ORIGINAL RESEARCH CONTRIBUTION

Procalcitonin as a Marker of Serious Bacterial Infections in Febrile Children Younger Than 3 Years Old

Prashant Mahajan, MD, MPH, MBA, Mary Grzybowski, PhD, MPH, Xinguang Chen, MD, PhD, Nirupama Kannikeswaran, MD, Rachel Stanley, MD, MHSA, Bonita Singal, MD, John Hoyle, Jr., MD, Dominic Borgialli, MD, MPH, Elizabeth Duffy, MA, and Nathan Kuppermann, MD, MPH

Abstract

Objectives: There is no perfectly sensitive or specific test for identifying young, febrile infants and children with occult serious bacterial infections (SBIs). Studies of procalcitonin (PCT), a 116-amino-acid precursor of the hormone calcitonin, have demonstrated its potential as an acute-phase biomarker for SBI. The objective of this study was to compare performance of serum PCT with traditional screening tests for detecting SBIs in young febrile infants and children.

Methods: This was a prospective, multicenter study on a convenience sample from May 2004 to December 2005. The study was conducted in four emergency departments (EDs): one pediatric ED and three EDs with pediatric units, all with academic faculty on staff. A total of 226 febrile children 36 months old or younger who presented to the four participating EDs and were evaluated for SBI by blood, urine, and/or cerebral spinal fluid (CSF) cultures were included.

Results: The test characteristics (with 95% confidence intervals [CIs]) of the white blood cell (WBC) counts including neutrophil and band counts were compared with PCT for identifying SBI. Thirty children had SBIs (13.3%, 95% CI = 8.85 to 17.70). Four (13.3%) had bacteremia (including one with meningitis), 18 (60.0%) had urinary tract infections (UTIs), and eight (26.6%) had pneumonia. Children with SBIs had higher WBC counts ($18.6 \times 10^9 \pm 8.6 \times 10^9$ cells/L vs. $11.5 \times 10^9 \pm 5.3 \times 10^9$ cells/L, p < 0.001), higher absolute neutrophil counts (ANCs; $10.6 \times 10^9 \pm 6.7 \times 10^9$ cells/L vs. $5.6 \times 10^9 \pm 3.8 \times 10^9$ cells/L, p = 0.009), higher absolute band counts ($0.90 \times 10^9 \pm 1.1 \times 10^9$ cells/L vs. $0.35 \times 10^9 \pm 0.6 \times 10^9$ cells/L, p = 0.009), and higher PCT levels (2.9 ± 5.6 ng/mL vs. 0.4 ± 0.8 ng/mL, p = 0.021) than those without SBIs. In a multivariable logistic regression analysis, the absolute band count and PCT were the two screening tests independently associated with SBI, although the area under the receiver operating characteristic (ROC) curve for PCT was the largest (0.80, 95% CI = 0.71 to 0.89).

Conclusions: Procalcitonin is a more accurate biomarker than traditional screening tests for identifying young febrile infants and children with serious SBIs. Further study on a larger cohort of young febrile children is required to definitively determine the benefit of PCT over traditional laboratory screening tests for SBIs.

ACADEMIC EMERGENCY MEDICINE 2014; 21:171–179 © 2014 by the Society for Academic Emergency Medicine

Fever is a common symptom in children younger than 3 years of age presenting to the emergency department (ED). Most children with fever without source will have nonbacterial causes of fever that will resolve without intervention.[1] Some febrile children, however, will have occult serious bacterial infections (SBIs) such as bacteremia, urinary tract infections (UTIs), bacterial meningitis, lobar pneumonia, or bacterial enteritis. Because several investigations have demonstrated that the clinical examination by itself is not a reliable method to identify children with SBIs, clinicians depend on various risk stratification strategies that use screening laboratory tests. For the youngest infants, those younger than 3 months, three commonly used strategies include the Rochester, Philadelphia, and Boston screening criteria.[1] For infants 3 months to 36 months of age, other screening strategies have been used, although the use, accuracy, and reliability of these screening methods have changed since the introduction of the conjugate pneumococcal vaccine.[2] Although the screening strategies for both younger and older infants aim to identify most children with SBIs, the economic costs and effect on clinical efficiency of extensive routine laboratory evaluation, including potential iatrogenic morbidity, have been debated to a great extent.[3] As of yet, there is no perfectly sensitive or specific test for identifying young, febrile children with occult SBIs, although several research studies and reviews have suggested the addition of specific biomarkers, including C-reactive protein (CRP) and interleukins (ILs; IL-6, IL-1, and IL-8) to routine screening tests in young febrile children.[4]

Much research has focused on evaluating screening tests and biomarkers that would allow the clinician to reliably and efficiently discriminate febrile children with occult SBIs from those with viral infections. Studies of procalcitonin (PCT), a 116-amino-acid precursor of the hormone calcitonin, have demonstrated its potential as an acute-phase biomarker for SBI.[5–9]

Since the first report of the association between serum PCT and sepsis,[10] several other studies have demonstrated that serum PCT levels rise more rapidly in bacterial infections when compared with CRP and other biomarkers such as the ILs. Furthermore, serum PCT levels correlate with severity of disease and mortality.[4,5] However, the marginal benefit of using serum PCT to screen young febrile children for SBIs above and beyond routine screening tests has not been definitively elucidated. The primary goal of this study was to determine whether serum PCT is a more accurate screening biomarker for detecting SBI in febrile infants and young children without obvious source who present to the ED, compared to traditional screening tests such as the white blood cell (WBC) count, absolute neutrophil count (ANC), and absolute band counts.

