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PROCALCITONIN TO DETECT INVASIVE BACTERIAL INFECTION IN NON–TOXIC-APPEARING INFANTS WITH FEVER WITHOUT APPARENT SOURCE IN THE EMERGENCY DEPARTMENT

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Abstract: The reliability of procalcitonin as a predictor of invasive infection in infants <36 months of age with fever and nontoxic appearance was assessed in 868 patients, 15 (1.7%) of whom had invasive infection. The area under the receiver operating characteristic curve for procalcitonin was 0.87 (optimum cutoff 0.9 ng/mL, sensitivity 86.7%, specificity 90.5%), whereas for C-reactive protein it was 0.79 (optimum cutoff 91 mg/L, sensitivity 33.3%, specificity 95.9%). In infants with fever of <8 hours duration, the area under the receiver operating characteristic curve was 0.97 for procalcitonin and 0.76 for C-reactive protein. Procalcitonin was a useful biomarker to predict invasive infection in non–toxic-appearing infants with fever without apparent focus, particularly in febrile episodes of <8 hours duration.

Key Words: bacterial infections/diagnosis, C-reactive protein, procalcitonin

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Fever is one of the most frequent reasons for pediatric emergency consultations and requires special attention in children between 1 and 36 months of age.[1] C-reactive protein (CRP) is an acute-phase reactant but lacks specificity and has limited value in the detection of serious bacterial infection in febrile children older than 3 months with a nontoxic appearance.[2] Procalcitonin (PCT) is a recent index of infection that can offer advantages compared with CRP.[3]

We examined the diagnostic performance of PCT in the pediatric emergency department for early detection of invasive bacterial infection (IBI) in febrile children with unrevealing physical examination, nontoxic appearance and absence of leukocyturia. The optimum cutoff for distinguishing febrile patients with IBI from those with fever of viral origin and/or self-limiting infection was also evaluated.

MATERIALS AND METHODS

This prospective, observational study was conducted at the pediatric emergency department of 7 acute-care teaching hospitals in Spain. Between March 2008 and September 2009, children who were 1–36 months of age with fever (rectal temperature) ≥38°C for infants <2 months old and ≥39°C for infants between 2 and 36 months of age, with nontoxic appearance, stable physiologic state according to the Pediatric Assessment Triangle[4] and urine reactive strip negative or positive not confirmed by urinary sediment were eligible, provided that blood samples were obtained for routine tests (complete blood count, CRP and culture). A positive reactive strip was defined as the presence of leukocytes and/or nitrites and positive urinary sediment when leukocytes or microorganisms on the Gram stain were detected. Excluded from the study were children treated with antibiotics before admission to the pediatric emergency department, known immunodeficiency and identification of the source of fever by history and/or physical examination or presence of an infiltrate diagnosed on the chest radiographs. Chest radiographs were performed only when ordered by the attending clinician according to laboratory findings (>20,000 leukocytes/mm^3). Informed consent was obtained from the parents or legal guardians. The study protocol was approved by the Ethics Committee of Hospital Sant Joan de Déu of Barcelona and Hospital de Cruces of Bilbao, Spain.

The battery of diagnostic tests given to infants younger than 2 months of age included white blood cell count (WBC) with differential, a determination of CRP and PCT and blood and urine culture (urine collection by transurethral bladder catheterization). Children between 2 and 36 months of age underwent the same diagnostic procedures when considered necessary by the pediatrician in charge to exclude IBI. A perineal bag was the routine method for urine collection in these patients. Positivity obtained by urinary sediment and/or reactive strip was confirmed by a sterile method (bladder catheterization) before the administration of antibiotics.[5]

PCT was measured by the B·R·A·H·M·S PCT sensitive Kryptor assay (BRAHMS GmbH, Hennigsdorf, Germany) and CRP by an immunoturbidimetric assay (Tina quant, Roche Diagnostics, Mannheim, Germany).

IBI included the following: a) meningitis, defined as a positive cerebrospinal fluid culture result with a pathogen microorganism; b) occult bacteremia as positive blood culture in non–toxic-appearing children with fever of unknown source; and c) sepsis, defined by the criteria of Levy et al,[6] which included documented infection and signs of inflammation, such as hemodynamic instability, altered tissue perfusion and signs of organ dysfunction. Infants with no evidence of clinical bacterial infection except for otitis media and negative cultures were included in the non-IBI group. Cultures yielding *Staphylococcus epidermidis*, *Propionibacterium acnes* and *Difteroides* spp. were considered contaminated. Possible IBI was considered in children with positive urine culture (>10,000 colony-forming units per field of a single microorganism in a urine sample collected by perineal bag) and initial negative urinary sediment/reactive strip. Lumbar puncture to investigate bacterial meningitis was done in the presence of suggestive laboratory findings (elevated CRP or leukocytosis) or according to the patient's age (children less than 2 months of age). A follow-up telephone call 28 days after discharge was made to assess the clinical outcome of patients.

