

Low Serum Procalcitonin Level Accurately Predicts the Absence of Bacteremia in Adult Patients with Acute Fever

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The ability of measurement of serum procalcitonin (PCT) levels to differentiate bacteremic from nonbacteremic infectious episodes in patients hospitalized for community-acquired infections was assessed. Serum samples were obtained from adult inpatients with fever to determine the serum PCT level, C-reactive protein (CRP) level, and erythrocyte sedimentation rate (ESR). Of 165 patients, 22 (13%) had bacteremic episodes and 143 (87%) had nonbacteremic episodes. PCT levels, CRP levels, and ESRs were significantly higher in bacteremic patients than in nonbacteremic patients ($P < .001$, $.007$, and $.024$, respectively). The best cutoff value for PCT was 0.4 ng/mL, which was associated with a negative predictive value of 98.8%. Area under the receiver operating characteristic curve was 0.83 for PCT, which was significantly higher than that for CRP (0.68; $P < .0001$) and ESR (0.65; $P < .05$). A serum PCT level of <0.4 ng/mL accurately rules out the diagnosis of bacteremia. The use of PCT assessment could help physicians limit the number of blood cultures to be processed and the number of antibiotic prescriptions.

Fever is the most frequent symptom of infection. When patients present with fever, physicians must evaluate the risk of bacteremia, a condition that is associated with a mortality rate as high as 30% [1]. However, unless there is clinical evidence of severe sepsis or septic shock [2], clinical information obtained from physical examination cannot reliably identify patients with bacteremia. Results of blood cultures take 24–48 h to become available; in the meantime, physicians have to decide whether the patient needs antibiotic treatment. In doubtful cases, physicians would prefer to prescribe useless or inappropriate antibiotics than to risk missing an indication for antibiotic administration. However,

such a policy participates in the unnecessary increase in antibiotic prescription in industrialized countries through so-called empirical or preemptive prescription, which has well-known consequences—notably, the emergence of antibiotic-resistant bacteria [3]. If physicians were able to rely on an early indicator of bacteremia, they could restrict their antibiotic prescriptions to the right indications, they could start therapy earlier, and they could limit the number of blood samples to be obtained for culture. However, such an indicator has not been identified to date.

Serum procalcitonin (PCT), a 13-kDa 116-amino acid prohormone of calcitonin, the level of which can be easily and rapidly determined, was proposed as a potential marker of bacterial infection. High serum PCT levels were found in patients with sepsis [4] and in children with bacterial meningitis [5], as well as in volunteers who had received an injection of endotoxin [6]. PCT induction is rapid: PCT levels increase within 2–6 h after a stimulus. In an experiment that involved healthy volunteers, PCT levels started to increase 4 h

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after administration of endotoxin and returned to the normal range within 24 h [6]. PCT measurement requires 2 h to perform, so that results can be available within 3 h, which is a much shorter time than that required for performing blood cultures.

The aim of this study was to assess the ability of PCT levels to differentiate bacteremic from nonbacteremic infection in patients admitted to the hospital who are suspected of having community-acquired infection. We assessed whether PCT levels could be used to accurately rule out the diagnosis of bacteremia.

PATIENTS AND METHODS

The study was performed from July 2000 through February 2001 at the departments of Infectious Diseases and Internal Medicine at the University Medical Center of Besançon and at the Department of Infectious Diseases at the University Medical Center of Nancy, France. All adult patients who were consecutively admitted to the hospital for acute fever (temperature, $\geq 38^{\circ}\text{C}$) were enrolled in the study. Excluded from the study were patients aged <18 years, patients who presented with a hospital-acquired infection, and patients who transferred from any medical institution.

Blood samples were obtained from each patient to have fulfilled the aforementioned criteria for determination of serum PCT level, C-reactive protein (CRP) level, and erythrocyte sedimentation rate (ESR); these samples were obtained at the same time that the first blood samples were obtained for culture. Additional blood cultures could be performed later, if the physician wished it.

