Procalcitonin in pediatric emergency departments for the early diagnosis of invasive bacterial infections in febrile infants: results of a multicenter study and utility of a rapid qualitative test for this marker

ANNA FERNÁNDEZ LÓPEZ, MD, C. LUACES CUBELLS, MD, J. J. GARCÍA GARCÍA, MD, J. FERNÁNDEZ POU, MD
AND THE SPANISH SOCIETY OF PEDIATRIC EMERGENCIES

Background. Procalcitonin (PCT) is a potentially useful marker in pediatric Emergency Departments (ED). The basic objectives of this study were to assess the diagnostic performance of PCT for distinguishing between viral and bacterial infections and for the early detection of invasive bacterial infections in febrile children between 1 and 36 months old comparing it with C-reactive protein (CRP) and to evaluate the utility of a qualitative rapid test for PCT in ED.

Methods. Prospective, observational and multicenter study that included 445 children who were treated for fever in pediatric ED. Quantitative and qualitative plasma values of PCT and CRP were correlated with the final diagnosis. To obtain the qualitative level of PCT the BRAHMS PCT-Q rapid test was used.

Results. Mean PCT and CRP values in viral infections were 0.26 ng/ml and 15.5 mg/l, respectively. The area under the curve obtained for PCT in distinguishing between viral and bacterial infections was 0.82 (sensitivity, 65.5%; specificity, 94.3%; optimum cutoff, 0.53 ng/ml), whereas for CRP it was 0.78 (sensitivity, 63.5%; specificity, 84.2%; optimum cutoff, 27.5 mg/l). PCT and CRP values in invasive infections (PCT, 24.3 ng/ml; CRP 96.5 mg/l) were significantly higher than those for noninvasive infections (PCT, 0.32 ng/ml; CRP, 23.4 mg/l). The area under the curve for PCT was 0.95 (sensitivity, 91.3%; specificity, 93.5%; optimum cutoff, 0.59 ng/ml), significantly higher ($P < 0.001$) than that obtained for CRP (0.81). The optimum cutoff value for CRP was >27.5 mg/l with sensitivity and specificity of 78 and 75%, respectively. In infants in whom the evolution of fever was <12 h ($n = 104$), the diagnostic performance of PCT was also greater than that of CRP (area under the curve, 0.93 for PCT and 0.69 for CRP; $P < 0.001$). A good correlation between the quantitative values for PCT and the PCT-Q test was obtained in 87% of cases (kappa index, 0.8). The sensitivity of the PCT-Q test (cutoff >0.5 ng/ml) for detecting invasive infections and differentiating them from noninvasive infections was 90.6%, with a specificity of 83.6%.

Conclusions. PCT offers better specificity than CRP for differentiating between the viral and bacterial etiology of the fever with similar sensitivity. PCT offers better sensibility and specificity than CRP to differentiate between invasive and noninvasive infection. PCT is confirmed as an excellent marker in detecting invasive infections in ED and can even make early detection possible of invasive infections if the evolution of the fever is <12 h. The PCT-Q test has a good correlation with the quantitative values of the marker.

INTRODUCTION

Fever is one of the most frequent reasons for pediatric emergency consultations and requires special attention in the child between 1 and 36 months of age. In this group the source of the febrile syndrome is often unidentified, and it is not always possible to differentiate between invasive and noninvasive bacterial infections with information provided by the medical history and physical examination. Pediatric Emergency Departments (ED) are faced with a need to provide early diagnosis of these potentially severe or invasive infections in daily clinical practice. This diagnosis is often difficult and requires research for new biochemical markers that can be useful in the differential diagnosis

of fever without source in infants and that can make possible an early diagnosis on which the child's vital and functional prognosis will depend.

Up to now, together with the past medical history, physical examination and blood analysis data (blood count and differential leukocyte count), the value of C-reactive protein (CRP) has been used as an acute phase reactor and marker of bacterial infection. CRP, used routinely by many teams, is a good marker but lacks specificity for differentiating between viral and bacterial infections. Used alone CRP determination results in the overprescription of antibiotics.[1, 2] CRP levels can be elevated in minor or viral infections and do not always enable confirmation of the severity of an infection, especially in the first 12 h of the process. Procalcitonin (PCT), the prohormone of calcitonin, was described as a new and innovative parameter of infection in 1993.[3] Serum levels are very low in healthy individuals (<0.5 ng/ml) and in severe infections can reach up to 1000 ng/ml without changes in serum calcitonin levels.[4] Assicot et al.[4] investigated its biosynthesis, molecular structure and amino acid sequence; and studies by Becker et al.[5] and Meisner et al.[6] have related it to other proinflammatory cytokines (interleukin-6 and tumor necrosis factor-alpha). Rapid induction starting 3 h after the injection of endotoxin in the bloodstream of healthy individuals has been demonstrated, with a peak at 6 h and a half-life of 25 to 30 h.[7, 8] The same authors demonstrated that there was no increase in CRP levels 6 h after the injection of endotoxin and that the drop in CRP concentrations was more delayed than that of PCT in these patients.[7] Because of its shorter half-life and the fact that elevated concentrations are achieved earlier than with CRP, PCT can offer advantages compared with CRP in the differential diagnosis of febrile syndrome in children. The primary objective of this study was to assess the diagnostic performance of this parameter in pediatric ED for the early detection of invasive bacterial infections in febrile children, comparing it with CRP.