TABLE 1. Final Diagnoses in Eight Hundred Sixty-eight Febrile Children Included in the Study

Cause of Fever	Number (%)
Invasive bacterial infection	15 (1.7)
Bacterial meningitis	8 (0.9)
Occult bacteremia	6 (0.7)
Sepsis	1 (0.1)
Noninvasive bacterial infection	832 (95.8)
Influenza respiratory infection	21 (2.4)
Enterovirus meningitis	19 (2.2)
Respiratory syncytial virus bronchiolitis	12 (1.4)
Parainfluenza respiratory infection	1 (0.1)
Upper respiratory tract infection	43 (4.9)
Gastroenteritis	30 (3.4)
Lymphocytic meningitis	20 (2.3)
Acute otitis media	20 (2.3)
Acute pharyngotonsillitis	17 (1.9)
Sudden exanthema	7 (0.8)
Acute stomatitis	2 (0.2)
Fever without source	631 (72.7)
Possible invasive bacterial infection	21 (2.4)
Urinary tract infection	21 (2.4)

The diagnostic properties of WBC, absolute neutrophil count (ANC), CRP and PCT for all children as well as for those with fever duration <8 hours were investigated by receiver operating characteristic analysis. The diagnostic reliability was calculated by the area under the receiver operating characteristic curve (AUC) and 95% confidence interval (CI). The sensitivity, specificity and predictive values for the optimal cutoff points were also assessed.

The statistical analysis was performed with Windows SPSS version 15.0 (SPSS, Chicago, IL), with the use of contingency tables, χ^2 test and Fisher exact test for categorical variables and the Student *t* test or the Mann-Whitney *U* test for continuous variables. Statistical significance was set at $P < 0.05$. Cutoff points were calculated using macros for SPSS (receiver operating characteristic analysis. Created 0.4.03.1998 last revised 10.03.2006; Bonillo A, Domenech JM, Granero R, Sesma M, e-mail: MacrosSPSS@metodo.uab.es).

RESULTS

The study population consisted of 868 children (480 boys, 388 girls), with a median age of 6.7 months (interquartile range 1.7–14.1); 325 (37.4%) children were younger than 3 months of age (median 42 days). The duration of fever was <24 hours in 535 (61.6%) patients and <8 hours in 275 (31.7%).

IBI diagnosed in 15 (1.7%) children included bacterial meningitis in 8 (53.3%), occult bacteremia in 6 (40%) and sepsis in 1 (6.7%). The incidence of IBI was similar in infants <3 months of age (1.8%, 6/325) and in those who were 3–36 months of age (1.7%, 9/543). There were 10 cases of positive blood cultures (*Streptococcus pneumoniae* in 3, *Neisseria meningitidis* in 2, *Haemophilus influenzae* in 2, *Escherichia coli* in 1, *Enterococcus faecalis* in 1 and *Streptococcus agalactiae* in 1) and 8 cases of positive cerebrospinal fluid culture (*N. meningitidis* in 5, *S. agalactiae* in 2 and *E. coli* in 1). Non-IBI was diagnosed in 832 children, and 21 children were diagnosed as possible IBI. Final diagnoses at follow-up are shown in Table 1.

The groups of IBI, non-IBI and possible IBI were comparable except for age and maximum temperature, which was lower in the possible IBI group than in the other 2 groups, and CRP and PTC values, which were significantly higher in the IBI group than in other 2 groups (Table, Supplemental Digital Content 1, http://links.lww.com/INF/B113). In patients with fever of <8 hours duration, there were only statistically significant differences in PCT values.