The PCT level was measured by use of an immunoluminometric assay (Brahms Diagnostica). The lower limit of detection of the assay was 0.08 ng/mL [7]. All PCT assays were processed at a single laboratory (Laboratoire d'Explorations Fonctionnelles Rénales et Métaboliques, University Medical Center of Nancy). PCT samples from Besançon were centrifuged and immediately frozen and stored at -20°C ; assays were performed in batches at the end of the study period. Blood cultures were processed according to each hospital's usual procedures. Bottles were incubated in aerobic and anaerobic conditions in an automatic analyzer (either BACTEC 9240 or Vital [Becton Dickinson Diagnostic Instrument Systems and bioMérieux, respectively]) until flagged positive or for as long as 5 days. CRP levels and ESRs were measured according to the routine methods used in each hospital.

For each patient, we recorded data regarding age, sex, medical history, and previous antimicrobial therapy. Laboratory data included PCT level, CRP level, and ESR. Microbiological information included results of blood cultures and cultures of any other relevant sample (urine, CSF, and peritoneal and pleural fluid). Whenever blood culture results were positive, the

number of blood cultures performed, the number of positive blood culture results, and the microorganism identified were recorded. The final diagnosis and the outcome were also recorded. All of these data were entered into a computerized database.

A bacteremic episode was defined by a positive blood culture that was associated with clinical symptoms of infection. If a single blood culture yielded coagulase-negative staphylococci, corynebacteria, or *Bacillus* species, the culture was considered to have been contaminated or to represent transient bacteremia but not a bacteremic episode. Patients with such a single positive blood culture and patients with no positive blood cultures were regarded as having had a nonbacteremic episode.

The 2 groups of patients (the bacteremic episode group and the nonbacteremic episode group) were compared with regard to demographic data, previous antibiotic therapy, outcome, and mean PCT level, CRP level, and ESR by χ^2 test or Mann-Whitney *U* test, as appropriate. Because we wanted to evaluate the capacity of PCT findings to rule out the diagnosis of bacteremia, we decided ahead of time that the diagnostic threshold would be the cutoff value associated with a negative predictive value of $>98\%$. To do so, we sorted the values of PCT into 10 deciles and calculated sensitivity, specificity, and positive and negative predictive values associated with the 9 cutoff values that separated the 10 deciles.

Receiver operating characteristic curves were plotted for PCT level, CRP level, and ESR. The diagnostic accuracy of each parameter was assessed by calculating its area under receiver operating characteristic curves (AUROCCs), as described elsewhere [8]. AUROCC is a validated way to measure the diagnostic accuracy of a test or the discriminative power of a prediction rule. AUROCC values can have a range of 0.5–1.0; 0.5 would be the value of a test that is no more accurate than tossing a coin, whereas 1.0 would be that of a perfectly discriminative test [8]. In medical practice, a diagnostic test with an AUROCC of <0.75 would be regarded as noncontributive. Two-by-two comparisons of AUROCC were performed by the method described by Hanley and McNeil [9]. The study was powered to ensure that the lower 95% CI boundary of the targeted 0.98 negative predictive value was not <0.95 .

RESULTS

Patient characteristics. Of the 171 patients enrolled in the study, 6 were excluded because they had fever of unknown origin. None of the remaining 165 patients were enrolled more than once—that is, there was 1 episode per patient. There were 95 men and 70 women; the mean age was 57 years (range, 18–96 years). Antibiotics had been administered to 27 patients before admission to the study. Bacteremic episodes and nonbacteremic episodes accounted for 22 (13%) and 143 (87%)