PATIENTS AND METHODS

Study design. To conduct the study, a working group of the Spanish Society for Pediatric Emergencies was set up for the study of procalcitonin in emergency departments. The group was made up of nine hospitals: Hospital Sant Joan de Déu, Barcelona; Hospital de Cruces, Vizcaya; Hospital Central de Asturias, Oviedo; Hospital Gregorio Marañón, Madrid; Hospital Niño Jesús, Madrid; Hospital Vall d'Hebró, Barcelona; Hospital La Fe, Valencia; Hospital La Paz, Madrid; Hospital 9 Octubre, Valencia).

This was a prospective, observational and multicenter study conducted in the pediatric ED of the participating hospitals between April 2000 and March 2001. The basic objectives of the study were: to evaluate the utility of PCT in distinguishing between viral and bacterial infections in febrile children in the ED, comparing PCT with CRP and the rest of the parameters used up to now (total leukocyte and total neutrophil count); to determine the diagnostic performance of PCT and CRP in detecting invasive infections and differentiating them from noninvasive infections; to compare both markers in the group of infants with evolution of fever <12 h; and to assess the utility of the BRAHMS PCT-Q semiquantitative rapid test in the febrile child.

The study included children between 1 and 36 months of age treated for fever in pediatric ED and who were required to undergo blood analysis to rule out the possibility of bacterial infection. These children also required hospital admission. Blood samples were obtained for routine tests (complete blood count, CRP and culture), and for each patient included in this study a serum sample was frozen for later determination of the procalcitonin level. Fever was defined as the presence of an axillary temperature ≥38°C. The temperature reading was taken in the emergency room with a mercury thermometer for at least 3 min. The following were considered as exclusion criteria for potential study subjects: (1) antibiotic treatment in the 48 h before admission to the hospital; (2) vaccination in the days before the study, which may have caused the febrile syndrome; (3) surgery performed in the 7 days before inclusion in the study; (4) any chronic pathology that could alter CRP values (rheumatic disease, intestinal inflammatory disease or other causes); and (5) a history of prior urinary infection, pathology involving malformation of the kidney or of the urinary tract and vesicoureteral reflux.

Study groups. The patients were distributed in four groups corresponding to viral infections (Group 1), localized bacterial infections (Group 2), invasive bacterial infections (Group 3) and control group (Group 4). Group 1 was composed of children with fever of viral etiology without evidence of bacterial superinfection and with negative bacterial cultures (blood, urine and cerebrospinal fluid culture if lumbar puncture was performed). Respiratory infections (caused by respiratory syncytial virus, adenovirus and parainfluenza virus) were diagnosed by means of direct immunofluorescence in nasopharyngeal secretions, and serologic techniques were used to confirm the etiology of Epstein-Barr and herpes type 6 viruses. The detection of herpes simplex virus in cerebrospinal fluid was by polymerase chain reaction, and enterovirus meningitis was demonstrated by culture. Immunochromatographic tests in feces confirmed the etiology of enteritis caused by rotavirus and adenovirus. The localized infections group included bacterial tonsillitis infections (demonstrated by culture or rapid test), peritonsillar abscesses caused by *Streptococcus pyogenes* with neg-

ative blood culture, acute otitis media infections verified by the Otorhinolaryngology Department, mastoiditis and/or otoantritis without osteitis (diagnosed by computerized axial tomography), bacterial acute gastroenteritis infections without systemic involvement in children >3 months of age and lower urinary tract infections (>50 000 colonies of a single microorganism in a urine sample obtained by bladder probe). The following were considered as potentially invasive or severe bacterial diseases: meningitis infections confirmed by a positive culture of cerebrospinal fluid; sepsis confirmed by microbiologic analysis; bone or joint infections confirmed by local isolation or in blood culture of the microorganism; acute pyelonephritis infections; lobar pneumonia; bacterial enteritis in infants <3 months; amd and occult bacteremia. The differentiation between acute pyelonephritis and lower urinary tract infections was determined by renal gammagraphy with dimercaptosuccinic acid, which enabled the differential diagnosis to be made upon revealing a lesion in the renal parenchyma. The control group comprised children in the same age group who were given a blood test for reasons unrelated to infectious disease and who met none of the exclusion criteria.

Obtaining and processing the samples. The samples obtained in each center were frozen and processed later once the patients had been selected according to the diagnosis upon discharge and results of the additional examinations had been determined. In 176 cases PCT and PCT-Q values were determined from the blood tests requested by the pediatrician in the ED on making up the plasma or serum of this sampling without involving additional blood volume. In the rest an additional amount was extracted in the same sampling carried out in the emergency room, which in no case exceeded 0.5 ml of blood. No blood sample was taken solely for inclusion in the study. The parents or guardians were informed previously about the nature and objectives of the study and authorized inclusion in the study after signing a document of informed consent. Serum from samples taken for reasons unrelated to infectious disease in infants from the same age group were used to obtain PCT and CRP in the control cases.

