Diagnostic Value of Procalcitonin in Well-Appearing Young Febrile Infants

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KEY WORDS
procalcitonin, fever, young infant, serious bacterial infection, invasive bacterial infection

ABBREVIATIONS
ANC—absolute neutrophil count
CI—confidence interval
CRP—C-reactive protein
CSF—cerebrospinal fluid
FWS—fever without source
IBI—invasive bacterial infection
LR—likelihood ratios
PCT—procalcitonin
PED—pediatric emergency department
SBI—serious bacterial infection
UD—urine dipstick
UTI—urinary tract infection
WBC—white blood cell

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BACKGROUND AND OBJECTIVE: Procalcitonin (PCT) has been introduced in many European protocols for the management of febrile children. Its value among young, well-appearing infants, however, is not completely defined. Our objective was to assess its performance in diagnosing serious bacterial infections and specifically invasive bacterial infections (IBIs) in well-appearing infants aged <3 months with fever without source (FWS).

METHODS: Well-appearing infants aged <3 months with FWS admitted to 7 European pediatric emergency departments were retrospectively included. IBI was defined as the isolation of a bacterial pathogen in blood or cerebrospinal fluid culture.

RESULTS: We included 1112 infants who had PCT measured and a blood culture performed. IBI was diagnosed in 23 cases (2.1%). In the multivariate analysis including clinical and laboratory data, PCT was the only independent risk factor for IBI (odds ratio 21.69; 95% confidence interval [CI] 7.81–59.28 for PCT ≥0.5 ng/mL). Positive likelihood ratios for PCT ≥2 ng/mL and C-reactive protein (CRP) >40 mg/L were 11.14 (95% CI 7.81–15.89) and 3.45 (95% CI 2.20–5.42), respectively. Negative likelihood ratios for PCT <0.5 ng/mL and CRP <20 mg/L were 0.25 (95% CI 0.12–0.55) and 0.41 (95% CI 0.22–0.76), respectively. Among patients with normal urine dipstick results and fever of recent onset, areas under the receiver operator characteristic curve for PCT and CRP were 0.819 and 0.563, respectively.

CONCLUSIONS: Among well-appearing young infants with FWS, PCT performs better than CRP in identifying patients with IBIs and seems to be the best marker for ruling out IBIs. Among patients with normal urine dipstick results and fever of recent onset, PCT remains the most accurate blood test. Pediatrics 2012;130:815–822.
The rate of serious bacterial infection (SBI) is higher among febrile infants <3 months of age than among older children, with a prevalence varying from 10% to 20%.1,2 As in older children, urinary tract infections (UTIs) account for the great majority of SBIs. However, young infants more often develop invasive bacterial infections (IBIs), that is, bacteremia, sepsis, and meningitis.3 Thus, these patients are managed more aggressively, and several laboratory tests are usually performed systematically in an attempt to identify patients at higher risk of SBI and especially IBI. Recent studies have shown that white blood cell (WBC) count has limited value in the diagnosis of bacteremia and other SBIs in this age group.4–6 In fact, WBC count has been omitted in recently developed scores for identifying children with fever without source (FWS) at higher risk of SBI.7,8 C-reactive protein (CRP) has proved more accurate in identifying febrile young infants with bacterial infections.9,10

Over the past decade, procalcitonin (PCT) has been introduced in many management protocols for the febrile child in Europe. PCT is a good marker to differentiate between viral and bacterial meningitis11,12 and also between lower UTI and pyelonephritis.13–15 In relation to the management of the child with FWS, some authors have concluded that it is a better marker than WBC count10 and, in some cases, even than CRP for identifying those patients with a SBI.16,17 The correlation with the invasiveness of the infection,16–19 and its more rapid kinetics make PCT a potentially ideal marker for febrile infants <3 months of age, who, in addition to having a higher rate of IBI, are most often brought to the pediatric emergency department (PED) after only a few hours of fever. Although several studies have assessed PCT as a marker of SBI, only 2 have selectively focused on infants <3 months of age,17,20 and none has specifically considered well-appearing febrile infants, for whom laboratory tests results are particularly useful to guide the subsequent management.

Our primary objective was to assess the value of PCT in diagnosing SBI and, in particular, IBI in well-appearing infants <3 months of age with FWS. The secondary objective was to evaluate the role of PCT as a marker of IBI in the subgroup of well-appearing infants with normal urine dipstick (UD) and early-onset fever.

