Clinical Progress Note: Procalcitonin in the Identification of Invasive Bacterial Infections in Febrile Young Infants

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Febrile infants 60 days of age or younger pose a significant diagnostic challenge for clinicians. Most of these infants are well appearing and do not have localizing signs or symptoms of infection, yet they may have serious bacterial infections (SBI) such as urinary tract infection (UTI), bacteremia, and meningitis. While urinalysis is highly sensitive for predicting UTI,[1] older clinical decision rules and biomarkers such as white blood cell (WBC) count, absolute neutrophil count (ANC), and C-reactive protein (CRP) lack both appropriate sensitivity and specificity for identifying bacteremia and meningitis (ie, invasive bacterial infection [IBI]),[2,3] which affect approximately 2.4% and 0.9% of febrile infants during the first 2 months of life, respectively.[4] The lack of accurate diagnostic markers can drive overuse of laboratory testing, antibiotics, and hospitalization despite the low rates of these infections. As a result, procalcitonin (PCT) has generated interest because of its potential to serve as a more accurate biomarker for bacterial infections. This review summarizes recent literature on the diagnostic utility of PCT in the identification of IBI in febrile young infants 60 days or younger.

MECHANISM OF PROCALCITONIN

Procalcitonin is undetectable in noninflammatory states but can be detected in the blood within 4 to 6 hours after initial bacterial infection.[5] Its production is stimulated throughout various tissues of the body by cytokines such as interleukin-6 and tumor necrosis factor, which are produced in response to bacterial infections. Interferon-γ, which is produced in response to viral infections, attenuates PCT production. While these characteristics suggest promise for PCT as a more specific screening test for underlying bacterial infection, there are caveats. PCT levels are physiologically elevated in the first 48 hours of life and vary with gestational age, factors that should be considered when interpreting results.[6] Additionally, PCT levels can rise in other inflammatory states such as autoimmune conditions and certain malignancies,[5] though these states are unlikely to confound the evaluation of febrile young infants.

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DIAGNOSTIC ACCURACY OF PROCALCITONIN

Because of PCT's potential to be more specific than other commonly used biomarkers, multiple studies have evaluated its performance characteristics in febrile young infants. Gomez et al retrospectively evaluated 1,112 well-appearing infants younger than 3 months with fever without a source in seven European emergency departments (EDs).[7] Overall, 23 infants (2.1%) had IBI (1 with meningitis). A PCT level of 0.5 ng/mL or greater was the only independent risk factor for IBI (adjusted odds ratio, 21.69; 95% CI, 7.93-59.28). Four infants with IBI had a PCT level less than 0.5 ng/mL, and none of these four had meningitis. PCT was superior to CRP, ANC, and WBC in detecting IBI (area under the curve [AUC], 0.825; 95% CI, 0.698-0.952). PCT was the also the best marker for identifying IBI among 451 infants with a normal urine dipstick and fever detected ≤6 hours before presentation (AUC, 0.819; 95% CI, 0.551-1.087).

In the largest prospective study to date evaluating the diagnostic accuracy of PCT in febrile young infants, Milcent et al studied 2,047 previously healthy infants aged 7-91 days admitted for fever from 15 French EDs.[8] In total, 21 (1%) had an IBI (8 with meningitis). PCT performed better than CRP, ANC, and WBC for the detection of IBI with an AUC of 0.91 (95% CI, 0.83-0.99). In a multivariable model, a PCT level of 0.3 ng/mL or greater was the only independent risk factor for IBI with an adjusted odds ratio of 40.3 (95% CI, 5.0-332). Only one infant with IBI had a PCT level less than 0.3 ng/mL. This infant was 83 days old, had 4 hours of fever, and became afebrile spontaneously prior to the blood culture revealing Streptococcus pneumoniae. PCT also performed better than CRP in the detection of IBI in infants 7-30 days of age and those with fever for less than 6 hours, though both subgroups had small numbers of infants with IBI. The authors determined that a PCT level of 0.3 ng/mL was the optimal cutoff for ruling out IBI; this cutoff had a sensitivity of 90% and negative likelihood ratio (LR) of 0.1 (Table). In contrast, the more commonly studied PCT cutoff of 0.5 ng/mL increased the negative LR to 0.2. The authors suggested that PCT, when used in the context of history, exam, and tests such as urinalysis, could identify infants at low risk of IBI.