METHODS

Study Design

This was a prospective, multicenter cross-sectional study. The institutional review boards of all participating hospitals approved this study.

Study Setting and Population

We enrolled a convenience sample of well-appearing febrile children without obvious source 36 months old or younger who presented to four participating EDs between May 2004 and December 2005. All such children with documented fever (defined as rectal temperature measured in the ED or at home of ≥38°C if ≤3 months of age and ≥39°C if >3 months of age) and who were otherwise being evaluated for SBI, and were documented to be well-appearing, were eligible for enrollment. Children were excluded if they had received antibiotics within 48 hours of ED presentation, had obvious sources for fever (e.g., cellulitis; otitis media, however, was not considered an exclusion criterion), had known immunologic or systemic diseases, had histories of prematurity in febrile infants younger than 3 months (≤36 weeks of gestation), had received any immunization during the previous 2 days, or if the guardians/parents did not provide informed consent. Febrile infants and children who did not have blood cultures obtained as a part of SBI evaluations were ineligible for enrollment. At the initiation of the study, we conducted training sessions for all site investigators, research assistants, and ED nurses. During these training sessions we specified that only well-appearing febrile infants who were being evaluated for SBI with blood cultures were eligible for inclusion. Additionally, we discussed procedures for sample processing, storage, and transportation at these sessions. At the end of the study we ensured that in fact only well-appearing febrile infants and children were included by a review of patient medical records, searching for key words such as "well appearing," "non-toxic," "alert and interactive," etc.

Study Protocol

We used a structured case report form to collect historical and clinical data at the time of patient enrollment. We recorded demographic information including age, sex, and race and ethnicity at the time of ED evaluation. We collected the following historical variables: temperature at ED triage (rectal in centigrade), duration of fever (in days), history of antipyretic use, history of antibiotic use, and receipt of immunizations within the previous 48 hours. The decision to obtain blood for WBC counts, blood cultures, and other laboratory tests (including urinalyses and cultures, cerebral spinal fluid [CSF] analyses, and chest radiographs) was made at the discretion of the ED attending physician. We collected an extra 1 mL of blood for a quantitative determination of PCT and gathered information regarding antibiotic treatment and ED disposition (discharged home or admitted to the hospital). We obtained the final culture results from a review of each enrolled patient's medical record and conducted a follow-up telephone interview 7 to 10 days after the index visit to determine patient status. The PCT analyses were performed at an outside laboratory facility at a later time and therefore these results were not available to the clinicians at the time of patient enrollment and evaluation.

Laboratory Methods. The WBC count was quantified by automated laboratory equipment using a Coulter counter. Laboratory personnel calculated the differential WBC manually using microscopy. Blood cultures were processed using site-specific standardized methods. Urine samples were obtained by catheterization of the bladder under aseptic technique and analyzed in the laboratory by standardized methods with microscopy. PCT was measured by using an immunoluminometric assay (LUMItest PCT, Brahms Diagnostica, Berlin, Germany).[11] To determine PCT levels, the blood samples were centrifuged at 1700 × *g* for 15 minutes to separate the serum from the samples. The serum was then extracted and transferred into plastic aliquot tubes and stored in freezers with temperatures between –20 and –80°C until the samples were ready to be shipped to an off-site laboratory (Hemostasis Reference Laboratory, Hamilton, Ontario, Canada) for quantitative PCT analysis.

Measures

The primary outcome measure of the study was SBI, defined as the presence of at least one of the following: bacteremia, bacterial meningitis, lobar pneumonia, or UTI. We defined bacteremia and bacterial meningitis as growth of a known pathogen in blood or CSF cultures.[12] Growth of organisms that are not commonly regarded as pathogens, such as *Staphylococcus epidermidis*, α- or γ-hemolytic *Streptococcus*, *Bacillus* sp., and diphtheroids in blood or CSF, were considered to be contaminants.[12] We defined a lobar pneumonia as the presence of a focal infiltrate on chest radiograph as interpreted by a pediatric radiologist or ED attending physician. Any other findings on chest radiographs were classified as negative for the presence of pneumonia. We defined UTI as the growth of a single known pathogen with colony counts meeting one of three criteria: 1) ≥1,000 CFU/mL for urine cultures obtained by suprapubic bladder aspiration, 2) ≥50,000 CFU/mL from a catheterized specimen, or 3) ≥10,000 CFU/mL from a catheterized specimen in association with an abnormal urinalysis.[12] We defined abnormal urinalysis as a dipstick test positive for leukocyte esterase or nitrite, or >5 WBCs per high-power field on microscopic examination.[13]

