

## Original Investigation

# Use of Procalcitonin Assays to Predict Serious Bacterial Infection in Young Febrile Infants

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**IMPORTANCE** The procalcitonin (PCT) assay is an accurate screening test for identifying invasive bacterial infection (IBI); however, data on the PCT assay in very young infants are insufficient.

**OBJECTIVE** To assess the diagnostic characteristics of the PCT assay for detecting serious bacterial infection (SBI) and IBI in febrile infants aged 7 to 91 days.

**DESIGN, SETTING, AND PARTICIPANTS** A prospective cohort study that included infants aged 7 to 91 days admitted for fever to 15 French pediatric emergency departments was conducted for a period of 30 months (October 1, 2008, through March 31, 2011). The data management and analysis were performed from October 1, 2011, through October 31, 2014.

**MAIN OUTCOMES AND MEASURES** The diagnostic characteristics of the PCT assay, C-reactive protein (CRP) concentration, white blood cell (WBC) count, and absolute neutrophil cell (ANC) count for detecting SBI and IBI were described and compared for the overall population and subgroups of infants according to the age and the duration of fever. Laboratory test cutoff values were calculated based on receiver operating characteristic (ROC) curve analysis. The SBIs were defined as a pathogenic bacteria in positive culture of blood, cerebrospinal fluid, urine, or stool samples, including bacteremia and bacterial meningitis classified as IBIs.

**RESULTS** Among the 2047 infants included, 139 (6.8%) were diagnosed as having an SBI and 21 (1.0%) as having an IBI (11.0% and 1.7% of those with blood culture ( $n = 1258$ ), respectively). The PCT assay offered an area under the curve (AUC) of ROC curve similar to that for CRP concentration for the detection of SBI (AUC, 0.81; 95% CI, 0.75-0.86; vs AUC, 0.80; 95% CI, 0.75-0.85;  $P = .70$ ). The AUC ROC curve for the detection of IBI for the PCT assay was significantly higher than that for the CRP concentration (AUC, 0.91; 95% CI, 0.83-0.99; vs AUC, 0.77; 95% CI, 0.65-0.89;  $P = .002$ ). Using a cutoff value of 0.3 ng/mL for PCT and 20 mg/L for CRP, negative likelihood ratios were 0.3 (95% CI, 0.2-0.5) for identifying SBI and 0.1 (95% CI, 0.03-0.4) and 0.3 (95% CI, 0.2-0.7) for identifying IBI, respectively. Similar results were obtained for the subgroup of infants younger than 1 month and for those with fever lasting less than 6 hours.

**CONCLUSIONS AND RELEVANCE** The PCT assay has better diagnostic accuracy than CRP measurement for detecting IBI; the 2 tests perform similarly for identifying SBI in febrile infants aged 7 to 91 days.

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The prevalence of severe bacterial infections (SBIs), defined as urinary tract infection (UTI), bacterial gastroenteritis, and more invasive bacterial infections (IBIs), such as bacteremia and meningitis, varies from 5% to 15% in infants younger than 3 months, and diagnostically reliable symptoms or clinical signs are few.<sup>1-5</sup> Therefore, it can be difficult to distinguish young infants with SBIs from those with viral infection. As a result, a complete sepsis evaluation, empirical antibiotic therapy, and hospital admission are recommended for febrile infants up to 1 month of age and are common for those 1 to 2 months of age.<sup>1,2,4,6</sup> Clinicobiological scores to identify patients at low risk of SBI have been developed to allow optimal treatment.<sup>1,6-8</sup> These scores are less accurate in infants younger than 1 month,<sup>9-11</sup> difficult to use in practice,<sup>12</sup> and variably applied by physicians.<sup>3,12-15</sup> Their cost and the associated iatrogenic morbidity have not been extensively evaluated. Management of such cases could be improved by new tools, and candidates include diagnostic tests for viral infection<sup>9,16</sup> and procalcitonin (PCT) assays with earlier detection than usual biomarkers. The value of the PCT assay has been evaluated for the detection of SBI in infants<sup>17-22</sup> and more specifically of IBI,<sup>23-25</sup> and the findings are favorable. However, to our knowledge, few studies<sup>26-29</sup> have assessed the performance of PCT assays for infants up to 3 months of age. The objective of this prospective study was to assess the diagnostic accuracy of PCT assays and to compare it with other, routinely used biomarkers for detecting SBI and IBI in febrile infants aged 7 to 91 days and for subgroups of infants according to their age (7-30 days or >30 days) and the duration of fever ( $\leq 6$  hours).

## Methods

### Study Design, Setting, and Participants

We performed a prospective, multicenter, cohort study in 15 French pediatric emergency departments for a period of 30 months from October 1, 2008, through March 31, 2011. The data management and analysis were performed from October 1, 2011, through October 31, 2014. Infants older than 7 days and younger than 91 days with temperatures of 38°C or higher at home or on admission, without antibiotic treatment within the previous 48 hours, and without major comorbidities (immune deficiency, congenital abnormality, or chronic disease) were eligible. We did not include infants 6 days or younger because they are likely to have early-onset sepsis related to perinatal factors<sup>9</sup> and because physiologic PCT concentrations during the first 3 days of life are higher than thereafter.<sup>30</sup>

A list of eligible patients not included was established, and a systematic search for SBI in these patients was conducted. The Saint Germain en Laye Ethics Committee approved the study. Parental written informed consent was obtained.