Gomez et al conducted a prospective, single-center study of well-appearing infants with fever without a source and negative urine dipsticks.[9] They identified IBI in 9 of 196 infants (4.5%) 21 days or younger and 13 of 1,331 infants (1.0%) 22-90 days old. PCT was superior to CRP and ANC for IBI detection in both age groups. However, in infants 21 days or younger, both the positive and negative LRs for PCT levels of 0.5 ng/mL

TABLE. Performance of Procalcitonin (PCT) and Clinical Decision Rules in the Detection of Invasive Bacterial Infection in Febrile Young Infants

	Sensitivity (95% CI)	Specificity (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)
Procalcitonin alone (PCT cutoff [ng/mL])				
Gomez[7] (≥0.5)	NR	NR	5.68 (4.37-7.38)	0.25 (0.12-0.55)
Milcent[8] (≥0.3)	90 (68-99)	78 (75-80)	4.0 (3.3-4.8)	0.1 (0.03-0.4)
Milcent[8] (≥0.5)	85 (62-97)	85 (82-87)	5.6 (4.4-7.0)	0.2 (0.06-0.5)
Gomez[9] – Infants ≤21 days old (≥0.5)	44 (19-73)	84 (78-89)	2.77 (1.24-6.17)	0.66 (0.36-1.21)
Gomez[9] – Infants 22-90 days old (≥0.5)	54 (29-77)	95 (93-96)	9.72 (5.61-16.86)	0.49 (0.27-0.88)
Select risk stratification rules with PCT				
Step-by-Step[10,a]	92 (84-96)	47 (45-49)	1.73 (1.61-1.85)	0.17 (0.08-0.4)
PECARN[11,b]	97 (83-99)	62 (59-64)	2.51 (2.30-2.75)	0.05 (0.008-0.372)
Select risk stratification rules without PCT				
Rochester criteria – Gomez[10,c]	82 (72-88)	45 (42-47)	1.47 (1.32-1.64)	0.41 (0.26-0.65)
Rochester criteria – Aronson[12,c]	82 (74-88)	60 (54-66)	2.0 (1.7-2.4)	0.3 (0.2-0.4)
Modified Philadelphia criteria[12,d]	92 (86-96)	35 (29-41)	1.4 (1.3-1.6)	0.2 (0.1-0.4)

[a]The Step-by-Step approach uses a PCT cutoff of ≥0.5 ng/mL, in addition to the following characteristics to identify patients who are not low risk: ill appearance, age ≤21 days, positive urine dipstick, CRP >20 mg/L, and ANC >10,000/μL.

[b]These data from Kupperman et al represent performance of the PECARN rule with the outcome of IBI when using a positive urinalysis and nonrounded cutoffs (PCT >1.71 ng/mL and ANC >4,090/μL) to identify patients who are not low risk.

[c]Rochester low-risk criteria: Previously healthy, no skin or soft tissue infection, normal urinalysis, peripheral WBC of ≥5,000 and ≤15,000/mm3, and absolute band count of ≤1,500 per μL. Infants who do not fulfill all of these criteria are considered to not be low risk.

[d]Modified Philadelphia low-risk criteria: Age >28 days, previously healthy, no skin or soft tissue infection, normal urinalysis, peripheral WBC of ≥5,000 and ≤15,000/mm3, and bands-to-total neutrophil ratio of <0.2. Infants who do not fulfill all of these criteria are considered to not be low risk.

Abbreviations: IBI, invasive bacterial infection; LR, likelihood ratio; N/A, not applicable; NR, not reported; PECARN, Pediatric Emergency Care Applied Research Network; PCT, procalcitonin.

or greater were poor (Table). Differences in results from the prior two studies[7,8] may be related to smaller sample size and differences in patient population because this study included infants younger than 7 days and a higher proportion of infants presenting within 6 hours of fever.

CLINICAL DECISION RULES

PCT has also been incorporated into clinical decision rules for febrile young infants, primarily to identify those at low risk of either IBI or SBI. The Step-by-Step approach[10] classified well-appearing febrile infants 90 days or younger as having a high risk of IBI if they were ill appearing, younger than 21 days old, had a positive urine dipstick or a PCT level of 0.5 ng/mL or greater, and classified them as intermediate risk if they had a CRP level greater than 20 mg/L or ANC level greater than 10,000/μL. The remaining infants were classified as low risk and could be managed as outpatients without lumbar puncture or empiric antibiotics. Of note, derivation of this rule excluded patients with respiratory signs or symptoms. In a prospective validation study with 2,185 infants from 11 European EDs, 87 (4.0%) had an IBI (10 with bacterial meningitis). Sequentially identifying patients as high risk using general appearance, age, and urine dipstick alone identified 80% of infants with IBI and 90% of those with bacterial meningitis. The remaining case of meningitis

would have been detected by an elevated PCT. A total of 7 of 991 infants (0.7%) classified as low risk had an IBI and none had meningitis. Six of these infants had a fever duration of less than 2 hours, which would not be enough time for PCT to rise. The Step-by-Step approach, with a sensitivity of 92% and negative LR of 0.17, performed well in the ability to rule out IBI.

