UA ≤10 WBC/hpf Stool ≤5 WBC/hpf if diarrhea/ bloody stools	WBC <15,000/mm^3 I:T ratio < 0.2 UA <10 WBC/hpf Negative urine gram stain CSF WBC <8/mm^3 Negative CSF gram stain Stool with minimal WBC and 0 RBC/hpf if diarrhea/bloody stools Negative CXR if respiratory symptoms	WBC <20,000/mm^3 UA <10 WBC/hpf CSF WBC <10/mm^3 Negative CXR if respiratory symptoms

[1] ≥38.0 used in subsequent studies and in clinical practice

Abbreviations: AOM, acute otitis media; SSTI, skin and soft tissue infection; WBC, white blood cell; UA, urinalysis; I:T, immature(bands):total neutrophil; CXR, chest X-Ray

Table 2

Comparison of studies evaluating the characteristics of newer diagnostic tools for the detection of serious bacterial infection in febrile infants ≤90 days of age

Test	Study design	Participants ≤90 days old (n)	Prevalence of SBI (%)	Cut off value	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR− (95% CI)
CRP								
Olaciregui[29]	Retrospective	347	24%	30mg/L	59% (48,70)	89% (85,93)	5.4 (NR)	0.46 (NR)
Stein[30]	Prospective	112	17%	30mg/L	45% (NR)	82% (NR)	NR	NR
Gomez[31]	Retrospective	1112	26%	20mg/L	NR	NR	2.2 (1.2,4.0)	0.85 (0.70,1.04)
Bilavsky[32]	Prospective	892	11%	20mg/L	56% (46,65)	82% (79,85)	3.1 (2.5,3.9)	0.5 (0.4,0.7)
Milcent[33]	Prospective	2047	7%	20mg/L	77% (66,86)	75% (72,77)	3.1 (2.6,3.6)	0.3 (0.2,0.5)
PCT								
Maniaci[38]	Prospective	234	13%	0.13ng/mL	97% (81,100)	30% (24,38)	NR	0.11 (0.02,0.76)
Stein[30]	Prospective	112	17%	0.2ng/mL	55% (NR)	75% (NR)	NR	NR
Woelker[39]	Prospective	155[1]	8%	0.26ng/mL	92% (62,100)	64% (55,72)	NR	0.01 (0.001, 0.09)
Milcent[33]	Prospective	2047	7%	0.3ng/mL	74% (62,84)	78% (75,80)	3.3 (2.8,3.9)	0.3 (0.2,0.5)
Olaciregui[29]	Retrospective	347	24%	0.5ng/mL	63% (52,74)	87% (83,91)	4.8 (NR)	0.43 (NR)
Gomez[31]	Retrospective	1112	26%	0.5ng/mL	NR	NR	3.9 (2.1,7.3)	0.80 (0.66,0.97)
Lab score								
Bressan[41]	Retrospective	1012	28%	≥3	52% (46,58)	95% (93,96)	10.2 (9.5,10.9)	0.5 (0.5,0.5)
Step-by-Step								
Gomez[42]	Prospective	2185	23%	Positive screen	98% (96,99)	58% (56,61)	NR	NR

[1] Included infants 2–60 days of age

Abbreviations: SBI, serious bacterial infection; CI, confidence interval; LR, likelihood ratio; CRP, C-reactive protein; PCT, procalcitonin; NR, not reported

Table 3

Comparison of studies evaluating the characteristics of newer diagnostic tools for the detection of invasive bacterial infection in febrile infants ≤90 days of age

Test	Study design	Participants ≤90 days old (n)	Prevalence of IBI (%)	Cut off value	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR− (95% CI)
CRP								
Diaz[34]	Retrospective	318	3%	30mg/L	18% (5,46)	84% (79,88)	1.24 (0.27,3.36)	0.97 (0.77,1.3)
Gomez[31]	Retrospective	1112	2%	20mg/L	NR	NR	2.7 (2.1,3.7)	0.41 (0.22,0.76)
Milcent[33]	Prospective	2047	1%	20mg/L	75% (51,91)	75% (72,77)	3.0 (2.3,3.9)	0.3 (0.2,0.7)
PCT								
Diaz[34]	Retrospective	318	3%	0.5ng/mL	73% (43,90)	86% (82,89)	5.14 (3.3,8.7)	0.32 (0.12,0.84)
Gomez[31]	Retrospective	1112	2%	0.5ng/mL	NR	NR	5.7 (4.4,7.4)	0.25 (0.12,0.55)
Milcent[33]	Prospective	2047	1%	0.3ng/mL	90% (68,99)	78% (75,80)	4.0 (3.3,4.8)	0.1 (0.03,0.4)
Lab Score								
Gomez[42]	Prospective	2185	4%	≥3	60% (49,69)	84% (82,86)	3.74 (3.07,4.56)	0.48 (0.37,0.62)
Bressan[41]	Retrospective	1012	2%	≥3	70% (49,84)	84% (81,86)	4.3 (4.0,4.6)	0.4 (0.3,0.5)
Step-by-Step								
Gomez[42]	Prospective	2185	4%	Positive screen	92% (84,96)	47% (45,49)	1.73 (1.61,1.85)	0.17 (0.08,0.35)

Abbreviations: IBI, invasive bacterial infection; CI, confidence interval; LR, likelihood ratio; CRP, C-reactive protein; PCT, procalcitonin; NR, not reported

Table 4

Components of the Lab Score and Step-by-Step approach to define a high-risk population of febrile infants ≤90 days of age

	Lab Score	Step-by-Step Approach
Age Cutoff	N/A	≤21 days
Clinical Appearance	N/A	Ill-appearing
Laboratory	+nitrite or leukocyte esterase (1 point) PCT ≥0.5 ng/mL (2 points) PCT ≥2.0 ng/mL (4 points) CRP ≥ 40 mg/L (2 points) CRP ≥100 mg/L (4 points)	+leukocyturia PCT ≥0.5 ng/mL CRP >20mg/L ANC >10,000/mm^3
Low-risk	Score < 3 points	None of the above present

Abbreviations: PCT, procalcitonin; CRP, C-reactive protein; ANC, absolute neutrophil count