Data Analysis

We calculated means, standard deviations (SDs), rates, and ratios for all continuous and categorical variables, as appropriate. For variables that were not normally distributed we used medians and interquartile ranges. We evaluated differences in patient characteristics stratified by SBI status using either Student's t-test for parametric data or the Mann-Whitney U-test for nonparametric data. We analyzed categorical data using chi-square testing if the cell sizes were sufficiently large or with Fisher's exact test if the expected number of observations in any cell was less than five. We calculated odds ratios (OR) with 95% confidence intervals (CIs) for bivariable associations. In addition, we assessed diagnostic test accuracies based on suggested thresholds from previous studies of biomarkers for SBI and based on thresholds established by area under the receiver operating characteristic (ROC) curve (AUC) analyses. These biomarkers included: 1) WBC count > 15 × 10⁹ cells/L, 2) absolute band count > 1.5 × 10⁹ cells/L, 3) ANC >10 × 10⁹ cells/L, and 4) serum PCT > 0.5 ng/mL.[10,14] Values above each biomarker threshold were considered to represent positive screens for SBI. We also constructed ROC curves for our four continuous biomarkers to assess overall diagnostic accuracy of each biomarker. In addition, we compared the accuracy of PCT at a cutoff of 0.5 ng/mL with a positive urinalysis for diagnosing UTI. Finally, to determine the marginal benefit of PCT over and above commonly used screening tests, we performed three multiple logistic regression analyses with SBI as the outcome variable and using laboratory data including PCT as continuous predictor variables, in addition to age and body temperature. In one of these multivariable analyses, we removed patients with positive urinalyses (to explore the utility of PCT after removing children with obvious UTIs). In another multivariable analysis we removed children diagnosed with pneumonia (as the etiology of even lobar pneumonias may at times be viral). Because more than one continuous covariate was modeled, the Hosmer-Lemeshow method was used with a smaller chi-square value and a large p-value indicating a better data-model fit. We constructed the multivariable model using the direct method and selected the variables based on previous research literature and on biologic plausibility. We evaluated the relationship among all covariates and excluded collinear variables, including the band-to-neutrophil ratio. Before the analysis, we checked data quality and found no outlier values for the predictor variables. We assumed the linear assumption for the continuous covariates for the logistic regression.

Sample Size. We estimated the sample size using the null hypothesis that a PCT value of greater than 0.5 ng/mL would be no more sensitive than a WBC greater than 15 × 10⁹ cells/L for diagnosing SBI. The criterion for significance (alpha) was set at 0.05, and with a sample size of 17 patients with SBI, the study would have a power of 80% to yield a statistically significant result. This computation assumes that the difference in proportions is 0.4 (specifically, 0.93 sensitivity of PCT versus 0.53 sensitivity of an elevated WBC count of 15 × 10⁹ cells/L).[7,8] Assuming a pretest probability of a SBI rate of 10%, approximately 200 patients would need to be enrolled.[1,15]

For all statistical analyses, we considered p-values < 0.05 (two-tailed) to be significant. Except where indicated, we performed the analyses using SAS, version 9.1.3 (SAS Institute Inc., Cary, NC).

RESULTS

We approached the guardians of 260 febrile infants and young children for participation in the study, of whom 226 (87%) consented, enrolled, and were included in the analysis. Nine additional patients were excluded because we were unable to obtain sufficient blood for PCT analysis, while 25 patients were excluded for the following reasons: prematurity (*n* = 7), preexisting

conditions such as ventriculoperitoneal shunts (n = 4), obvious focus of infection such as cellulitis (n = 3), did not meet age criterion (n = 2), history of antibiotic use (n = 2), and did not meet inclusion criteria or were not evaluated for SBI by the ED physician (n = 7).

Among the final analytic population of 226 patients, the mean (±SD) age was 10.5 (±8.4) months (range = 1 to 35 months) with slightly more than one-half being female (58%) and 88.5% being of non-white race. A total of 224 of 226 (99%) patients had WBC counts performed. Blood cultures were obtained from all 226 children, urine cultures from 219 (96.9%), and CSF cultures from 31 (13.7%). A total of 132 children (58.4%) received chest radiographs. Nineteen of 226 (8.4%) patients had all of the following studies: blood culture, urine culture, chest radiograph, CSF culture, and WBCs. The overall prevalence of SBI was 13.3% (30 patients). Of the 30 patients with SBIs, four (13.3%) had only positive blood cultures; 18 (60.0%) had only positive urine cultures, eight (26.6%) had only positive chest radiographs, and one (3.0%) had a positive CSF culture (this patient also had a positive blood culture).

Results from the simple comparison analysis indicated that patient demographics and presenting symptoms stratified by SBI status were not significantly different (Table 1). There was no significant difference in the duration of fever or temperature at presentation to the ED between patients with and those without SBIs. Patients with SBIs had higher presenting mean WBC counts, absolute band counts, and ANCs than non-SBI patients. On average, those with SBIs had 2.5 ng/mL mean higher PCT level than those without SBIs.

The diagnostic accuracies of the screening tests and biomarkers at their predetermined cutoff values in addition to the cutoff values determined by AUC analyses are demonstrated in Table 2. The WBC count at a predetermined threshold of 15 × 10^9 cells/L had the highest

sensitivity at 56.7%, followed by PCT at a threshold of >0.5 ng/mL (53.3%) and ANC at a threshold of 10 × 10^9 cells/L (46.7%). The absolute band count, at a threshold of 1.5 × 10^9 cells/L, correctly identified only 20.0% of patients with SBIs. The specificity of the tests ranged from 76.3% to 93.3%; the PCT at a threshold of >0.5 ng/mL correctly identified approximately 90% of the non-SBI patients. The PCT at a threshold of >0.5 ng/mL had the highest positive likelihood ratio (LR) of 5.39, followed by the ANC, absolute band count, and WBC count. PCT also had the lowest negative LR (–LR; 0.52), followed by the WBC count, ANC, and absolute band count.

We also assessed the diagnostic properties of the four biomarkers using ROC curves (Figure 1). The AUC for PCT was the largest (0.80, 95% CI = 0.71 to 0.89) followed by the WBC count (0.76, 95% CI = 0.66 to 0.86), ANC (0.73, 95% CI = 0.63 to 0.84), and absolute band count (0.67, 95% CI = 0.55 to 0.78). When the four curves were compared, there was an overall difference between the AUCs (p < 0.0001). The optimal thresholds, determined by maximizing both the sensitivity and the specificity on ROC analysis, for each biomarker in predicting SBI were as follows: WBC count > 19 × 10^9 cells/L, absolute band count > 1.8 × 10^9 cells/L, ANC > 13 × 10^9 cells/L, and PCT > 0.6 ng/mL.