PCT values were determined in duplicate by the LUMItest PCT immunoluminometric analysis (ATOM SA; Brahms Diagnostica), which uses two specific monoclonal antibodies and requires 20 μl of serum or plasma.[4] The CRP was obtained by the immunoturbidimetry procedure (Cobs INTEGRA; Roche). PCT and CRP values of ≤0.5 ng/ml and 15 mg/l, respectively, were considered normal.[2, 4] The semiquantitative rapid test used was the BRAHMS PCT-Q test, which required 250 μl of serum or plasma and uses a monoclonal mouse anti-catacalcin antibody conjugated with colloidal gold (tracer) and a polyclonal sheep anti-calcitonin antibody (solid phase). When the patient

sample is applied to the test strip, the tracer binds to the PCT in the sample, forming a labeled antigen-antibody complex. On passing the test band region, the labeled antigen-antibody complex binds to the anti-calcitonin antibody immobilized on the solid phase and forms a sandwich complex. At PCT concentrations of ≥0.5 ng/ml, this sandwich complex can be seen as a reddish band. The color intensity of the band is directly proportional to the PCT concentration of the sample. Unbound tracer diffuses into the control band zone, where it is bound by the antitracer antibody and produces an intensely colored red control band in 30 min. This control band is used to check the correct functioning of the test. The test is read with a reference card, which shows three clinically relevant PCT concentrations. The patient's PCT level may be classified into one of four semiquantitative categories by comparing test results with the card (<0.5 ng/ml, 0.5 to 2 ng/ml, 2 to 10 ng/ml and >10 ng/ml). Instruments are therefore not required.

Statistical analysis. The data were analyzed with the Access 2000 computer program, and the statistical analysis with Windows SPSS Version 9.0, with the use of the Mann-Whitney test to compare quantitative variables with a statistical significance of $P < 0.05$. The diagnostic properties of the test were investigated by receiver operating characteristic (ROC) analysis. This technique summarizes the validity coefficients of a test and provides an overall index of diagnostic accuracy (the area under the ROC curve) from a plot of sensitivity against the false positive rate (1 − specificity) for all possible cutoff scores. MedCalc Version 6.0 was the computer program for ROC analysis used in this study, which indicated the optimum cutoff for each parameter tested. The sensitivity, specificity and predictive values for the optimal cutoff points were then assessed.

RESULTS

The study included 445 children with a mean age of 12.9 months (SD 9.9) and a range of 1 to 36 months. The viral infections group ($n = 122$) was composed of bronchiolitis cases (caused by respiratory syncytial virus, adenovirus and parainfluenza virus) without bacterial superinfection, gastroenteritis caused by rotavirus, infections caused by the Epstein-Barr virus, meningoencephalitis caused by the herpes simplex virus and infections caused by the herpes zoster and herpes type 6 viruses (Table 1). All infants with viral infections had PCT values of <0.7 ng/ml (range, 0.08 to 0.6 ng/ml); CRP values fluctuated between <3 mg/l and 121.5 mg/l (Fig. 1). Moreover 22.5% of the viral infections had CRP values higher than 20 mg/l. The localized bacterial infection group ($n = 80$) included lower urinary tract infections, gastroenteritis in children >3 months of age and otorhinolaryngeal infections (Table 1). In this group the PCT and CRP mean values were

TABLE 1. Causes of infection in the 352 febrile infants included in this study

Cause of Fever	n
Group 1: viral infection	122
Respiratory syncytial virus bronchiolitis	52
Epstein-Barr virus infection	11
Rotavirus gastrointestinal infection	18
Enterovirus meningitis	18
Herpes simplex virus 6 infection	8
Parainfluenza respiratory infection	4
Adenovirus respiratory infection	4
Herpes simplex virus encephalitis	3
Herpes zoster virus infection (chickenpox)	3
Adenovirus gastrointestinal infection	1
Group 2: localized bacterial infections	80
Lower urinary tract infection (*Escherichia coli*)	43
Lower urinary tract infection (*Proteus mirabilis*)	1
Acute medial otitis	14
Acute tonsillitis (*Streptococcus pyogenes*)	7
Bacterial diarrhea (*Salmonella enteritidis*)	5
Bacterial diarrhea (*Campylobacter jejuni*)	5
Mastoiditis without osteitis	3
Peritonsillar abscess (*S. pyogenes*)	1
Bacterial diarrhea (*Yersinia enterocolitica*)	1
Group 3: invasive bacterial infection	150
Acute pyelonephritis (*E. coli*)	48
Lobar pneumonia	30
Sepsis/meningitis (*Neisseria meningitidis* B)	33
Sepsis/meningitis (*N. meningitidis* C)	17
Arthritis/osteomyelitis (*Staphylococcus aureus*)	4
Pleuropneumonia by *Streptococcus pneumoniae*	4
Mastoiditis with osteitis	3
Bacterial meningitis (*S. pneumoniae*)	3
Bacterial meningitis (*Haemophilus influenzae*)	1
Sepsis by *E. coli*	3
Occult bacteremia by *S. pneumoniae*	1
Occult bacteremia by *S. pyogenes*	1
Intestinal septicemia (*S. enteritidis*)	1
Ventriculitis (*Pseudomonas aeruginosa*)	1

FIG. 1. Individual PCT and CRP values in groups of infants. Values are mean ± SD. *LUTI,* lower urinary tract infection; *ORL,* otorhinolaryngeal infection.