METHODS

Study Design

We performed a retrospective study including well-appearing infants <3 months of age with FWS admitted to 5 Spanish and 2 Italian PEDs in whom PCT levels were measured and a blood culture was performed. The protocols for the management of infants <3 months of age with FWS in these PEDs are similar: UD testing, measurement of CRP, PCT levels, and WBC count and obtaining blood and urine cultures are recommended in all cases. A lumbar puncture is recommended on a case-by-case basis, according to the age of the infant, the general appearance and the blood tests results.

Patients were retrospectively included from December 31, 2010, backward to a maximum of 3 years, depending on when PCT testing was introduced in each hospital. Regardless of the date when PCT started to be used, the study period for each hospital was required to be a multiple of 12 months to avoid possible bias due to seasonal variations.

PCT was measured by using a quantitative immunochemiluminescence assay according to the instructions of the manufacturer (Roche Diagnostics, Mannheim, Germany).

Exclusion Criteria

1. Patients in whom the anamnesis and/or the physical examination performed on arrival in the PED allowed the origin of the fever to be identified.

2. Patients classified as not well appearing on arrival to the PED; patients initially classified as well appearing but whose clinical situation subsequently worsened were included.

3. Patients who were afebrile in the PED and had been judged to have fever at home without the use of a thermometer. Patients who were afebrile in the PED but in whom fever was confirmed by measurement of the infant’s temperature at home were included.

4. Patients in whom PCT was not measured or its value was not recorded in the patient’s medical record and those in whom a blood culture was not performed.

Nevertheless, data from patients with exclusion criteria 2 and 4 were also collected, to be compared with the study population.

Data Collection

The principal investigator of each hospital received by e-mail a Microsoft Access database specifying the data to collect for each patient. Patients included were assigned a 5-digit code. The completed database for each hospital was sent to the research coordinator.

The following data were recorded: demographics (age, gender), month when care was provided, medical history, time between when fever was first detected and when the infant was brought to hospital, temperature registered at home and at the PED, general appearance, results of any tests performed, treatment received, diagnosis, and site of care.
The following additional data related to the study period were also collected:

- Total number of patients admitted
- Number of infants <3 months of age with FWS admitted
- Number of infants excluded and the reasons.

This study was approved by the ethical committees of Cruces, Treviso, and Padova hospitals. To maintain patient confidentiality, the database received by the research coordinator did not include any data that would have allowed identification of patients. Because the data were extracted retrospectively, identities remaining anonymous, and no intervention was performed on patients, informed consent was not required.

**Definitions**

FWS was defined as axillary or rectal temperature at home or rectal temperature in the PED of ≥38°C, without catarrhal or other respiratory signs or symptoms or a diarrheal process, in patients who had a normal physical examination.

Well-appearing was defined by a normal pediatric assessment triangle in those departments in which these data are systematically recorded. For the other departments, infants were considered not to be well appearing if the findings of the physical examination documented in the patient medical record indicated any clinical suspicion of sepsis. Descriptors that led to exclusion included but were not limited to "poor/bad general appearance," "irritable," "cyanosis," "hypotonic," and "cutis marmorata."

Normal UD was negative for leukocyte esterase and nitrites.

Fever of recent onset was defined as fever detected ≤6 hours before the infant was brought to hospital.

SBI was defined as the isolation of a bacterial pathogen from the blood, cerebrospinal fluid (CSF), urine, or stools. Infants with a urine culture yielding mixed growth or growth of <50 000 cfu/mL of a single bacterial species and also a normal UD were considered possible cases of UTI, and, accordingly, as possible SBIs. The remaining patients, that is, those with a positive urine culture, and any with a positive blood or CSF culture were considered definite cases of SBI. Urine samples for culture were collected by bladder catheterization or suprapubic aspiration in the hospitals in Spain, and mainly using sterile infant collection bags changed every 30 minutes, as per local protocol, in the two hospitals in Italy. When bags were used, two different positive samples with a bacterial growth >100 000 CFU/mL were required for a definitive diagnosis of UTI.

IBI was defined as isolation of a bacterial pathogen from the blood or CSF. Positive blood and CSF cultures were those leading to the isolation of bacteria characterized as true pathogens including *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Enterococcus* spp. groups A and B *Streptococcus*, *Staphylococcus aureus* and *Salmonella* spp. Growth of *Staphylococcus epidermidis*, *Propionibacterium acnes*, *Streptococcus viridans*, and *Diphtheroids* from previously healthy immunocompetent infants (with no history of heart disease, ventriculoperitoneal shunts, indwelling catheters, or other prothetetic devices) were categorized as contaminants.