### Data Collection

Physicians recorded demographic and neonatal data, onset of fever, fever in family members, symptoms, and clinical findings, including the Yale Observation Scale.<sup>31</sup> At the end of the clinical examination and before the results of the tests were available, the physician classified the clinical appearance as well or minimally,

### At a Glance

- The area under the curve (AUC) of the receiver operating characteristic curve for the detection of invasive bacterial infection (IBI) for the procalcitonin (PCT) assay was significantly higher than that for the C-reactive protein (CRP) concentration (AUC, 0.91; 95% CI, 0.83-0.99; vs AUC, 0.77; 95% CI, 0.65-0.89;  $P = .002$ ).
- The PCT assay offered an AUC similar to that for CRP for the detection of SBI (AUC, 0.81; 95% CI, 0.75-0.86; vs AUC, 0.80; 95% CI, 0.75-0.85;  $P = .70$ ).
- With a cutoff value of 0.3 ng/mL for PCT and 20 mg/L for CRP, negative likelihood ratios for identifying IBI were 0.1 (95% CI, 0.03-0.4) and 0.3 (95% CI, 0.2-0.7), respectively.
- The PCT assay has better diagnostic accuracy than CRP measurement for detecting IBI in very young febrile infants.

moderately, or very ill. The investigations, including white blood cell (WBC), absolute neutrophil cell (ANC), and C-reactive protein (CRP) measurement, blood culture, urinalysis, lumbar puncture, stool culture, and chest radiography, and the decision to treat with antibiotics or to hospitalize were left to the discretion of the physicians. Admitted patients were followed up until discharge, and discharged patients were followed up 48 hours after the initial admission with a medical visit or a telephone call.

### Clinical Diagnoses

The attending physician made the diagnosis, categorized as SBI or no bacterial infection, masked to the PCT value. Definite SBI was defined as the isolation of a bacterial pathogen from the culture of blood, cerebrospinal fluid, stool sample, or urine collected by catheterization with 50 000 CFUs/mL or greater of a single pathogen with a pyuria ( $>5$  WBCs per high-power field) and/or bacteriuria on microscopic analysis or a positive dipstick test result for leukocyte esterase or nitrite.<sup>32</sup> Infants with a urine culture from a bag specimen of 100 000 CFUs/mL or greater of a single pathogen were considered to possibly have a UTI, and infants with infiltrate on chest radiography interpreted by an experienced radiologist were considered to possibly have pneumonia and, accordingly, SBIs. The IBIs were bacteremia and bacterial meningitis defined as a pathogenic bacteria in positive culture of blood and cerebrospinal fluid, including *Streptococcus pneumoniae*, *Neisseria meningitidis*, groups A and B *Streptococcus*, *Staphylococcus aureus*, and *Escherichia coli*. *Staphylococcus epidermidis* and *Streptococcus viridans* were categorized as contaminants. Patients with possible SBIs and all other patients were recorded as not having definite bacterial infection for the diagnostic test performances analysis. All cases of IBI were reviewed by 2 pediatric infectious disease specialists and 2 bacteriologists, all masked to the PCT results.

### Laboratory Tests Measurement

Serum samples were collected after the initial clinical examination for quantitative PCT assays. The PCT analysis was performed retrospectively, and the laboratory was not informed of the clinical features. Blood samples were centrifuged immediately after collection, and the serum samples were frozen in the laboratory of each participating center and sent frozen ( $-80^{\circ}\text{C}$ ) to the laboratory of the main investigating center (CHU Antoine

Table 1. Demographic, Clinical, Biological, and Care Data

Characteristics	No. (%) of Study Participants (N = 2047)
Demographic and clinical	
Male sex	1218 (59.5)
Age ≤30 d	415 (20.3)
Maternal risk factor	478 (23.4)
Febrile family member	553 (27.0)
Duration of fever ≤6 hours	889 (43.4)
Poor general condition according to parents	627 (30.6)
Clinical appearance moderately or very ill	637 (31.1)
Laboratory tests and care	
PCT measurement	2047 (100)
WBC measurement	2022 (98.8)
CRP measurement	2037 (99.5)
Blood culture	1258 (61.5)
Lumbar puncture	1326 (64.8)
Urine culture or dipstick test	1995 (97.5)
Urine culture alone	1377 (67.3)
Chest radiography	1320 (64.5)
Hospital admission	1505 (73.5)
Antibiotic treatment	856 (41.8)

Abbreviations: CRP, C-reactive protein; PCT, procalcitonin; WBC, white blood cell.

Béclère, Clamart-France). Samples were stored at  $-80^{\circ}\text{C}$  until testing. Procalcitonin is stable after long-term deep-frozen storage.<sup>33</sup> All samples were tested with the VIDAS B.R.A.H.M.S. PCT assay (BioMérieux) by a semiautomated enzyme-linked immunosorbent assay immune analysis. The CRP was measured using a rapid immunometric method (Vitros Fusion 5.1, Ortho Clinical Diagnostics) according to the instructions of the manufacturer. The WBC and ANC counts were measured using an automated cell counter.