The data fit the multivariable logistic regression model well, with a chi-square of 5.02 (p = 0.76) for the Hosmer-Lemeshow goodness-of-fit test and R^2 = 0.407 (p < 0.01; Table 3). When evaluating the predictor variables in their continuous forms in the multivariable analysis, apart from age, the PCT and the absolute band count were the two screening tests that were independently associated with SBI (Table 3). This analysis was adjusted for the effects of age, temperature, and the other blood screening laboratory tests. None of the other commonly used blood screening tests were

Table 1
Demographic, Clinical, and Laboratory Characteristics of Enrolled Patients (Stratified by SBI Status)*

Characteristic	All Patients, N = 226	SBI Negative, n = 196	SBI Positive, n = 30	Difference in Means or Percentages (95% CI)
Demographics				
Age (months)	10.5 (±8.4)	10.6 (±8.4)	9.6 (±8.1)	–1.0 (–2.2 to 4.3)
% < 3 months	43 (19.0)	38 (19.4)	5 (16.7)	–2.7 (–17.1 to 11.7)
Male sex (%)	95 (42.0)	88 (44.9)	7 (23.3)	–21.6 (–4.9 to –38.3)
Nonwhite race (%)	200 (88.5)	174 (88.8)	22 (86.7)	–2.1 (–15.0 to 10.8)
Presenting symptoms				
Duration of fever (days)	1.9 (±1.5)	1.8 (±1.4)	2.5 (±2.1)	–0.7 (–1.2 to –0.1)
Presenting temperature (°C)	39.3 (±0.9)	39.3 (±0.8)	39.4 (±0.9)	0.1 (–0.4 to 0.2)
Test results				
WBC count (×10^9 cells/L)	12.4 (±6.3)	11.5 (±5.3)	18.6 (±8.6)	7.1 (4.8 to 9.3)
ANC (×10^9 cells/L)	6.3 (±4.6)	5.6 (±3.8)	10.6 (±6.7)	5.0 (3.4 to 6.7)
Absolute band count (×10^9 cells/L)	0.42 (±0.70)	0.35 (±0.60)	0.90 (±1.10)	0.55 (0.15 to 0.95)
PCT (ng/mL)	0.7 (±2.3)	0.4 (±0.8)	2.9 (±5.6)	2.5 (0.4 to 4.6)
Treatments				
Antibiotics administered in ED	134 (59.3)	106 (54.1)	28 (93.3)	39.2 (27.9 to 50.5)
Antibiotics prescribed at discharge	65 (29.0)	54 (27.8)	11 (36.7)	8.9 (–9.5 to 27.3)
ED disposition				
Admitted to hospital	55 (24.3)	36 (18.4)	19 (63.3)	44.9 (26.8 to 63.0)

Data are reported as mean (±SD) or number (%).
ANC = absolute neutrophil count; PCT = procalcitonin; SBI = serious bacterial infection; WBC = white blood cell.

Table 2
Diagnostic Parameters of Screening Tests for SBI*

Biomarker	Sensitivity (95% CI)	Specificity (95% CI)	+LR (95% CI)	PPV[†] (95% CI)	−LR (95% CI)	NPV[†] (95% CI)
WBC count ($\times 10^9$ cells/L)						
>15.0[†]	56.7(37.7–74.0)	76.3(69.6–82.0)	2.39(1.60–3.57)	0.27(0.17–0.40)	0.57(0.38–0.86)	0.92(0.86–0.95)
>19.0[§]	46.7(28.8–65.4)	90.2(84.9–93.8)	4.76(2.69–8.45)	0.15(0.11–0.20)	0.59(0.42–0.83)	0.85(0.80–0.89)
ANC ($\times 10^9$ cells/L)						
>10.0[†]	46.7(28.8–65.4)	88.1(82.5–92.2)	3.94(2.29–6.77)	0.38(0.23–0.55)	0.61(0.43–0.85)	0.91(0.86–0.95)
>13.0[§]	30.0(15.4–49.6)	94.3(89.8–97.0)	5.29(2.40–11.69)	0.45(0.24–0.68)	0.74(0.59–0.94)	0.90(0.84–0.93)
Absolute band count ($\times 10^9$ cells/L)						
>1.5[†]	20.0(8.0–39.1)	93.3(88.6–96.2)	2.99(1.23–7.25)	0.32(0.14–0.56)	0.86(0.72–1.03)	0.88(0.83–0.92)
>1.8[§]	20.0(8.4–39.1)	96.4(92.4–98.4)	5.54(2.00–15.38)	0.06(0.03–0.10)	0.83(0.69–0.99)	0.94(0.90–0.97)
PCT (ng/mL)						
>0.5[†]	53.3(34.6–71.2)	90.1(84.8–93.8)	5.39(3.13–9.27)	0.46(0.29–0.63)	0.52(0.35–0.76)	0.93(0.88–0.96)
>0.6[§]	51.6(33.4–69.4)	92.7(87.8–95.8)	7.04(3.83–12.94)	0.13(0.09–1.89)	0.52(0.36–0.75)	0.86(0.81–0.91)

ANC = absolute neutrophil count; AUC = area under the receiver operating characteristic curve; +LR = positive likelihood ratio; −LR = negative likelihood ratio; NPV = negative predictive value; PCT = procalcitonin; PPV = positive predictive value; SBI = serious bacterial infection; WBC = white blood cell.
*All values above and below the cutoff points are considered as screening positive for SBI and screening negative for SBI, respectively.
†Pretest probability used in computing the posttest positive predictive values were 13.3% based on the prevalence of SBI (30/226) observed in this study.
§All values above and below optimal cutoff points determined by the AUC (Figure 1) are considered as screening positive for SBI and screening negative for SBI.

independently associated with SBI, after adjusting for the PCT.