A clinical prediction rule developed by the Pediatric Emergency Care Applied Research Network (PECARN) found that urinalysis, ANC, and PCT performed well in identifying infants 60 days or younger at low risk for SBI and IBI.[11] This prospective observational study of 1,821 infants 60 days or younger in 26 US EDs found 170 (9.3%) with SBI and 30 (1.6%) with IBI; 10 had bacterial meningitis. Only one patient with IBI was classified as low risk, a 30-day-old whose blood culture grew *Enterobacter cloacae* and who had a negative repeat blood culture prior to antibiotic treatment. Together, a negative urinalysis, ANC of 4,090/μL or less, and PCT level of 1.71 ng/mL or less were excellent in predicting infants at low risk for both SBI and IBI, with a sensitivity of 97% and negative LR of 0.05 for the outcome of IBI. When applying these variables with "rounded cutoffs" of PCT levels less than 0.5 ng/mL (chosen by the authors because it is a more commonly used cutoff) and ANC of 4,000/μL or less to identify infants at low risk for SBI, their performance was similar to nonrounded cutoffs. Data for the rule with rounded

cutoffs in identifying infants at low risk for IBI were not presented. The PECARN study was limited by the small numbers of infants with IBIs, and the authors recommended caution when applying the rule to infants 28 days or younger.

Older clinical decision rules without PCT, such as the Rochester and modified Philadelphia criteria, use clinical and laboratory features to assess risk of IBI.[3] Recent studies have evaluated these criteria in cohorts with larger numbers of infants with IBI since the derivation studies included mostly infants with SBI and small numbers with IBI.[3] Gomez et al demonstrated that the Rochester criteria had lower sensitivity and higher negative LR than the Step-by-Step approach in IBI detection.[10] In a case-control study of 135 cases of IBI with 249 matched controls, Aronson et al reported that the modified Philadelphia criteria had higher sensitivity but lower specificity than the Rochester criteria for IBI detection.[12] The ability of the Rochester and modified Philadelphia criteria to rule out IBI, as demonstrated by the negative LR (range 0.2-0.4), was inferior to the negative LRs documented by Milcent et al[8] (PCT cutoff value of 0.3 ng/mL), the Step-by-Step approach,[10] and the PECARN rule[11] (range 0.05-0.17; Table). However, clinical decision rules with and without PCT suffer similar limitations in having poor specificity in identifying infants likely to have IBI.

GAPS IN THE LITERATURE

Several key knowledge gaps around PCT use for diagnosing neonatal infections exist. First, the optimal use of PCT in context with other biomarkers and clinical decision rules remains uncertain. A meta-analysis of 28 studies involving over 2,600 infants that compared PCT level (with and without CRP) with isolated CRP and presepsin levels found that PCT in combination with CRP had greater diagnostic accuracy than either PCT or CRP alone, which highlights a potential opportunity for prospective study.[13] Second, more data are needed on the use of PCT in the ≤ 28-day age group given the increased risk of both IBI and neonatal herpes simplex virus infection (HSV), compared with that in the second month of life. Neonatal HSV poses diagnostic challenges because half of infants will initially present as afebrile,[14] and delays in initiating antiviral treatment dramatically increase the risk of permanent disability or death.[15] There have been no prospective studies evaluating PCT use as part of neonatal HSV evaluations.

CLINICAL APPLICATIONS AND CONCLUSIONS

In summary, PCT can play an important adjunctive diagnostic role in the evaluation of febrile young infants, especially during the second month of life when outpatient management is more likely to be considered. PCT is superior to other inflammatory markers in identifying IBI, though the optimal cutoffs to maximize sensitivity and specificity are uncertain. Its performance characteristics, both alone and within clinical decision rules, can help clinicians better identify children at low risk for IBI when compared with clinical decision rules without PCT. PCT measurement can help clinicians miss fewer infants with IBI and identify infants for whom safely doing less is an appropriate option, which can ultimately reduce costs and hospitalizations. PCT may be particularly helpful when the clinical history is difficult to assess or when other diagnostic test results are missing or give conflicting results. Centers that use PCT will need to ensure that results are available within a short turnaround time (a few hours) in order to meaningfully affect care. Future studies of PCT in febrile infant evaluations should focus on identifying optimal strategies for incorporating this biomarker into risk assessments that present information to parents in a way that enables them to understand their child's risk of a serious infection.

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