### Study Size and Main Outcome Measure

The sample size was calculated on the primary outcome measure: this required an accurate estimate of the area under the curve (AUC) of the receiver operating characteristic (ROC) curve of the value of the PCT assay for the diagnosis of IBI. The number of individuals to be included was determined from the accuracy of the 95% CI of this AUC. The sample size was estimated so that the 95% CI for AUC of the PCT assay would have a  $\pm 5\%$  accuracy. Assuming an AUC at 0.85 and an IBI prevalence of 2%, a sample of 2000 infants was needed.<sup>34</sup>

### Statistical Analysis

First, the general characteristics of the patients and clinical care conditions were described. The diagnosis was reported for the population as a whole and according to age ( $\leq 30$  or  $> 30$  days). Categorical variables were reported as percentages and compared using the Fisher exact test or  $\chi^2$  test. The following analyses were performed between definite SBIs and no definite bacterial infection. For analysis of definite SBIs and IBIs that included laboratory data as predictors, we included only patients for whom a blood culture was obtained.

Second, clinical characteristics and laboratory values were compared between those with and without definite SBIs and IBIs. Third, a multiple logistic regression model was performed that included clinical and laboratory markers (PCT, CRP, WBC, and ANC as binary variables) that were significantly associated in the univariable analysis with the outcome variables (definite SBI and IBI). The optimal statistical cutoff values for each biomarker were calculated based on ROC curve analysis as the maximum (sensitivity + specificity - 1). Fourth, the diagnostic performances of the laboratory markers considered for detecting definite SBI and IBI were investigated by drawing a ROC curve and comparing the AUC<sup>34,35</sup> for all infants with blood cultures and among them, for those 30 days or younger and for those with fever lasting for less than 6 hours. A sensitivity analysis with definite plus possible SBIs was performed. Fifth, sensitivity, specificity, and positive and negative likelihood ratios were assessed for optimal cutoffs obtained from our ROC curve analysis and other previously published cutoffs.<sup>19,20</sup>  $P < .05$  was considered statistically significant. STATA/SE statistical software, version 12 (StataCorp), was used for statistical analyses.

## Results

### Patient Characteristics

In total, 2981 consecutive infants were eligible and 2273 patients enrolled. The rate of bacterial infection did not differ among the 708 eligible but excluded patients for whom parental consent or data collection could not be obtained and the patients enrolled (39 [5.5%] vs 139 [6.1%],  $P = .50$ ). After verification of the exclusion criteria, complete follow-up, and availability of PCT assay results, 2047 infants were included in the final analysis (eFigure 1 in the Supplement). Among excluded patients, the prevalence of definite SBI was 5.8% (6.8% among included infants,  $P = .60$ ). The demographic, clinical, and care data for the study population are reported in Table 1. Among infants without lumbar puncture performed, only 23 were discharged and treated with oral antibiotics. None had clinical worsening after the 48-hour follow-up.

### Diagnoses

Among the 139 infants with a definite SBI (11.0% of those with blood culture), 115 (9.1% of those with blood culture) had UTI as diagnosed from catheterized urine specimens, with similar proportions in the 2 age groups (7.4% in those aged  $\leq 30$  days vs 9.6% in those aged  $> 30$  days,  $P = .26$ ). Bacteremia was diagnosed in 13 infants and bacterial meningitis in 8 infants (1.0% and 0.6% of those with blood culture, respectively). Invasive bacterial infections were more frequent in the first month of life (3.3% of patients with blood culture) than in the following 2 months (1.2%;  $P = .01$ ). *Escherichia coli* was the causative organism in 105 (91.3%) of the 115 UTIs and the species most frequently isolated from blood cultures (8 [61.5%] of 13) (Table 2).

### Predictive Factors of Definite SBIs and IBIs

The clinical and laboratory data compared between the categories of diagnosis using univariate and multivariate analyses are reported in Table 3. The optimal cutoff points were 0.3

**Table 2. Bacterial Infections**

Infection Type	No. (%) of Study Participants <sup>a</sup>			Pathogens
	All (N = 2047)	Aged 7-30 d (n = 415)	Aged 31-91 d (n = 1632)	
Definite SBI	139 (6.8/11.0)	30 (7.2/11.0)	109 (6.7/11.0)	...
No IBI				
UTI <sup>b</sup>	115 (5.6/9.1)	20 (4.8/7.4)	95 (5.8/9.6)	<i>Escherichia coli</i> (n = 105) <i>Klebsiella</i> (n = 6) <i>Enterococcus</i> (n = 4)
Gastroenteritis	3	1	2	<i>Salmonella typhimurium</i> (n = 3)
IBI				
Bacterial meningitis	8 (0.4/0.6)	4 (1.0/1.5)	4 (0.2/0.4)	<i>Streptococcus agalactiae</i> (n = 3) <i>E coli</i> (n = 2) <i>Neisseria meningitidis</i> (n = 1) <i>Streptococcus pneumoniae</i> (n = 1) <i>Gemella hemolysans</i> (n = 1)
Bacteremia	13 (0.6/1.0)	5 (1.2/1.8)	8 (0.5/0.8)	<i>E coli</i> (n = 8) <i>S pneumoniae</i> (n = 1) <i>N meningitidis</i> (n = 1) <i>S agalactiae</i> (n = 1) <i>Staphylococcus aureus</i> (n = 1) <i>Proteus mirabilis</i> (n = 1)
No definite SBI				
Possible SBI	217	58	159	...
UTI	173	53	120	<i>E coli</i> (n = 159) <i>Klebsiella</i> (n = 6) <i>Enterococcus</i> (n = 7) <i>Citrobacter</i> (n = 1)
Pneumonia	44	5	39	...
No bacterial infection	1691	327	1364	...