As it is empirical that it would be difficult to identify a blood test that was as accurate as the urinalysis to diagnose UTI, we compared PCT at a threshold of 0.5 ng/mL versus a positive urinalysis as a screen for UTI. As anticipated, the urinalysis as a screening test performed better than PCT among patients with UTIs. After removing non-UTI SBIs from the database, there were 182 of 226 (80.5%) patients with all three tests: urinalysis, urine culture, and PCT performed. Forty-six of the 182 (25%) patients had positive urinalyses, and 14.2% (26/182) had PCT levels above the threshold of 0.5 ng/mL. For a positive urinalysis, sensitivity was 81.25% (95% CI = 54.34% to 95.73%), specificity was 80.12% (95% CI = 73.23% to 85.90%), positive likelihood ratio (+LR) was 4.09 (95% CI = 2.78 to 6.01), and negative likelihood ratio (−LR) was 0.23 (95% CI = 0.08 to 0.65), while for PCT above 0.5 ng/mL, sensitivity was 43.75% (95% CI = 19.83% to 70.08%), specificity was 88.55% (95% CI = 82.70% to 92.96%), +LR was 3.82 (95% CI = 1.9 to 7.68), and −LR was 0.64 (95% CI = 0.41 to 0.98) for detecting UTI. Furthermore, we evaluated the performance of PCT in the regression model with the 77 patients who had either positive urinalyses (*n* = 49) or missing urinalyses (*n* = 28) removed from the analysis. PCT was the only marker that was independently associated with SBI (PCT OR = 1.57 for each ng/mL increase, 95% CI = 1.05 to 2.34, p = 0.027). Age, temperature, WBC, ANC, and absolute band count were not independently associated with SBI in this analysis.

Because some patients with lobar pneumonias may nevertheless have viral infections as their etiology, we performed a separate multivariable analysis to test the performance of PCT on patients with SBI excluding those diagnosed with pneumonia (eight patients among 30 SBI were diagnosed as pneumonia and were there-

fore removed). Age, absolute band count, and PCT were all independently associated with SBI, with PCT demonstrating the highest OR (1.42, 95% CI = 1.01 to 2.00; Table 4).

DISCUSSION

In this study, we found that the serum PCT was superior to traditional laboratory screening tests for detecting SBIs in febrile infants and young children without obvious sources of infection presenting to the ED. In addition, a PCT cutoff value of 0.6 ng/mL performed better than the more traditional cutoff value of 0.5 ng/mL in predicting SBI. In the multivariable logistic regression analysis, young age, the absolute band count, and PCT were all independently associated with SBI. The incidence of SBI is higher in younger febrile infants compared to older febrile children, consistent with prior research.[16] PCT appears to be more accurate as a screening test for SBI than other traditional blood screening tests, demonstrated by the greater AUC for PCT. Although we also found the absolute band count to also be significant in both the bivariate and the multivariable analyses, the utility of absolute band counts in identifying children with SBI has been questioned by some,[17–19] while others have demonstrated that absolute band counts may vary between laboratories.[20]