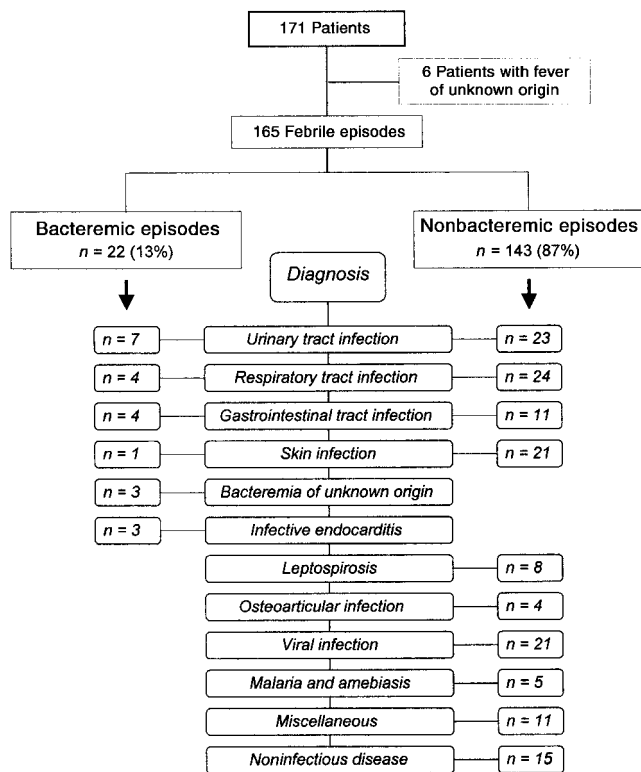


Figure 1. Etiologies and sites of the 165 febrile episodes

of all cases, respectively. All patients with a bacteremic episode had ≥ 2 positive blood cultures. Etiologies and sites of infection of the 165 febrile episodes are shown in figure 1. Among patients who had nonbacteremic episodes, there were 15 instances of noninfectious disease.

For technical reasons, the PCT level could not be measured in 1 patient from the bacteremic episode group and in 2 patients from the nonbacteremic episode group. The CRP level could be measured in all patients, and ESR could be assessed in 139 (84%) of the 165 patients.

Microorganisms responsible for the 22 bacteremic episodes included gram-negative enteric bacilli in 14 episodes (*Escherichia coli*, in 11 cases; *Klebsiella pneumoniae*, in 1; *Enterobacter aerogenes*, in 1; and *Salmonella enterica* serotype Typhimurium, in 1) and gram-positive cocci in 8 episodes (*Streptococcus pneumoniae*, in 4 cases; *Streptococcus bovis*, in 2; *Streptococcus mitis*, in 1; and *Streptococcus dysgalactiae* subspecies *equisimilis*, in 1).

Four of the 165 patients died during the hospital stay. None of these patients belonged to the bacteremic episode group.

Comparison of the bacteremic episode and nonbacteremic episode groups. There were no significant differences between the 2 groups with regard to demographic characteristics, previous antibiotic therapy, and outcome (table 1). Mean serum PCT levels, CRP levels, and ESRs were significantly higher in the bacteremic episode group than in the nonbacteremic epi-

sode group. The most significant difference was found for PCT level (table 2).

Diagnostic threshold and diagnostic accuracy of PCT findings. Sensitivity, specificity, and positive and negative predictive values of PCT findings for the 9 cutoff values of PCT distribution are shown in table 3. The highest negative predictive value was 98.8%, which was associated with the cutoff value of 0.4 ng/mL. This value was retained as the diagnostic threshold for PCT. For this cutoff value, there were 60 false-positive findings (60 [42.6%] of 141) and only 1 false-negative finding (1 [4.8%] of 21).

Figure 2 presents the receiver operating characteristic curves of each of the 3 inflammatory parameters assessed and displays their respective AUROCCs. The AUROCC for PCT was 0.83, which was significantly higher than that for CRP (0.68; $P < .001$) and ESR (0.65; $P < .05$).

DISCUSSION

The early assessment of the risk of bacteremic infection in patients presenting with fever relies on a combination of information derived from clinical examination and laboratory parameters, such as CRP level, ESR, and WBC count. However, these parameters lack accuracy for early diagnosis of bacteremic infections [10]. In this study, we wanted to evaluate the ability of determination of PCT level to rule out the diagnosis of bacteremic infection in patients admitted to the hospital for suspected community-acquired infection.

We found that a PCT value of < 0.4 ng/mL could rule out bacteremia with a high degree of accuracy, because the negative predictive value associated with this threshold was as high as 98.8%. We also found that PCT findings performed significantly better than did findings for both CRP and ESR in predicting the diagnosis of bacteremia.

We selected 0.4 ng/mL as the PCT diagnostic threshold value for 2 reasons. First, this value was associated with a negative predictive value as high as 98.8% (95% CI, 0.95–1). Second, 50% of our study population had PCT values of < 0.4 ng/mL,

Table 1. Comparison of patients with bacteremic and those with nonbacteremic infectious episodes, among patients hospitalized for community-acquired infections.