Abbreviations: ellipses, data not applicable; IBI, invasive bacterial infection; SBI, severe bacterial infection; UTI, urinary tract infection.

<sup>a</sup> The second percentage listed is the percentage when the denominator included only those who had blood cultures performed (n = 1258 of all infants, n = 271 of infants aged 7 to 30 days, and n = 987 of infants aged 31 to 91 days).

<sup>b</sup> Urinary tract infection with bacteremia and bacterial meningitis occurring simultaneously are not included.

**Table 3. Clinical and Laboratory Predictors of Patients With Bacterial Infections<sup>a</sup>**

Predictor	Patients With Definite SBI (n = 139)			P Value <sup>b</sup>	Patients With IBI (n = 21)			P Value <sup>c</sup>
	Crude OR (95% CI)	P Value <sup>b</sup>	AOR (95% CI)		Crude OR (95% CI)	P Value <sup>c</sup>	AOR (95% CI)	
Age ≤30 d	1.7 (1.0-2.9)	.04	0.8 (0.4-1.5)	.50	3.0 (1.3-7.5)	.01	0.6 (0.2-1.5)	.20
Male sex	1.5 (1.0-2.1)	.04	1.6 (0.9-2.8)	.10	1.6 (0.6-4.1)	.30	0.7 (0.2-2.1)	.50
Temperature ≥39°C in PED	2.0 (1.1-3.9)	.03	0.7 (0.4-1.2)	.20	3.2 (1.2-9.1)	.02	0.6 (0.2-1.7)	.40
Febrile family member	0.2 (0.08-0.5)	.001	0.3 (0.1-0.7)	.01	0.3 (0.06-1.3)	.10	0.4 (0.1-1.7)	.20
YOS score >10 <sup>d</sup>	1.2 (0.7-2.1)	.70	1.0 (0.5-1.8)	.10	3.9 (1.1-13.5)	.03	1.1 (0.4-3.1)	.80
PCT ≥0.3 ng/mL	10.0 (5.7-17.3)	<.001	4.5 (2.3-8.8)	<.001	31.0 (7.2-134)	<.001	40.3 (5.0-332)	.001
CRP ≥20 mg/L	10.0 (5.7-17.8)	<.001	4.2 (2.1-8.4)	<.001	8.9 (3.2-24.8)	<.001	3.3 (1.1-10.8)	.05
WBCs ≥10 000/μL	3.2 (1.9-5.5)	<.001	1.1 (0.5-2.3)	.80	1.2 (0.5-3.0)	.40	0.5 (0.1-1.7)	.20
ANCs ≥5000/μL	4.7 (2.8-8.0)	<.001	1.5 (0.7-3.1)	.30	2.4 (1.0-5.9)	.06	0.9 (0.3-3.2)	.90

Abbreviations: ANCs, absolute neutrophil cells; AOR, adjusted odds ratio; CRP, C-reactive protein; IBI, invasive bacterial infection; OR, odds ratio; PCT, procalcitonin; PED, pediatric emergency department; SBI, serious bacterial infection; WBCs, white blood cells; YOS, Yale Observation Scale.

SI conversion factors: To convert CRP to nanomoles per liter, multiply by 9.524; to convert WBCs to ×10<sup>9</sup>/L, multiply by 0.001; to convert ANCs to ×10<sup>9</sup>/L, multiply by 0.001.

<sup>a</sup> Cutoff points of laboratory tests were calculated as the maximum

(sensitivity + specificity - 1) using receiver operating characteristic curve analysis. Only those with blood cultures are included (n = 1258).

<sup>b</sup> P value of the comparison between patients with definite SBI and without definite SBI (including possible SBI).

<sup>c</sup> P value of the comparison between patients with IBI and without definite SBI (including possible SBI).

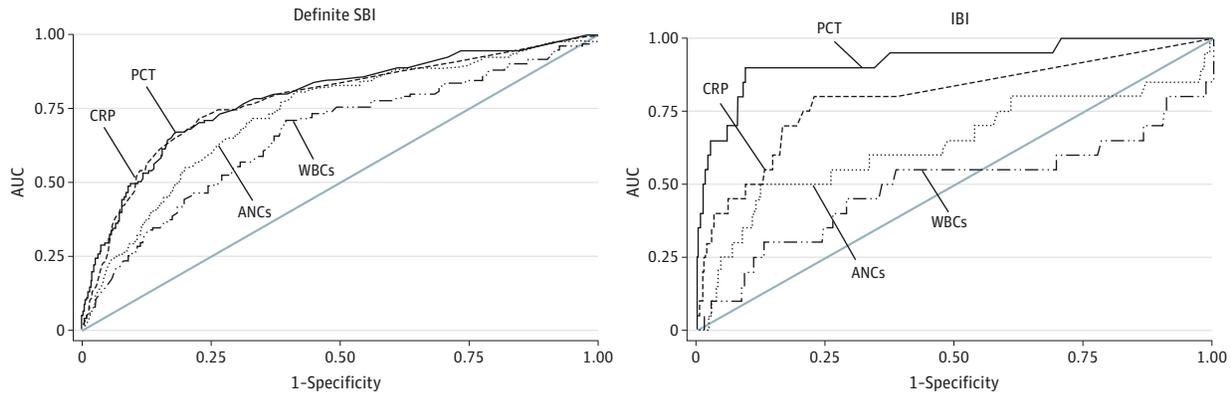
<sup>d</sup> A YOS score greater than 10 denotes a high risk of SBI.

ng/mL for PCT, 20 mg/L for CRP (to convert to nanomoles per liter, multiply by 9.524), 10 000/μL for WBC count (to convert to ×10<sup>9</sup>/L, multiply by 0.001), and 5000/μL for ANC count (to convert to ×10<sup>9</sup>/L, multiply by 0.001). In the multivariable analysis, a PCT level at the 0.3-ng/mL cutoff point was the only independent risk factor for IBI.