The management of febrile infants and young children without obvious foci of infection remains a clinical conundrum for clinicians. To minimize the risk of misdiagnosing a child who in fact has an SBI, many ED practitioners rely on published guidelines and screening diagnostic tests, including lumbar punctures, particularly in the youngest infants 90 days of age and younger.[1,21] Considerable debate exists in the evaluation of these infants, with much controversy regarding the published guidelines because: 1) studies pertaining to
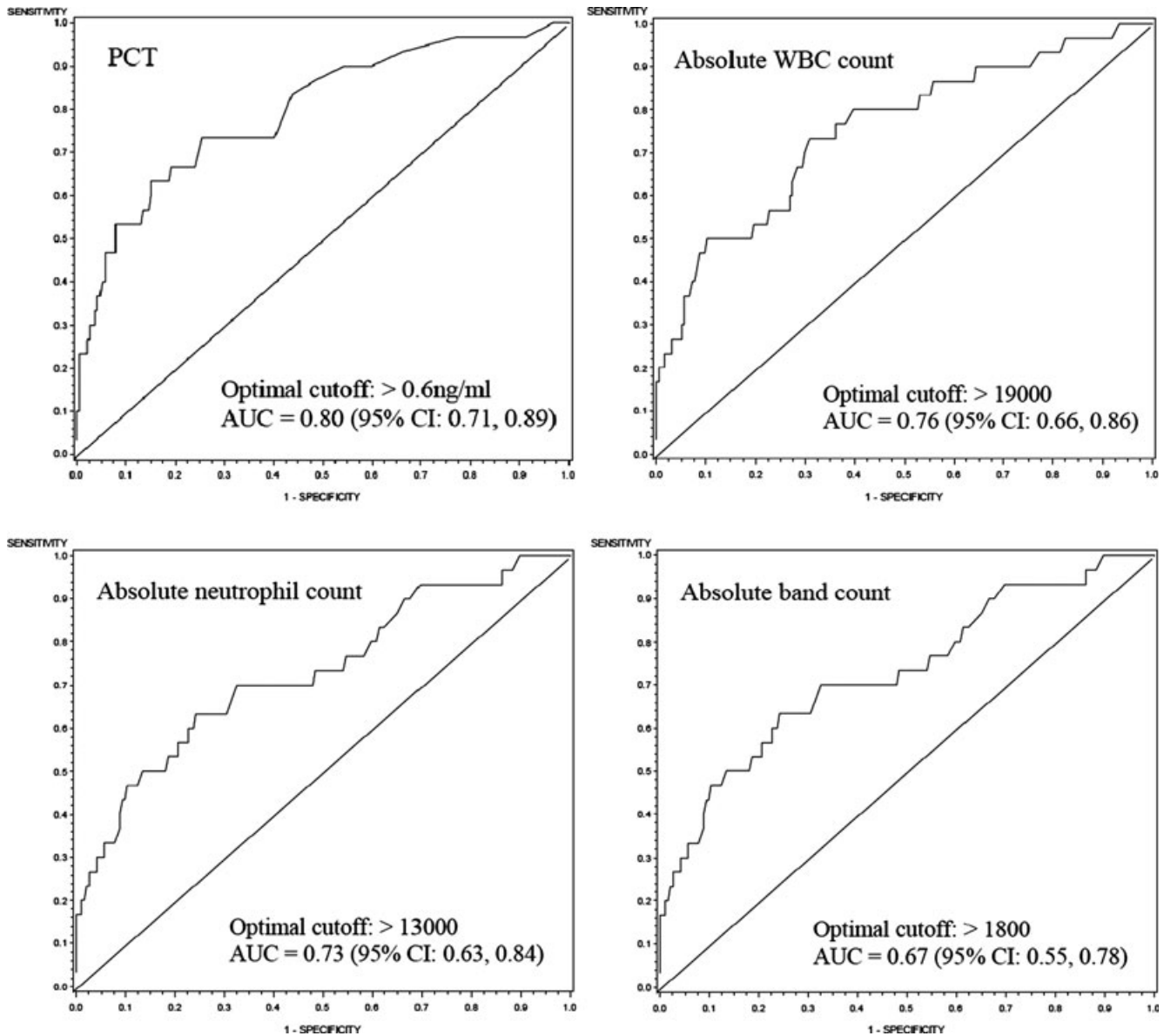
Figure 1. Receiver operating characteristic curve of PCT and three blood count biomarkers for SBI. Note: The optimal cutoff points were determined by observation while maximizing both sensitivity and specificity. The units for PCT are in ng/ml, while white blood cell count, absolute neutrophil count, and absolute band counts are in cells/mm^3
PCT = procalcitonin; SBI = serious bacterial infection.

febrile infants have been conducted in a single or small groups of academic centers[1]; 2) studies have used retrospective designs, different inclusion criteria (e.g., with respect to age and temperature cutoffs to define fever), and different laboratory criteria for distinguishing high-risk versus low-risk infants[4]; and 3) solid evidence questioning the discriminatory ability of commonly used screening tests such as WBC and ANC in the youngest febrile infants.[21]

The availability of a biomarker that could accurately and rapidly identify SBI in febrile infants and children without obvious source would frequently obviate the need for invasive procedures such as lumbar punctures and reduce the use of empirical antibiotics and hospitalization and would be of significant importance to patients, their families, and clinicians. Prior studies on

the accuracy of PCT in screening febrile infants and children for SBI in the ED setting have revealed inconsistent results. One study demonstrated that PCT was the single best laboratory screening test when compared to IL-6, IL-8, and IL-1 receptor antagonists and CRP in 124 well-appearing febrile infants 7 days to 36 months of age.[8] Similarly, a large multicenter study of 445 well-appearing febrile infants 1 to 36 months old also concluded that PCT was superior to the CRP and other routinely used laboratory screening tests for distinguishing those with viral and bacterial infections.[6] In contrast, the findings of another study of 72 febrile children 1 to 36 months of age suggest the diagnostic accuracy of PCT, CRP, and WBC are comparable to clinical scoring (Yale Observational Scale)[22] and do not change posttest probabilities to a clinically useful extent.[23] In a

Table 3
Multivariable Logistic Regression Analysis of Predictors of
Serious Bacterial Infection ($n = 226$)

Predictor Variable	Adjusted OR (95% CI)	p-value
Age (months)	0.90 (0.82–0.98)	0.015
Presenting temperature (°C)	1.21 (0.66–2.20)	0.537
PCT (ng/mL)	1.67 (1.12–2.49)	0.013
WBC count ($\times 10^9$ cells/L)	1.01 (0.99–1.02)	0.526
ANC ($\times 10^9$ cells/L)	1.01 (0.99–1.04)	0.199
Absolute band count ($\times 10^9$ cells/L)	1.07 (1.01–1.14)	0.018
Model fit		
Hosmer-Lemeshow test	$\chi^2 = 5.02$	0.76
Variance explained	$R^2 = 0.407$ (maximum re-scaled)	<0.01

The ANC and absolute band count were divided by 100 to
rescale the measurement range for robust statistical analysis.
ANC = absolute neutrophil count; PCT = procalcitonin;
WBC = white blood cell.