**Statistical Analysis**

Normally distributed data were expressed as mean ± SD; nonnormally distributed data were expressed as median and interquartile range; categorical variables were reported as percentages. For nonnormally distributed data, comparisons were performed by using Mann-Whitney U tests, and comparisons of normally distributed data were performed by using independent samples t tests. For categorical data, the χ² test was used. A P value <.05 was considered statistically significant.

Multivariate analysis using polychotomous logistic regression was performed to identify the independent risk factors for having an IBI.

The diagnostic performance of the different blood tests considered was compared by using receiver operating characteristic analysis. Positive and negative likelihood ratios (LRs) were calculated for a range of PCT and CRP cutoff points.

**RESULTS**

Five Spanish and 2 Italian PEDs participated in the study. According to the date on which PCT testing was introduced at each hospital, 3 of them contributed data on patients admitted during 1 year, another 3 contributed data for 2 years, and 1 contributed data for 3 years. Over the study period, 533 133 pediatric patients were admitted, including 1531 (0.28%) infants <3 months of age with FWS (Table 1). After applying the exclusion criteria (Fig 1), 1112 infants were finally included (Table 2).

Two hundred eighty-nine patients were diagnosed with a definite SBI (26%, Table 3) and 23 with an IBI (2.1%). All the IBIs were diagnosed by blood culture. *E. coli* was responsible for 81% of the UTIs and was the bacterial pathogen most frequently isolated in blood cultures (12/23). Among the excluded patients, prevalences of definite SBI and IBI were 35% (P < .05) and 18.9% (P < .05) for not well-appearing infants (n = 143) and 17.6% (P < .05) and 0.8% (NS) for well-appearing infants in whom PCT was not measured (n = 131). Previously identified risk factors for IBI were compared in patients with and without IBI (Table 4). Variables
found to be significantly associated with IBI were included in a multivariate logistic regression analysis. Cutoff points studied were PCT $\geq 0.5$ ng/mL, CRP $\geq 20$ mg/L, WBC count $\geq 15,000$/mm$^3$ and absolute neutrophil count (ANC) $\geq 10,000$/mm$^3$. Only PCT $\geq 0.5$ ng/mL was found to be an independent risk factor for IBI in the multivariate analysis (odds ratio 21.69; 95% confidence interval 7.93 – 59.28). Figure 2 A and B show the receiver operating characteristic curves for each laboratory marker for detecting definite SBI and IBI. Table 5 summarizes the LR obtained for some of the most commonly used cutoff points for CRP and PCT levels.

Among the 23 patients diagnosed with an IBI, 6 had a CRP $< 20$ mg/L (4 of them had a PCT $> 2$ ng/mL), and 4 had a PCT $< 0.5$ ng/mL (none with a CRP $> 40$ mg/L). In 1 case of occult bacteremia due to *Enterococcus faecalis*, there were no abnormal results in any of the laboratory markers (a 79-day-old girl with a 6-hour history of fever who did well).

As a secondary objective, a separate analysis was carried out on infants with fever of recent onset and a normal UD (n = 451; prevalence of definite SBI 9.3%; prevalence of IBI, 1.3%). Figure 3 A and B show the receiver operating characteristic curves for each laboratory marker for detecting definite SBI and IBI, showing that PCT level was the best marker for identifying patients with IBIs. Table 6 summarizes the LR obtained for the previously examined cutoff points for CRP and PCT levels. According to our results, a PCT level $< 0.5$ ng/mL reduces the posttest probability of IBI to 0.5% in our overall sample and to 0.4% in those infants with a normal UD and fever of recent onset. Similarly, a PCT level $> 2$ ng/mL increases the posttest probability of IBI to 19.3% and 24.1%, respectively.

**DISCUSSION**

When evaluating young, well-appearing infants with FWS, our results show that PCT is the best biomarker for ruling in an IBI and seems to perform also better than CRP for ruling out IBIs. Furthermore, among those patients with fever of recent onset and normal UD, PCT seems to be the best marker both to rule in and rule out IBIs. Because all the cases of IBI in our study were diagnosed by blood culture, these conclusions can be extrapolated to the identification of young febrile infants with bacteremia. For toxic or ill-appearing infants, the risk of SBI is high and the subsequent management clear, regardless of screening test results, and thus laboratory markers for risk stratification are important mainly in well-appearing infants. To the best of our knowledge, this study is the first to selectively evaluate the accuracy of biochemical markers in well-appearing infants $< 3$ months of age with FWS.
similar to those reported in other recent publications. 7, 10, 24 Our results show that, overall, PCT and CRP provided similar and moderately useful information to diagnose SBI in well-appearing infants with FWS. However, the most commonly diagnosed type of SBI was UTI, which can be more easily identified than other bacterial infections with urine test results. Thus, the real challenge in clinical practice is to identify well-appearing infants at higher risk of more invasive infections, such as bacteremia and meningitis. For these reasons, the main aim of this study was to assess the accuracy of laboratory markers in selectively predicting IBI. We found that PCT has great value for this purpose and is significantly more useful than CRP, especially for ruling in this type of infection.