**Test Performances**

The AUC for the PCT assay for the identification of IBI was significantly better than those for CRP, ANC, and WBC measurements. The AUC for the identification of definite SBI for the PCT assay did not differ significantly from those for CRP and ANC measurements and was better than that for WBC mea-

**Figure. Area Under the Curve (AUC) for the Receiver Operating Characteristic Curves for Biomarkers to Detect Definite Serious Bacterial Infections (SBIs) and Invasive Bacterial Infections (IBIs)**



Biomarker	Definite SBI (n = 139)		IBI (n = 21)	
	AUC (95% CI)	P Value*	AUC (95% CI)	P Value*
PCT, ng/mL	0.81 (0.75-0.86)		0.91 (0.83-0.99)	
CRP, mg/L	0.80 (0.75-0.85)	.70	0.77 (0.65-0.89)	.002
ANCs, / $\mu$ L	0.73 (0.66-0.79)	.08	0.61 (0.45-0.77)	.004
WBCs, / $\mu$ L	0.66 (0.58-0.73)	<.001	0.48 (0.31-0.66)	<.001

\*Compared with PCT.

ANCs indicates absolute neutrophil cells; CRP, C-reactive protein; PCT, procalcitonin; and WBCs, white blood cells.

**Table 4. Sensitivity, Specificity, and Likelihood Ratios (95% CIs) for Definite SBI and IBI at Various Thresholds**

Biomarkers	Sensitivity	Specificity	Positive Likelihood Ratio	Negative Likelihood Ratio
<b>Definite SBI</b>				
PCT $\geq$ 0.3 ng/mL	74 (62-84)	78 (75-80)	3.3 (2.8-3.9)	0.3 (0.2-0.5)
PCT $\geq$ 0.5 ng/mL	60 (48-72)	85 (83-87)	3.9 (3.1-5.0)	0.5 (0.4-0.6)
PCT $\geq$ 2.0 ng/mL	36 (25-48)	94 (92-95)	5.7 (3.9-8.4)	0.7 (0.6-0.8)
CRP $\geq$ 20 mg/L	77 (66-86)	75 (72-77)	3.1 (2.6-3.6)	0.3 (0.2-0.5)
CRP $\geq$ 40 mg/L	59 (46-70)	86 (84-88)	4.2 (3.7-6.3)	0.5 (0.4-0.6)
<b>IBI</b>				
PCT $\geq$ 0.3 ng/mL	90 (68-99)	78 (75-80)	4.0 (3.3-4.8)	0.1 (0.03-0.4)
PCT $\geq$ 0.5 ng/mL	85 (62-97)	85 (82-87)	5.6 (4.4-7.0)	0.2 (0.06-0.5)
PCT $\geq$ 2.0 ng/mL	60 (36-81)	94 (92-95)	9.6 (6.3-14.7)	0.4 (0.2-0.7)
CRP $\geq$ 20 mg/L	75 (51-91)	75 (72-77)	3.0 (2.3-3.9)	0.3 (0.2-0.7)
CRP $\geq$ 40 mg/L	45 (23-69)	86 (84-88)	3.2 (1.9-5.3)	0.6 (0.4-0.9)

Abbreviations: CRP, C-reactive protein; IBI, invasive bacterial infection; PCT, procalcitonin; SBI, serious bacterial infection.

SI conversion factors: To convert CRP to nanomoles per liter, multiply by 9.524.

urement (Figure). The AUC for the PCT assay and CRP measurement for the detection of definite SBIs did not differ significantly among patients with fever duration of less than 6 hours or those younger than 1 month. However, the AUC for the PCT assay was better than for CRP measurement in the detection of IBIs in both subgroups (eFigure 2 and eFigure 3 in the Supplement). Taking into account definite plus possible SBIs, the ROC curve had an AUC for PCT and CRP of 0.81 (95% CI, 0.78-0.84) and 0.83 (95% CI, 0.80-0.86;  $P = .06$ ), respectively (eFigure 4 in the Supplement). The performances of the PCT assay and CRP measurement at selected and standard thresholds are summarized in Table 4. Of the 21 patients diagnosed as having IBIs, 5 had a CRP level less than 20 mg/L, and only 1 had a PCT level less than 0.3 ng/mL (eTable in the Supplement).

## Discussion

We report the results of a large prospective study that indicate that the PCT assay has better test characteristics compared with CRP, ANC, and WBC measurements for diagnosing IBIs in febrile infants aged 7 to 91 days admitted to a pediatric emergency department. Considering the AUC and selected and standard cutoff values, the PCT assay has better test indexes than CRP measurement for identifying IBIs, whereas the PCT assay has similar diagnostic properties as CRP measurement for detecting definite SBI in this same population. However, urinalyses are reliable to rule out SBI, contrary to IBI, considering that the most common type of bacterial infection in this age group is UTI. Among infants 30 days or younger and

also those with fever with recent onset, our analysis led to the same conclusions.