Table 4
Multivariable Logistic Regression Analysis of Predictors of
Serious Bacterial Infection (Patients Diagnosed With Pneumonia
Removed; $n = 218$)

Predictor Variable	Adjusted OR (95% CI)	p-value
Age (months)	0.87 (0.78–0.96)	0.01
Presenting temperature (°C)	1.39 (0.68–2.85)	0.37
PCT (ng/mL)	1.42 (1.01–2.01)	0.04
WBC count ($\times 10^9$ cells/L)	1.0 (0.99–1.02)	0.62
ANC ($\times 10^9$ cells/L)	1.01 (0.99–1.04)	0.19
Absolute band count ($\times 10^9$ cells/L)	1.10 (1.03–1.18)	0.004

ANC = absolute neutrophil count; PCT = procalcitonin;
WBC = white blood cell.

different study of febrile infants, although PCT and CRP
were found to be better markers than the WBC in iden-
tifying SBI in febrile infants, the authors concluded that
the CRP may be the most convenient for use in the ED
setting.[24] Finally, two evidence-based reviews of pub-
lished studies on the use of PCT as a screening test for
SBI in febrile children younger than 3 years of age con-
cluded that PCT is still not sufficiently sensitive to be
used as a single screening tool to exclude the possibility
of SBI.[25,26] The direct comparison of the current study
with those mentioned above is difficult because of the
study heterogeneity with regard to inclusion criteria,
screening test thresholds, and definitions of SBI, among
others.

There remain important, pressing issues regarding
the evaluation of young febrile children. The successful
introduction of conjugate pneumococcal vaccines has
dramatically altered the evaluation of febrile children
older than 3 months of age in the past two decades.[27,28]
Further research should be focused on the effect
of novel biomarkers, rapid turnaround identification of

pathogens, and DNA/RNA expression patterns to
distinguish febrile infants with SBIs from those with
viral infections. Additionally, the test characteristics of
PCT need to be studied in substantially larger numbers
of febrile children who have bacteremia and/or menin-
gitis. Two recent studies on the usefulness of PCT as a
biomarker in young febrile infants (<90 days of age) are
notable.[29,30] In one of these studies, the test characteris-
tics of PCT, CRP, and WBC counts were compared in
347 febrile infants < 90 days of age (who had an SBI
rate of 23.6%).[29] The investigators demonstrated that
although PCT and CRP had similar AUCs (0.77 and
0.79); both these variables were better predictors than
the WBC count (AUC = 0.67). In a subset of infants
with more invasive bacterial infections (sepsis, bactere-
mia, bacterial meningitis) in that study, the diagnostic
value of PCT (AUC = 0.84) was higher than that of the
CRP (AUC = 0.68). In another study, the investigators
studied the accuracy of PCT in 234 febrile infants youn-
ger than 90 days of age (with a 12.8% SBI rate) and
demonstrated that mean PCT levels for those infants
with SBIs was significantly higher than for those with-
out SBIs (2.21 ng/mL vs. 0.38 ng/mL, AUC 0.82) and
concluded that PCT had better test characteristics than
any other biomarker.[30] To more definitively evaluate
the role PCT testing in this patient population, however,
we suggest that an adequately powered multicenter
prospective study of young febrile infants be conducted
to determine the test characteristics and marginal bene-
fit of PCT over routinely used screening tests.

LIMITATIONS

As this was an observational study of a convenience
sample of febrile infants and children, without a stan-
dardized evaluation and management protocol enforced
at the participating sites, we recognize that there may
have been a selection bias of the study population. Vari-
ation in the evaluation of febrile children based on
patient age, degree of fever, and training of the ED phy-
sician has been well described previously.[1] We did not
document clinical scores (such as the Yale Observation
Scale score[22]) on all patients because this was not a part
of institutional practice; however, every enrolled patient
was documented to be well-appearing on the ED physi-
cians' initial evaluations. There were also relatively
few patients with bacteremia, and more with UTIs.
Although we demonstrated that the urinalysis was a
better screening test for UTI than was PCT, the PCT
nevertheless was a significant predictor of UTI in the
multivariable analysis when patients with positive uri-
nalyses were removed from the analysis. This highlights
the potential utility of PCT as a screening test for UTI in
patients with undifferentiated sources of fever from
whom urine is not initially obtained. We also did not
compare the test characteristics of PCT to that of CRP
because the latter test is not routinely performed at the
four participating institutions. Finally, we used the ED
attending or radiologist interpretation of chest radio-
graphs for definition of pneumonia, and it is possible
that we could have missed patients with pneumonias
who had negative radiographs or included those with
viral etiologies for their pneumonias. Despite removing

patients with pneumonia in a subanalysis, however, PCT was independently associated with SBI.

CONCLUSIONS

Procalcitonin appears to be a more accurate marker than the white blood cell count, the absolute neutrophil count, or the absolute band count in identifying young febrile infants and children with serious bacterial infections. Further study on a larger cohort is required to more definitively determine the marginal benefit of procalcitonin over traditionally used screening laboratory tests in these patients.