As far as we are aware, this is also the first study analyzing the value of PCT in identifying bacterial infections among young febrile infants focused on well-appearing patients with normal UD and fever of recent onset, the most challenging group in clinical practice. Among this subset of patients, the performance of PCT as a predictor of IBI seems to be even higher, although as the sample size decreases, confidence intervals for LR become wider. Increases in PCT level occur more rapidly than increases in CRP level, 25 reaching a peak concentration 6 hours after the infectious trigger. Andreola et al reported that among children with a <8-hour history of fever, PCT seemed to be a poor value for identifying infants at low risk of SBI (sensitivity of 95.2%, negative predictive value of 96.1% and specificity of 25.5%). In comparison, in our series, a cutoff point of 0.5 ng/mL was found to be a poor value for identifying infants at low risk of SBI (negative LR 0.66) but of moderate value for ruling out IBIs (negative LR 0.25). Four of the 5 IBIs with a PCT <0.5 ng/mL had a PCT of 0.1 ng/mL, so reducing the cutoff point even down to 0.12 ng/mL would not substantially improve its performance and would dramatically increase the false-positive rate. On the other hand, a cutoff point of 2 ng/mL was a good threshold for identifying infants at high risk of SBI (positive LR 7.12) and even better for ruling in an IBI (positive LR 11.14).

CRP, Olaciregui et al17 reported similar predictive values for PCT and CRP for identifying SBI among young febrile infants, but with a trend toward greater diagnostic accuracy for PCT in predicting IBI and among those with a <12-hour history of fever. In their study, including 347 patients (258 with fever of recent onset), no separate analysis was carried out for well-appearing infants (4 cases of sepsis were included).

One of the most widely used cutoff points for PCT is 0.5 ng/mL. Sensitivity and specificity reported for this threshold range from 63% to 94% and from 68% to 87%, respectively, for identifying SBIs among young febrile infants. 7, 10, 17, 20 When assessing an infectious marker, we must know whether what we want is to diagnose any bacterial infections or specifically IBIs and whether we want to confirm or rule out diagnoses. Few authors have studied new cutoff values for these different purposes. Maniaci et al20 reported an optimal cutoff point of 0.12 ng/mL for identifying infants <90 days old at low risk of SBI (sensitivity of 95.2%, negative predictive value of 96.1% and specificity of 25.5%). In comparison, in our series, a cutoff point of 0.5 ng/mL was found to be a poor value for identifying infants at low risk of SBIs (negative LR 0.66) but of moderate value for ruling out IBIs (negative LR 0.25).
at higher risk of having an SBI, we
selected 40 mg/L as it was one of the
cutoff points obtained as useful when
the laboratory-score was created. 7,8
Notably, the best results for PCT were
obtained in the subgroup of well-
appearing infants brought to the PED
soon after detection of the fever and
had a negative UD.

Our study has several limitations. First,
its retrospective design may have re-
duced the number of patients included.

All febrile infants’ medical records
were reviewed to identify those with
FWS to ensure we did not miss any
patients. Furthermore, to ensure good
data quality, variables such as FWS and
appearance were defined a priori, and
detailed instructions on data collection
were provided. However, as is usual
in clinical practice, rates of adherence
to the management protocol did
not reach 100%. In particular, a blood
culture was not obtained in 145

FIGURE 2
Receiver operating characteristic (ROC) curves to detect definite (A) SBIs and (B) IBIs.