Our results are consistent with studies<sup>26-28</sup> that included only infants younger than 3 months. The only such prospective study included 234 infants and reported an AUC curve for the PCT assay of 0.82 for definite SBI; this value was greater than those for ANC and WBC measurements but was not compared with that for CRP measurement.<sup>26</sup> The studies by Olaciregui et al<sup>27</sup> and Gomez et al<sup>28</sup> retrospectively included 1112 and 347 infants, respectively, and found better AUC curves for the PCT assay than for CRP measurement for identifying IBIs. Both reported similar discriminative capability of the PCT assay and CRP measurement to predict SBI in the whole population; this capability may be improved if only infants with fever of recent onset are considered.<sup>27,28</sup> However, these findings should be interpreted with caution. Olaciregui et al<sup>27</sup> indicated that the trend for improvement in the predictive value of PCT in infants with fever lasting for 12 hours or less was small. Gomez et al<sup>28</sup> included infants not only with fever lasting for less than 6 hours but also with normal urinalysis results. Although we cannot ensure that the onset of fever reported by parents is absolutely reliable, we assumed that parents of very young infants were very careful.

No marker can replace clinical judgment in cases of severely ill patients or patients with sepsis. In the multivariate analysis, clinical features were not independent predictive factors for IBI. It would be extremely valuable to find a marker with high diagnostic value to rule out this type of infection. Our findings provide further evidence that PCT is the best marker for this purpose and, in particular, when using a cutoff value of 0.3 ng/mL.

This threshold is lower than the 0.5 ng/mL value commonly used for PCT and provides the best diagnostic accuracy for bacterial infections overall. This finding is supported by a meta-analysis<sup>36</sup> of the same age group and outcome. Lowering the cutoff to 0.12 ng/mL as suggested by Maniaci et al<sup>26</sup> would have detected all IBIs in our sample, but the specificity would have been decreased to 26%. Increasing the cutoff to 0.5 ng/mL may lead to a lower negative likelihood ratio (likelihood ratio of 0.2), whereas a cutoff point of 0.3 ng/mL provided a useful negative likelihood ratio (likelihood ratio of 0.1) in our study.

Urinary tract infections were the most frequent SBI, accounting for 80% of all SBIs. Consistent with published findings, UTIs were found in 5.6% in the total sample by analysis of urine from catheterization<sup>3</sup> and in 14.1% by analysis of urine from catheterization and bag.<sup>28</sup> In cases in which PCT alone failed to identify a UTI, combination with rapid urine analysis, eg, urine dipstick tests, might help improve practice.<sup>29</sup> Urine dipsticks have been previously reported to have good diagnostic performance in this age group and in older infants, such that this approach may be adequate for screening for UTIs.<sup>37,38</sup> In addition, PCT is useful as a predictor of late renal scars and vesicoureteral reflux and may be useful for identifying infants who may benefit from a dimercaptosuccinic acid scan, thereby helping to avoid unnecessary cystourethrography.<sup>21,39</sup>

Bacteremia and bacterial meningitis were detected in 13 (1.0%) and 8 (0.6%) of 1258 infants from whom blood cultures were obtained, respectively. These results were close to those of 2 previous large series,<sup>3,4</sup> despite a lower frequency of bacteremia,<sup>5,26-28</sup> but cannot be extrapolated because blood culture and lumbar puncture were only obtained in 1258 (61.5%) and 1326 (64.8%) of 2047 included infants, respectively. Patients without blood culture were excluded from the analysis. Although lumbar puncture was not performed in all patients, especially discharged infants who received antibiotics, the favorable clinical course makes it improbable that bacterial meningitis was misdiagnosed. In addition, urine culture was not always performed in the case of a normal dipstick result. We considered that those patients are unlikely to have UTIs.<sup>37,38</sup>

Our study has other limitations. The treatment of the infants enrolled was at the discretion of the investigator, which may have introduced variability of care. These variations indicate, however, the clinical practice conditions. In addition, not all febrile infants younger than 3 months presenting at participating centers during the study period were enrolled for analysis. Nevertheless, the frequencies of SBI among these infants were not significantly different from those of the 2047 infants included in the analysis.

A higher UTI prevalence was reported for bag specimens than for catheterization specimens. Bag collection is known as a method that overestimates UTI diagnosis. Nevertheless, positive culture results from bag specimens are classified as possible UTIs and not as definite SBIs. We also did not consider pneumonia as a definite SBI. This bias did not, however, affect the results obtained for prediction of definite SBI and IBI. The performances of the PCT assay and CRP measurement are, however, slightly different between definite SBI and definite plus possible SBI identification. Catheterization is probably the best urine collection procedure, but bags are still widely used for urine collection from infants, and because viral or bacterial pneumonia can be indistinguishable, these findings have implications for current practice.

Our results suggest that it may be possible to improve clinical practice for the treatment of young febrile infants. Despite the rarity of IBIs, our sample size and primary outcome based on the diagnosis of IBI allowed us to assess the performance of the PCT assay in this population and to identify a threshold that would adequately distinguish infants at low risk for IBIs. Although our optimal PCT threshold is calculated in isolation and may be different in the multivariable model, one advantage of our results may be the potential to avoid lumbar puncture, particularly in patients older than 1 month with a PCT level less than 0.3 ng/mL. Although the PCT assay is probably the best biological predictor currently available to distinguish between IBI and viral infection,<sup>40</sup> false-negative or false-positive results are possible but rare.<sup>24</sup> Although it would be unwise to use the PCT assay alone, combined with careful analysis of the case history, physical examination, and appropriate tests, it provides important information for the detection of IBIs in this population.