References

1. Harper MB. Update on the management of the febrile infant. Clin Pediatr Emerg Med 2004; 5:5–12.
2. Chancey RJ, Jhaveri R. Fever without localizing signs in children: a review in the post-Hib and post-pneumococcal era. Minerva Pediatr 2009;61:489–501.
3. DeAngelis C, Joffe A, Wilson M, Willis E. Iatrogenic risks and financial costs of hospitalizing febrile infants. Am J Dis Child 1983;137:1146–9.
4. Hsiao AL, Baker MD. Fever in the new millennium: a review of recent studies of markers of serious bacterial infection in febrile children. Curr Opin Pediatr 2005;17:56–61.
5. Carrol ED, Newland P, Riordan FA, Thomson AP, Curtis N, Hart CA. Procalcitonin as a diagnostic marker of meningococcal disease in children presenting with fever and a rash. Arch Dis Child 2002;86:282–5.
6. Fernández Lopez A, Luaces Cubells C, García García JJ, Fernández Pou J; Spanish Society of Pediatric Emergencies. Procalcitonin in pediatric emergency departments for early diagnosis of invasive bacterial infections in febrile infants: results of a multicenter study and the utility of a rapid qualitative test for this marker. Pediatr Infect Dis J 2003;22:895–903.
7. Galetto-Lacour A, Zamora SA, Gervaix A. Bedside procalcitonin and C-reactive protein tests in children with fever without localizing signs of infection seen in a referral center. Pediatrics 2003;112:1054–60.
8. Lacour AG, Gervaix A, Zamora SA, et al. Procalcitonin, IL-6, IL-8, IL-1 receptor antagonist and C-reactive protein as identificators of serious bacterial infections in children with fever without localising signs. Eur J Pediatr 2001;160:95–100.
9. Yo CH, Hsieh PS, Lee SH, et al. Comparison of the test characteristics of procalcitonin to C-reactive protein and leukocytosis for the detection of serious bacterial infections in children presenting with fever without source: a systematic review and meta-analysis. Ann Emerg Med 2012;60:591–600.
10. Assicot M, Gendrel D, Carsin H, Raymond J, Guilbaud J, Bohuon C. High serum procalcitonin concentrations in patients with sepsis and infection. Lancet 1993;341:515–8.
11. Meisner M. Procalcitonin. A New Innovative Marker for Severe Infection and Sepsis: Biochemical and Clinical Aspects. Berlin, Germany: Brahms Diagnostica 1996, pp 14–21.
12. Levine DA, Platt SL, Dayan PS, et al. Risk of serious bacterial infection in young febrile infants with respiratory syncytial virus infections. Pediatrics 2004;113:1728–34.
13. Hoberman A, Wald ER. Urinary tract infections in young febrile children. Pediatr Infect Dis J 1997;16:11–7.
14. Irwig L, Bossuyt P, Glasziou P, Gatsonis C, Lijmer J. Evidence base of clinical diagnosis: Designing studies to ensure that estimates of test accuracy are transferable. BMJ 2002;324:669–71.
15. Fleiss JL. Statistical Methods for Rates and Proportions, 2nd ed. New York, NY: John Wiley and Sons Ltd., 1981.
16. Baraff LJ. Management of infants and young children with fever without source. Pediatr Ann 2008;37:673–9.
17. Wenz B, Gennis P, Canova C, Burns ER. The clinical utility of the leukocyte differential in emergency medicine. Am J Clin Pathol 1986;86:298–303.
18. Ardron MJ, Westengard JC, Dutcher TF. Band neutrophil counts are unnecessary for the diagnosis of infection in patients with normal total leukocyte counts. Am J Clin Pathol 1994;102:646–9.
19. Kuppermann N, Walton EA. Immature neutrophils in the blood smears of young febrile children. Arch Pediatr Adolesc Med 1999;153:261–6.
20. Luxmore B, Powell KR, Díaz SR, Novak RW. Absolute band counts in febrile infants: know your laboratory. Pediatrics 2002;110(1 Pt 1):e12.
21. Bonsu BK, Chb M, Harper MB. Identifying febrile young infants with bacteremia: is the peripheral white blood cell count an accurate screen? Ann Emerg Med 2003;42:216–25.
22. McCarthy PL, Sharpe MR, Spiesel SZ, et al. Observation scales to identify serious illness in febrile children. Pediatrics 1982;70:802–9.
23. Thayyil S, Shenoy M, Hamaluba M, Gupta A, Frater J, Verber IG. Is procalcitonin useful in early diagnosis of serious bacterial infections in children? Acta Paediatr 2005;94:155–8.
24. Andreola B, Bressan S, Callegaro S, Liverani A, Plebani M, Da Dalt L. Procalcitonin and C-reactive protein as diagnostic markers of severe bacterial infections in febrile infants and children in the emergency department. Pediatr Infect Dis J 2007;26:672–7.
25. Herd D. In children under age three does procalcitonin help exclude serious bacterial infection in fever without focus? Arch Dis Child 2007;92:362–4.
26. Jones AE, Fiechtl JF, Brown MD, Ballew JJ, Kline JA. Procalcitonin test in the diagnosis of bacteremia: a meta-analysis. Ann Emerg Med 2007;5:34–41.
27. Bisgard KM, Kao A, Leake J, Strebel PM, Perkins BA, Wharton M. Haemophilus influenzae invasive disease in the United States, 1994-1995: near disappearance of a vaccine-preventable childhood disease. Emerg Infect Dis 1998;4:229–37.
28. Black S, Shinefield H, Baxter R, et al. Postlicensure surveillance for pneumococcal invasive disease after use of heptavalent pneumococcal conjugate vaccine in the Northern California Kaiser Permanente. Pediatr Infect Dis J 2004;23:485–9.

29. Olaciregui I, Hernández U, Muñoz JA, Emparanza JI, Landa JJ. Markers that predict serious bacterial infection in infants under 3 months of age presenting with fever of unknown origin. Arch Dis Child 2009;94:501–5.

30. Maniaci V, Dauber A, Weiss S, Nylen E, Becker KL, Bachur R. Procalcitonin in young febrile infants for the detection of serious bacterial infections. Pediatrics 2008;122:701–10.