0.38 mg/l (SD 0.52) and 35.2 ng/ml (SD 41.4), respectively. The invasive infection group included children with acute pyelonephritis caused by *Escherichia coli,* sepsis caused by *Neisseria meningitidis* and *E. coli,* meningitis caused by *Streptococcus pneumoniae,* arthritis caused by *Salmonella* spp., osteomyelitis caused by *Staphylococcus aureus* and lobar pneumonia, among other infections (Table 1). Group 4 was made up of 93 children of age comparable with those of the other three groups (mean, 16.76 months; SD 10.44). The PCT and CRP values in the control group were 0.15 ng/ml (SD 0.12) and 3 mg/l (SD 2.5), respectively, and were significantly lower than those in the other groups.

Table 2 shows the clinical data for children with viral and bacterial infections and compares the blood analysis findings. The figures for total leukocytes, total neutrophils and immature neutrophils were significantly higher in the bacterial infections group, although the diagnostic performance achieved for these parameters was low (Fig. 2). Mean PCT and CRP values for bacterial infections were higher than those for viral infections. The area under the curve for PCT and CRP was 0.82 (SD 0.02) and 0.78 (SD 0.02), respectively. The optimum cutoff value for PCT for distinguishing between viral and bacterial infections was
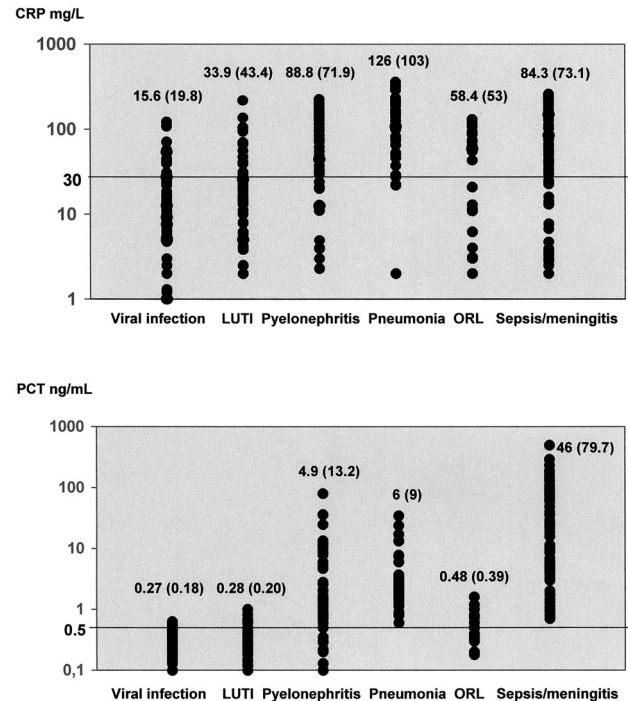
0.53 ng/ml (sensitivity, 65.5%; specificity, 94.3%). For CRP the optimum cutoff value in our sample was 27.5 mg/l (sensitivity, 63.5%; specificity, 84.2%). The PCT specificity was higher than that of CRP for distinguishing between viral and bacterial infections, but the diagnostic performance differences were not statistically significant (Fig. 2).

If we consider only Groups 2 (localized bacterial infection) and 3 (invasive bacterial infection), PCT obtained a better diagnostic performance for differentiating between both groups. The area under the curve for PCT was 0.93 (SD 0.01) and 0.74 (SD 0.03) for CRP ($P < 0.001$).

Table 3 compares the invasive infection group (Group 3) with the noninvasive infection group (Groups 1 + 2). Children with invasive bacterial infections presented decreased level of consciousness and worse general condition more often and were significantly older than the noninvasive infection group. The rest of the clinical parameters did not make it possible to distinguish between both groups at the time of the examination in the emergency room. The figures for total leukocytes, total neutrophils and immature neutrophils in blood analyses were significantly higher in the invasive bacterial infections group (Table 3), although its diagnostic performance was very low (Fig. 3). The area under the curve obtained was 0.65 (SD 0.03) for total leukocytes and 0.68 (SD 0.03) for total neutrophils with very low sensitivity (54 and 54.9%, respectively). Mean PCT and CRP values in invasive

TABLE 2. Description of the clinical data and analyses among infants with viral (Group 1) and bacterial (Groups 2 + 3) infections

	Viral Infection Group 1 (n = 122)	Bacterial Infection Groups 2 + 3 (n = 230)	P
Age (mo)	10.8 ± 9.4*	13 ± 10	0.04
Fever evolution (h)	36.2 ± 42.5	37.1 ± 43.7	NS
Maximum temperature (°C)	38.3 ± 3.5	38.9 ± 2.6	NS
Irritability (%)	30	29.6	NS
Refuses food (%)	40.5	36.7	NS
Altered general condition (%)	21.1	40.3	<0.001
Decreased level of consciousness (%)	6.6	11.7	NS
Seizures (%)	5	4	NS
Vomiting (%)	32.2	29.6	NS
Respiratory symptoms (%)	50.4	28.6	<0.001
Leukocytes/mm^3	12 424 ± 5926	18 528 ± 9082	<0.001
Total neutrophils/mm^3	6409 ± 4373	10 990 ± 7383	<0.001
Immature neutrophils/mm^3	240 ± 523	1444 ± 2347	<0.001
PCT (ng/ml)	0.26 ± 0.17	15.9 ± 47.7	<0.001
CRP (mg/l)	15.6 ± 19.8	75.2 ± 76.9	<0.001

* Mean ± SD.
NS, not significant.