## Conclusions

Our large prospective study reveals that PCT is the best marker for identifying bacteremia and bacterial meningitis in febrile infants 7 to 91 days old and that it is moderately useful for identifying infants with SBIs. However, urinalyses are reliable to de-

tect SBI, mainly represented by UTI in this age group, contrary to IBI. The performance of PCT testing should encourage the development of decision-making rules that incorporate PCT. Their effectiveness, cost, and the associated iatrogenic morbidity should be analyzed; these approaches should then be validated to determine how they should be combined to improve the management of febrile infants 7 to 91 days old.

### ARTICLE INFORMATION

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## Supplementary Online Content

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**eFigure 1.** Flow Diagram

**eFigure 2.** Receiver Operating Characteristic (ROC) Curves for Biomarkers to Detect Definite SBIs and IBIs Among Infants With Fever Duration of Less Than 6 Hours

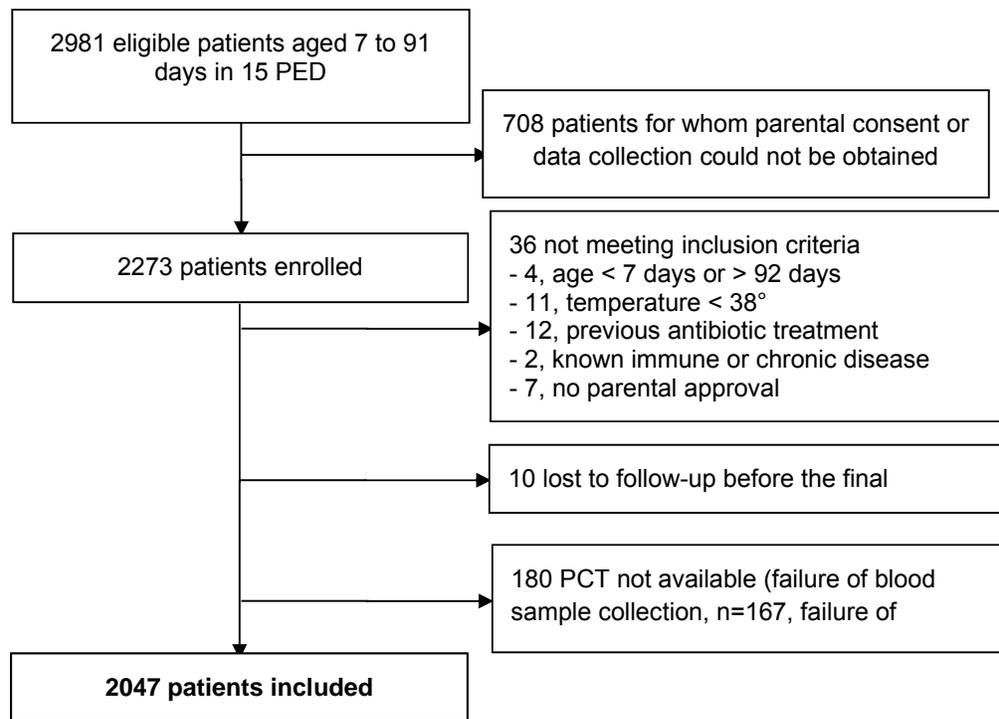
**eFigure 3.** Receiver Operating Characteristic (ROC) Curves for Biomarkers to Detect Definite SBIs and IBIs Among Infants Aged 7 to 30 Days

**eFigure 4.** Receiver Operating Characteristic (ROC) Curves for Biomarkers to Detect Definite and Possible SBIs

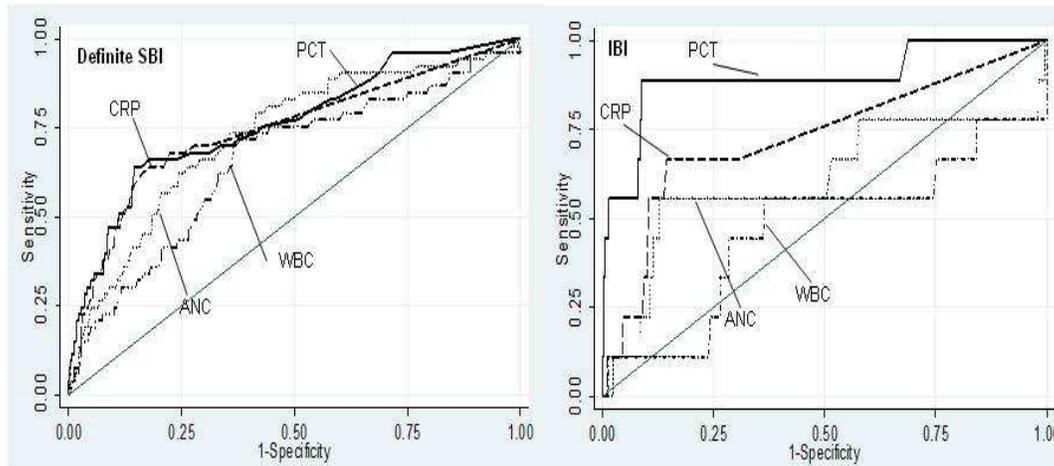
**eTable.** Cross-tabulation of Infant Counts Classified by the PCT Assay and CRP Measurement for Diagnosis of IBI and SBI