TABLE 5 Positive and Negative LRs for Ruling Out or Confirming SBIs and IBIs

<table>
<thead>
<tr>
<th>Infection biomarkers</th>
<th>Area Under the ROC Curve (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SBI</td>
</tr>
<tr>
<td>PCT</td>
<td>0.739 (0.702–0.776)</td>
</tr>
<tr>
<td>CRP</td>
<td>0.776 (0.741–0.811)</td>
</tr>
<tr>
<td>ANC</td>
<td>0.711 (0.674–0.748)</td>
</tr>
<tr>
<td>WBC</td>
<td>0.692 (0.655–0.729)</td>
</tr>
</tbody>
</table>

well-appearing patients. Although none
of them were diagnosed with an IBI in
a subsequent visit, these patients were
excluded from the analysis. Addition-
ally, PCT was not measured in 131 well-
appearing infants in whom a blood
culture was obtained. Although preva-
ience among these 131 patients
was lower than among patients in-
cluded in the study, differences in IBI
prevalence were not statistically sig-
ificant, and so their exclusion did not
affect conclusions regarding the accu-
cracy of PCT for IBI identi-

at definitely

TABLE 5 Positive and Negative LRs for Ruling Out or Confirming SBIs and IBIs

<table>
<thead>
<tr>
<th></th>
<th>Definite SBI</th>
<th>IB1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rule out</td>
<td>+LR</td>
<td>–LR</td>
</tr>
<tr>
<td>PCT (&lt;0.5 ng/mL)</td>
<td>5.70 (4.26–7.62)</td>
<td>0.66 (0.59–0.75)</td>
</tr>
<tr>
<td>CRP (≤20 mg/L)</td>
<td>4.20 (3.46–5.09)</td>
<td>0.47 (0.40–0.54)</td>
</tr>
<tr>
<td>Confirm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCT (≥2 ng/mL)</td>
<td>7.12 (4.52–11.21)</td>
<td>0.82 (0.75–0.88)</td>
</tr>
<tr>
<td>CRP (≥40 mg/mL)</td>
<td>7.39 (5.38–10.14)</td>
<td>0.63 (0.57–0.70)</td>
</tr>
</tbody>
</table>

Our study has several limitations. First,
its retrospective design may have re-
duced the number of patients included.
In infants without a lumbar puncture, we cannot rule this out with absolute certainty. Second, >90% of the urine cultures were collected by bladder catheterization in the Spanish hospitals, whereas samples were mainly obtained by using urine collection bags in the Italian hospitals. In these 2 hospitals, 2 positive urine cultures from different and consecutive urine samples were required for the diagnosis of UTI. Nevertheless, a higher UTI prevalence was reported in children enrolled in the Italian centers compared with the Spanish centers (30.8% vs 22.5%, \( P = .03 \)), suggesting a possible overestimation of UTI diagnoses. This bias does not, however, affect the results obtained for prediction of IBI. Finally, because dimercaptosuccinic acid scans were not routinely performed to distinguish pyelonephritis from lower UTI, the number of cases of febrile cystitis classified as an SBI is not known. Although this is likely to have affected the performance of laboratory markers for predicting SBI, it did not affect their accuracy for IBI identification.

We conclude that among young infants with FWS, PCT is a better marker than CRP for identifying patients with IBI and also seems to be the best marker for ruling out the presence of IBI. Among patients with normal UD and fever of recent onset, PCT remains the most accurate marker. The best cutoff point for PCT depends on whether the clinical focus is ruling in or ruling out IBI. We consider that these are useful findings that should be taken into account in clinical practice. Properly designed prospective studies are, however, needed to confirm our results.

### TABLE 6

<table>
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<th>Infection biomarkers</th>
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<tbody>
<tr>
<td><strong>Definite SBI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+LR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCT (&lt;0.5 ng/mL)</td>
<td>3.88 (2.07-7.25)</td>
<td>11.59 (7.10-18.90)</td>
</tr>
<tr>
<td>CRP (≤20 mg/L)</td>
<td>2.21 (1.20-4.06)</td>
<td>1.37 (0.23-8.36)</td>
</tr>
<tr>
<td>ANC (≤2 ng/mL)</td>
<td>0.91 (0.79-1.05)</td>
<td>0.52 (0.23-1.16)</td>
</tr>
<tr>
<td>WBC (≤40 mg/mL)</td>
<td>0.85 (0.73-1.00)</td>
<td>0.86 (0.84-1.19)</td>
</tr>
</tbody>
</table>

*From lower UTI, the number of cases of febrile cystitis classified as an SBI is not known. Although this is likely to have affected the performance of laboratory markers for predicting SBI, it did not affect their accuracy for IBI identification.*

*We conclude that among young infants with FWS, PCT is a better marker than CRP for identifying patients with IBI and also seems to be the best marker for ruling out the presence of IBI. Among patients with normal UD and fever of recent onset, PCT remains the most accurate marker. The best cutoff point for PCT depends on whether the clinical focus is ruling in or ruling out IBI. We consider that these are useful findings that should be taken into account in clinical practice. Properly designed prospective studies are, however, needed to confirm our results.*
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