	PCT	CRP
Area	0.82 (0.02)	0.78 (0.02)

Optimal cut-off PCT >0.53 ng/mL	
Sensitivity: 65.5 %	PPV: 95.5%
Specificity: 94.3 %	NPV: 59 %

Optimal cut-off CRP > 27.5 mg/L	
Sensitivity: 63.5 %	PPV: 88.5%
Specificity: 84.2 %	NPV: 54.9%

	Leukocytes	Total neutrophils
Area	0.65 (0.03)	0.69 (0.03)

Optimal cut-off leukocytes/mm³: 16500	
Sensitivity: 50.9 %	PPV: 81.8%
Specificity: 79.2 %	NPV: 45.6%

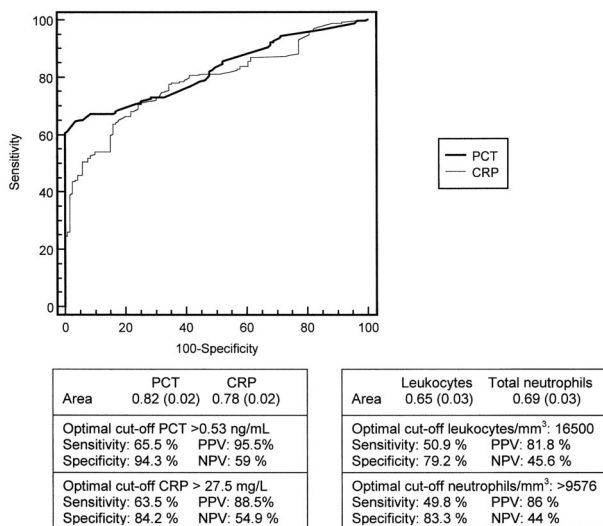| Optimal cut-off neutrophils/mm³: >9576	
Sensitivity: 49.8 %	PPV: 86 %
Specificity: 83.3 %	NPV: 44 %

FIG. 2. ROC curves for CRP and PCT for discrimination between viral (Group 1) and bacterial (Groups 2 + 3) infections. *PPV,* positive predictive value; *NPV,* negative predictive value. Comparison with the area under the curve and diagnostic performance for leukocytes and total neutrophils.

bacterial infections were statistically higher than those for noninvasive infections, but the diagnostic performance of PCT was considerably better (Fig. 3). The area under the curve for PCT was 0.95 (SD 0.01), significantly higher ($P < 0.001$) than that obtained for CRP (0.81; SD 0.02). In our study the optimum cutoff value for PCT in detecting invasive infections was >0.59 ng/ml (sensitivity, 91.3%; specificity, 93.5%); for CRP it was >27.5% mg/l (sensitivity, 78%; specificity, 75%). The positive and negative predictive values were also considerably higher for PCT (Fig. 3).

All the children with sepsis and meningitis ($n = 66$) had PCT >0.6 ng/ml even in the first analysis conducted in the ED (range, 0.7 to 500 ng/ml); in 17 cases the CRP values were <27.5 mg/l (range, 2 to 260 ng/l)

(Fig. 1). Patients with acute pyelonephritis showed mean PCT levels of 4.9 ng/ml (SD 13.2; range, 0.1 to 79.6 ng/ml), whereas the maximum PCT value in lower urinary tract infections was 1 ng/ml (mean, 0.28; SD 0.20). Conversely 9 patients with acute pyelonephritis had normal CRP (< 15 mg/l), and 5 of these patients had high PCT values, between 0.7 and 36 ng/ml. Eleven children with normal renal gammagraphy had CRP of >30 mg/l, but PCT values were <0.5 ng/ml in 9 (Fig. 1).

The mean evolution of fever time was 32.8 h (SD 38.63) with a range of 1 to 255 h. No statistically significant differences were found in fever evolution time between the groups compared (Tables 2 and 3) which could have affected the results obtained. In children with evolution of fever earlier than 12 h ($n = 104$), the mean PCT value in the invasive infections group was also significantly higher than in the noninvasive group. The statistical significance was lower for CRP, and no differences were found in the total leukocyte count (Table 4). In this group the area under the curve for PCT was 0.93 (SD 0.03), which was very significantly greater ($P < 0.001$) than that obtained for CRP (0.69; SD 0.05) (Fig. 4). In our cases the optimum cutoff value for PCT in detecting invasive bacterial infections in these patients was 0.69 ng/ml (sensitivity, 85.7%; specificity, 98.5%); for CRP this value was >19 mg/l (sensitivity, 61.3%; specificity, 80%). Positive and negative predictive values were also better for PCT (Fig. 4).