TABLE 2. Sensitivity, Specificity and Positive and Negative Likelihood Ratios of PCT, CRP, WBC and ANC for Predicting Invasive Bacterial Infection in Febrile Children With Unknown Focus

	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Positive Likelihood Ratio, %	Negative Likelihood Ratio, %
PCT, ng/mL				
≥0.5	86.7 (62.1–96.3)	83.3 (80.5–85.6)	5.15	0.16
≥0.9	86.7 (62.1–96.2)	90.5 (88.3–96.3)	9.13	0.15
≥1	73.3 (48.1–89.1)	91.6 (89.5–93.3)	8.72	0.29
≥2	60.0 (35.7–80.2)	95.3 (93.7–96.6)	12.80	0.42
PCR, mg/L				
≥20	80.0 (54.8–93.0)	66.1 (62.8–69.2)	2.36	0.30
≥40	46.7 (24.8–69.9)	82.8 (80.1–85.2)	2.72	0.64
≥80	33.3 (15.2–58.3)	94.8 (93.1–96.1)	6.45	0.70
≥91	33.3 (15.2–58.1)	96.9 (95.5–97.9)	8.16	0.70
WBC, mm^3				
≥15,000	40.0 (19.8–64.3)	75.2 (72.2–78.1)	1.62	0.80
≥24,400	40.0 (19.8–64.2)	97.1 (95.7–98.0)	13.87	0.62
ANC, mm^3				
≥10,000	33.3 (15.2–58.3)	85.7 (83.2–87.9)	2.33	0.78
≥15,374	33.3 (15.2–58.2)	97.0 (95.6–97.9)	11.09	0.69

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Sensitivity, specificity and positive and negative likelihood ratios for the different cutoff values of PCT, CRP, WBC and ANC are shown in Table 2. The AUC was 0.87 (95% CI: 0.85–0.89) for PCT, 0.79 (95% CI: 0.76–0.81) for CRP, 0.62 (95% CI: 0.59–0.66) for WBC and 0.62 (95% CI: 0.59–0.65) for ANC (Fig., Supplemental Digital Content 2, http://links.lww.com/INF/B114). The optimum cutoff for the detection of IBI was 0.9 ng/mL (sensitivity 86.7%, specificity 90.5%) for PCT, 91 mg/L (sensitivity 33.3%, specificity 95.9%) for CRP, 24,240 cells/mm^3 (sensitivity 40.0%, specificity 97.1%) for WBC and 15,374 cells/mm^3 (sensitivity 33.3%, specificity 97.0%) for ANC.

In the subgroup of children with duration of fever <8 hours, the AUC for the diagnosis of IBI was 0.97 (95% CI: 0.94–0.99) for PCT as compared with 0.76 (95% CI: 0.70–0.81) for CRP, 0.54 (95% CI: 0.47–0.60) for WBC and 0.67 (95% CI: 0.61–0.72) for ANC (Fig., Supplemental Digital Content 3, http://links.lww.com/INF/B115). The optimum cutoff to detect IBI was 0.9 ng/mL, with a sensitivity of 100% and a specificity of 93.9%.

DISCUSSION

In this study, either PCT or CRP had a higher diagnostic reliability than WBC and ANC. More importantly, in children with duration of fever <8 hours, PCT was the biomarker with the highest predictive value. The optimum threshold of PCT was 0.9 ng/mL, (86.7% sensitivity, 90.5% specificity) and the optimum cutoff for CRP 91 mg/L (33.3% sensitivity, 95.6% specificity). The AUC for all children was 0.87 (95% CI: 0.85–0.89) for PCT and 0.79 (95% CI: 0.76–0.81) for CRP, which confirms the superiority of PCT over CRP and agrees with previous reports.[7–10] In addition, the large number of children included in the study, higher than in previous studies,[10] allows us to establish narrower CIs. The present findings should be interpreted taking into account some limitations of the study. Despite a common protocol at the participating centers for the management of non–toxic-appearing febrile infants without apparent focus, a selection bias may be possible because the protocol may not have been strictly applied, particularly in children older than 2 months of age in whom decision to perform complementary tests relied on the criteria of the attending physician. On the other hand, it is possible that some of the children without antibiotic therapy followed for 28 days may have had asymptomatic bacteremia with spontaneous resolution. Although the provider's decision regarding blood sampling and indication of diagnostic procedures was a cause for excluding children from eligibility, it is unknown whether this group might behave differently than the rest.

In conclusion, PCT was the most useful biomarker to predict IBI in non–toxic-appearing children <3 years of age with fever without apparent focus and absence of leukocytes in urine. The PCT test was even more valuable in infants with evolution of fever <8 hours, in which a cutoff of 0.9 ng/mL was associated with 100% sensitivity and 93.9% specificity.

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COMMENTARY: PROCALCITONIN TO DETECT INVASIVE BACTERIAL INFECTION IN FEBRILE INFANTS

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Fever is commonly a cause of presentation to the emergency department in children less than 3 years of age, and a substantial number of them present no focus of infection despite a thorough history and clinical examination. In this setting, distinction between self-limiting viral infection and severe bacterial infection remains a challenge even for experienced pediatricians. Recently, a panel of