This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure 1. Flow Diagram



eFigure 2. Receiver Operating Characteristic (ROC) Curves for Biomarkers to Detect Definite SBIs and IBIs Among Infants With Fever Duration of Less Than 6 Hours

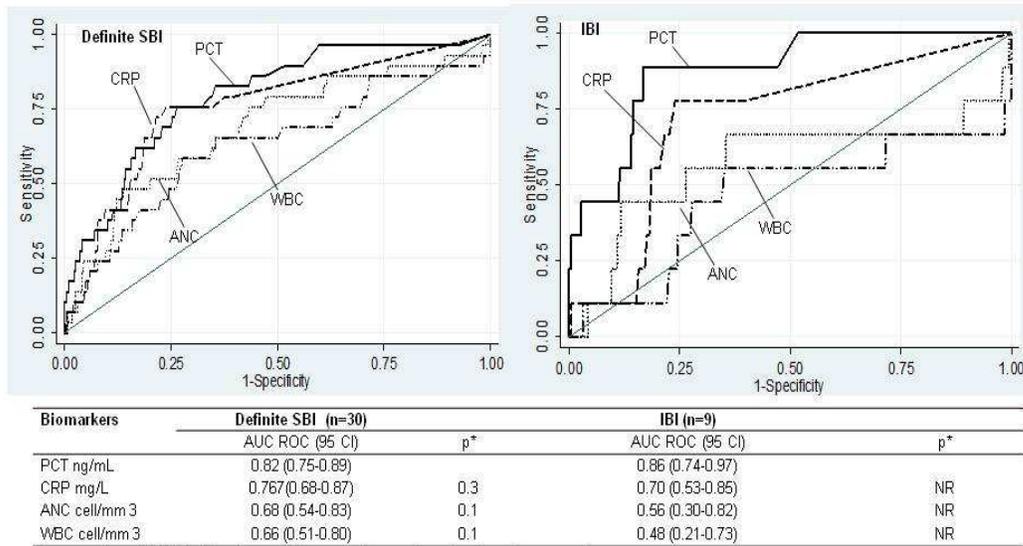


Biomarkers	Definite SBI (n=56)		IBI (n=10)	
	AUC ROC (95 CI)	p*	AUC ROC (95 CI)	p*
PCT ng/mL	0.77 (0.67-0.87)		0.88 (0.75-1.0)	
CRP mg/L	0.79 (0.71-0.88)	0.6	0.72 (0.55-0.88)	NR
ANC cell/mm <sup>3</sup>	0.70 (0.58-0.81)	0.5	0.61 (0.35-0.86)	NR
WBC cell/mm <sup>3</sup>	0.62 (0.50-0.74)	0.1	0.48 (0.25-0.70)	NR

\*compared to PCT, NR: Not Reported because the number of patients is too small

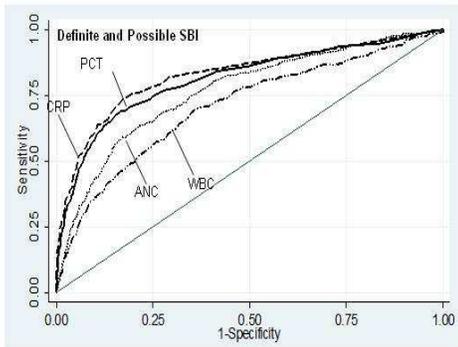
eFigure 2. Receiver operating characteristic (ROC) curves for biomarkers to detect definite SBIs and IBIs among infants with duration fever < 6 hours

eFigure 3. Receiver Operating Characteristic (ROC) Curves for Biomarkers to Detect Definite SBIs and IBIs Among Infants Aged 7 to 30 Days



eFigure 3. Receiver operating characteristic (ROC) curves for biomarkers to detect definite SBIs and IBIs among infants 7 to 30 days aged

eFigure 4. Receiver Operating Characteristic (ROC) Curves for Biomarkers to Detect Definite and Possible SBIs



Biomarkers	Definite and Possible SBI (n=356)	
	AUC ROC (95 CI)	p*
PCT ng/mL	0.81 (0.78-0.84)	
CRP mg/L	0.83 (0.80-0.86)	0.06
ANC cell/mm <sup>3</sup>	0.78 (0.74-0.81)	0.1
WBC cell/mm <sup>3</sup>	0.73 (0.69-0.76)	<0.001

\*compared to PCT

eFigure 4. Receiver operating characteristic (ROC) curves for biomarkers to detect definite and possible SBIs

**eTable. Cross-tabulation of Infant Counts Classified by the PCT Assay and CRP Measurement for Diagnosis of IBI and SBI**

Patients with IBI/SBI	PCT < 0.3 ng/mL	PCT ≥ 0.3 ng/mL	Total
CRP < 20 mg/L	1*/28	4/14	5/42
CRP ≥ 20 mg/L	0/17	16/80	16/97
Total	1/45	20/94	21/139

\*a 83 day-old patient with 4 hours fever duration and a group A *Streptococcus otitis media* who became spontaneously afebrile and was discharged before the blood culture result, positive for *Streptococcus pneumonia*, became available