Regarding the PCT-Q test, an exact correlation was found with the quantitative PCT values in 85.2% of cases. A kappa index of 0.80 was obtained, which indicates good correlation between both tests. Considering a cutoff value of >0.5 ng/ml for the PCT-Q test, a sensitivity of 61.5% and specificity of 94% were obtained to differentiate between viral and bacterial

TABLE 3. Description of the clinical data and analyses among infants with invasive (Group 3) and noninvasive (Groups 1 + 2) infections

	Invasive Infection Group 3 ($n = 150$)	Noninvasive Infection Groups 1 + 2 ($n = 202$)	P
Age (mo)	14.7 ± 10.3*	10.5 ± 9.1	0.01
Fever evolution (h)	41.2 ± 47.2	33.3 ± 39.6	NS
Maximum temperature (°C)	39 ± 3.2	38.4 ± 2.7	NS
Irritability (%)	33.1	27.2	NS
Refuses food (%)	39	37.1	NS
Altered general condition (%)	55.1	17.5	<0.001
Decrease of level of consciousness (%)	16	3.8	0.008
Seizures (%)	2	5.9	NS
Vomiting (%)	30.5	28.7	NS
Respiratory symptoms (%)	32.5	38.6	NS
Leukocytes/mm³	18 668 ± 10 342	13 604 ± 5929	<0.001
Total neutrophils/mm³	12 304 ± 8281	7328 ± 4554	<0.001
Immature neutrophils/mm³	1936 ± 2720	337 ± 581	<0.001
PCT (ng/ml)	24.3 ± 57.4	0.32 ± 0.38	<0.001
CRP (mg/l)	96.5 ± 82.9	23.4 ± 31.7	<0.001

* Mean ± SD.
NS, not significant.
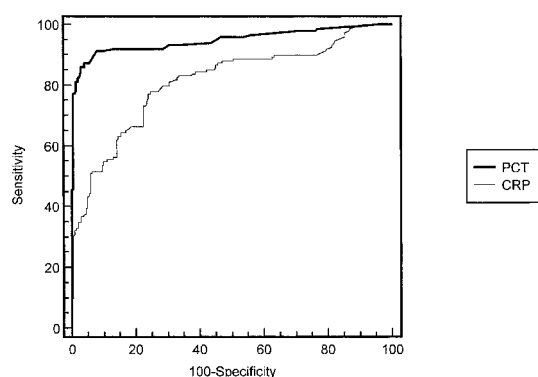
	PCT	CRP
Area	0.95 (0.01)	0.81 (0.02)

Optimal Cut-off PCT: >0.59 ng/mL
Sensitivity: 91.3 %   PPV: 90.8 %
Specificity: 93.5 %   NPV: 90.1 %

Optimal Cut-off CRP: >27.5 mg/L
Sensitivity: 78 %   PPV: 68.5 %
Specificity: 75 %   NPV: 80.8 %

	Leukocytes	Total neutrophils
Area	0.65 (0.03)	0.68 (0.03)

Optimal cut-off neutrophils/mm³:>9912
Sensitivity: 54.9 %   PPV: 67.8 %
Specificity: 79.1 %   NPV: 75.3 %

Optimal cut-off leukocytes/mm³:>17100
Sensitivity: 54 %   PPV: 69 %
Specificity: 76 %   NPV: 69.5 %

FIG. 3. ROC curves for CRP and PCT for differentiation between invasive (Group 3) and noninvasive (Groups 1 + 2) infections. *PPV,* positive predictive value; *NPV,* negative predictive value. Comparison with the area under the curve and diagnostic performance for leukocytes and total neutrophils.

infections (positive predictive value, 95%; negative predictive value, 57%). In our sample, for detection of invasive bacterial infections, the PCT-Q test achieved sensitivities and specificities of 90.6 and 83.6%, respectively (with positive and negative predictive values of 80.8 and 92.2%).

DISCUSSION

Since the publication in 1993 of elevated PCT values in adults with sepsis and infection, there have been numerous works describing the utility of this marker in adult patients with sepsis and septic shock,[9–11] cardiogenic shock,[10] trauma patients,[12, 13] postoperative[12] and transplant[15, 16] patients, cardiac surgery pa-

TABLE 4. Description of the data analysis in infants with fever evolution of <12 h

Fever Evolution <12 h	Invasive Infection Group 3 ($n = 42$)	Noninvasive Infection Groups 1 + 2 ($n = 62$)	P
Leukocytes/mm³	17 000 ± 9700*	14 118 ± 5227	NS
Total neutrophils/mm³	11 716 ± 7702	8414 ± 7045	0.04
Immature neutrophils/mm³	1228 ± 1673	323 ± 557	0.01
PCT (ng/ml)	25.3 ± 54.5	0.28 ± 0.16	<0.001
CRP (mg/l)	46.7 ± 51.8	16.7 ± 20.2	0.03

* Mean ± SD.

tients[10, 15, 17, 18] and many others. In 1995 findings of elevated PCT levels were reported in a 4-year-old liver transplant recipient with disseminated candidiasis.[19] Subsequently, it was evaluated in the neonatal period.[20–24] Chiesa and other authors[25–27] reviewed the possible applications of this marker in children. Gendrel et al.[28, 29] demonstrated high PCT levels in children with bacterial meningitis and compared PCT and CRP levels in children 2 months to 15 years of age.[1] In this study PCT levels with a cutoff value of 1 ng/ml provided the best compromise between sensitivity (83%) and specificity (93%) for distinguishing between bacterial and viral infections. Another study from the same working group conducted in 33 children 3 months to 13 years of age concluded that in viral infections, a cutoff value of 1.5 ng/ml is helpful in deciding whether to use antibiotic treatment in emergency situations.[26] Our work included only children between 1 and 36 months of age, and its results contrast with those obtained by these authors.

It is not often easy to decide in the ER if an infant with fever without source has a viral or bacterial infection. The total neutrophil and leukocyte count offers a very low sensitivity, not exceeding 50%, and a specificity of <85%. In our series the diagnostic performance of PCT was slightly better than that of CRP for
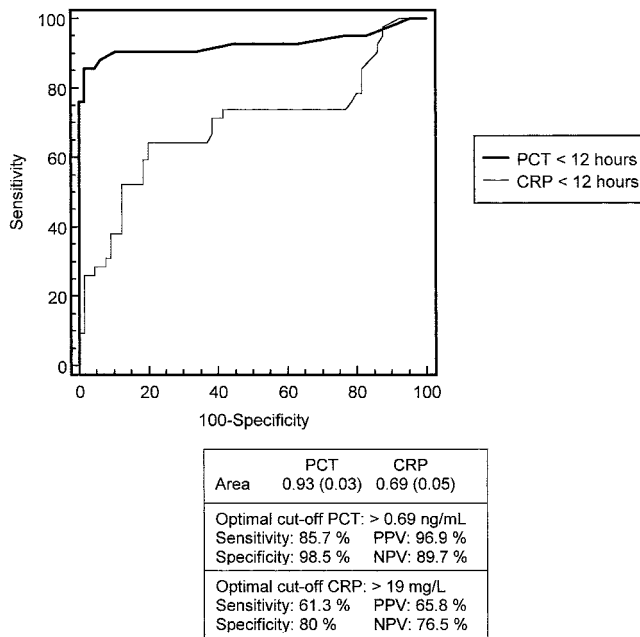
FIG. 4. ROC curves for CRP and PCT for differentiation between invasive (Group 3) and noninvasive (Groups 1 + 2) infections in infants with fever evolution of <12 h. *PPV,* positive predictive value; *NPV,* negative predictive value.

differentiating between the viral and bacterial etiology of the fever, although the differences are not statistically significant. The sensitivity achieved for both markers was ~70%, but determining PCT concentrations offers greater specificity (94.3% compared with 84.3% for CRP).

The risk of bacteremia is higher in children <36 months old compared with older children. For this reason in pediatric ED markers are needed for the early detection of a potentially severe or invasive infection in infants. In 1999 Hatherill et al.[30] evaluated the PCT level in children hospitalized in intensive care units and concluded that in critically ill patients PCT was a better marker than CRP and leukocyte count. This author obtained an optimum cutoff value of >2 ng/ml, which was put forward for differentiating severe bacterial infections with a sensitivity of 100% and a specificity of 62%. Before this multicenter work, a study was conducted in our hospital between 1998 and 2000, with 100 children not included in the present study. This study obtained an area under the curve of 0.95 (SD 0.03) for PCT and 0.81 (SD 0.05) for CRP (*P* < 0.001) for detecting invasive infections.[31] These results led to this multicenter study, which confirmed that PCT is an excellent marker for severe bacterial infections and that it has a diagnostic performance significantly greater than that of CRP and leukocyte count. A PCT value exceeding 0.59 ng/ml makes it possible to detect invasive infections in febrile children between 1 and 36 months of age.

In a recent study evaluating PCT in 64 children with confirmed meningococcal disease, it was concluded that PCT is a more sensitive and specific predictor of meningococcal disease than CRP and leukocyte count in children with fever and rash.[32] Among the 66 sepsis and meningitis cases included in our study, 15 (22.7%) had CRP values lower than the optimum cutoff for CRP (27.5 mg/l), because of its slower induction rate when confronted with bacterial stimulus. However, in our sepsis and meningitis group, the PCT value of >0.59 ng/ml provided a sensitivity of 100% and confirmed that PCT levels increased earlier than with CRP. These satisfactory results coincide with those published by Gendrel et al.,[1] who proposed a cutoff value of 2 ng/ml for distinguishing between invasive bacterial and localized bacterial or viral infections in children, with a sensitivity of 96% and a specificity of 87%. However, this study covers children between 1 month and 15 years of age with different performance and clinical implications in view of febrile symptoms in emergency rooms. The pneumonias and bacterial enteritis infections without age specification are considered localized infections. Moreover 23 urinary tract infections are included without differentiating between a lower urinary tract infection and acute pyelonephritis, which is a potentially severe or invasive infection in the child <3 years of age. Gendrel,[33] Benador et al.[34] and Gervaix et al.[35] demonstrated that serum PCT levels were increased significantly in children with febrile urinary tract infections when renal parenchymal involvement, assessed by dimercaptosuccinic acid scintigraphy, was present. Our study included only febrile children up to 36 months of age, differentiated between localized bacterial and invasive bacterial infections and confirmed the utility of PCT in pediatric ED and its application in children <3 years of age. Lacour et al.[36] studied 124 children between 7 days and 36 months of age with fever without source with good results but included only 28 severe bacterial infections.

None of the above mentioned studies considered the time of evolution of fever when the markers were determined. In our study PCT also provided better results than did CRP in children with evolution of fever <12 h and confirmed PCT to be a parameter marked by earlier concentration increases. In addition all patients with sepsis and meningitis had PCT levels higher than the cutoff value (0.6 ng/ml) in the first analysis in the ED, whereas in 17 cases the CRP values were <27.5 mg/l and had a slower subsequent elevation. These data support the research of Dandona et al.[7] and Petijean et al.,[8] which showed the more rapid increase of PCT concentrations compared with CRP after the injection of endotoxin in the bloodstream and confirmed the great utility of this parameter for the early detection of severe bacterial infections in febrile children.

The PCT-Q test has been validated in adults,[37] and

studies have been published on its utility in patients with severe acute pancreatitis and patients treated in intensive care units.[38, 39] The PCT-Q test allows a rapid, simple and semiquantitative measurement of plasma PCT to be made. Meisner et al. concluded that the validity of the test results and its ease of use are sufficient to support acute diagnostic decisions. In pediatrics there is only one reference to the semiquantitative rapid test for PCT, in children with urinary tract infections.[35] A positive PCT-Q value predicted renal involvement in 87 to 92% of children with febrile urinary tract infections, compared with 44 to 83% using CRP values.[35] Our results in 445 patients indicated that the PCT-Q test has a good correlation with the quantitative values of the marker in children up to 36 months of age. In this group the semiquantitative test offers better diagnostic performance than CRP, particularly in detecting invasive bacterial infections and differentiating them from viral and localized bacterial infections. In addition this test is easy to interpret, rapid and non-instrument-based. For these reasons it is highly useful in the pediatric ED, which may not have the quantitative determination procedures of the marker available. For the follow-up of PCT concentrations and routine daily measurements, the quantitative luminometric assay is preferable when available.

One of the limitations of our study is not to have been able to demonstrate the etiology of some of the conditions included in the sample (pneumonia, otitis and mastoiditis). However, for this reason only lobar pneumonias were included, confirmation of otitis was obtained from the Otorhinolaryngology Department and mastoiditis was confirmed by computerized axial tomography. We are also aware of the possibility of coinfection with another microorganism in some cases. We consider that this fact does not significantly affect the validity of our results and have tried to ensure that in the case of viral infections there were no signs of bacterial superinfection. All of the children in Group 1 had negative blood and urine cultures, showed no signs of bacterial superinfection on physical examination during admission and had fever that resolved without antibiotic treatment. Other studies have also demonstrated the low incidence of invasive bacterial infections in confirmed viral infections.[40] Finally some patients could not be included in the study because they could not be classified in any of the three groups given that the etiology of the process could not be recorded definitively.

In conclusion PCT offers better specificity than CRP for differentiating between the viral and bacterial etiology of the fever and offers better sensibility and specificity than CRP to differentiate between invasive and noninvasive infection. PCT is confirmed as an excellent marker of severe infection that is also applicable in febrile children between 1 and 36 months of age. In pediatric ED it makes it possible to detect invasive bacterial infections and to differentiate them from viral and localized bacterial infections with a diagnostic performance considerably superior to that of CRP, including providing early detection if the evolution of the fever is <12 h. Measuring PCT levels in these patients could make it possible to reduce the number of hospitalizations and hospital stays caused by febrile syndrome without source, because it could demonstrate that the child does not have an invasive bacterial infection and could therefore be monitored as an outpatient by the pediatrician. The PCT-Q test has a good correlation with the quantitative values of the marker, and it can be very useful at bedside.

Last we think that PCT alone is not an absolute criterion for deciding about the admission of the child or the administration of antibiotics, but it is the most useful criterion of those we now have assess this important issue.

APPENDIX

The Working Group of the Spanish Society of Pediatric Emergencies (SEUP) for the Study of Procalcitonin in Emergency Departments: Coordinators of the participating centers: A. Fernández López, M.D., C. Luaces Cubells, M.D., J. Pou Fernández, M.D., Hospital Sant Joan de Déu, Barcelona; J. Benito Fernández, M.D., Hospital de Cruces, Vizcaya; L. Fanjul Fernández, M.D., Hospital Central de Asturias, Oviedo; L. Sancho Pérez, M.D., Hospital Gregorio Marañón, J. Madrid; Casado Flores, M.D., Hospital Niño Jesús, Madrid; J. Ballabriga Vidaller, M.D., Hospital Vall d'Hebró, Barcelona; F. Asensi Botet, M.D., Hospital La Fe, Valencia; S. García García, M.D., Hospital La Paz, Madrid; I. Manrique Martínez, M.D., Hospital 9 Octubre, Valencia.

Collaborators: C. Valls Tolosa, M.D., J. Ortega Rodríguez, M.D., R. Garrido Romero, M.D., A. Mira Vallet, M.D., Hospital Sant Joan de Déu, Barcelona; M. A. Vázquez Ronco, M.D., M. Sasieta Altuna, M.D., Hospital de Cruces, Vizcaya; D. Pérez Tande, M.D., Hospital Central de Asturias, Oviedo; A. Carrillo Alvarez, M.D., Hospital Gregorio Marañón, Madrid; Anton J. Asensio, M.D., M. De la Torre Espi, M.D., Hospital Niño Jesús, Madrid; P. Magaña Morera, M.D., M. Sentís Vilalta, M.D., Hospital Vall d'Hebró, Barcelona; J. Aznar Lucena, M.D., A. Orti Martín, M.D., L. García Almiñana, M.D., Hospital La Fe, Valencia; P. Peña García, M.D., J. Martín Sánchez, M.D., Hospital La Paz, Madrid; V. Sebastián Barberán, M.D., Hospital 9 Octubre, Valencia.

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