Characteristic	Bacteremic episode group	Nonbacteremic episode group	P
Age, years			
Mean \pm SD	62 \pm 18.5	53 \pm 21.5	.08
Range	25–96	18–94	
Sex, no. male/no. female	13/9	82/61	.87
Previous antibiotic therapy, no. (%) of patients	4 (18.2)	23 (16.1)	.8
Death, no. (%) of patients	0 (0)	4 (2.8)	.42

Table 2. Comparison of patients with bacteremic episodes and those with nonbacteremic infectious episodes, among patients hospitalized for community-acquired infections, with regard to serum procalcitonin level, C-reactive protein level, and erythrocyte sedimentation rate.

Parameter	Bacteremic episode group	Nonbacteremic episode group	P
Serum procalcitonin level, ^a ng/mL			
Mean ± SD	32.9 ± 82.9	2.6 ± 10.2	<.001
Range	0.2–353	0.05–87	
C-reactive protein level, ^b mg/L			
Mean ± SD	217 ± 136	141 ± 114	.007
Range	74–560	5–542	
Erythrocyte sedimentation rate, ^c mm/h			
Mean ± SD	59 ± 40	40.17 ± 30	.024
Range	13–151	1–119	

^a Data are available for 21 patients in the bacteremic episode group and 141 patients in the nonbacteremic episode group.

^b Data are available for 22 patients in the bacteremic episode group and 143 patients in the nonbacteremic episode group.

^c Data are available for 21 patients in the bacteremic episode group and 118 patients in the nonbacteremic episode group.

which illustrates the clinical relevance of this parameter as a decision rule. Although its negative predictive value is not 100% and its AUROCC is <1, PCT findings performed better than did ESR findings and even CRP findings.

In our series, the only case of bacteremia associated with a PCT value of <0.4 ng/mL occurred in a patient with liver cirrhosis and chronic lymphocytic leukemia. He was admitted to the hospital for evaluation of fever and ascites. His serum PCT level was 0.2 ng/mL, although he had a bacteremic *E. coli* peritonitis. One can hypothesize that this low PCT level may have resulted from cirrhosis-induced liver failure. In fact, Nijsten et

al. [11] demonstrated that liver tissue appears to be a major site of production of PCT.

Although many studies have established that PCT levels can be effectively used to differentiate bacterial from viral infections (especially in children with meningitis [5]) and to identify bacterial infections in patients with sepsis admitted to intensive care units (ICUs) [12–14], only a few studies have evaluated the capacity of PCT findings to rule out bacteremia in patients with community-acquired infections. The study by Liaudat et al. [15] intended to evaluate the PCT level as an early predictive marker of bacteremia. In their hospital, where the prevalence of bacteremia was 8%, they found that PCT evaluation had a negative predictive value of 99% or 96% by use of PCT cutoff values of 0.2 ng/mL and 0.5 ng/mL, respectively. In a study by Engel et al. [16], a PCT value of >0.51 ng/mL was found to be a good predictor of bacteremia in febrile neutropenic patients.

Bossink et al. [17] evaluated performance indices of PCT in a prospective analysis of 300 hospitalized medical patients with fever. By using 0.5 ng/mL as the cutoff value, they found that the sensitivity, negative predictive value, and AUROCC of PCT for the diagnosis of bacteremia were 75%, 90%, and 0.7, respectively.

Some studies have compared the diagnostic value of PCT findings to that of other inflammatory parameters, such as CRP level and cytokine level. Müller et al. [12] used a cutoff value of 1 ng/mL and found that PCT had better predictive values than did both CRP and IL-6 for the diagnosis of sepsis in patients in the medical ICU. Two studies that involved children also confirmed that PCT assessment was more effective than CRP assessment, both for differentiating bacterial from viral infection [18] and for the diagnosis of septic shock [19]. In these 2 studies, 2 ng/mL served as the diagnostic threshold. In contrast, Ugarte et al. [14] pointed out that the best PCT cutoff value (0.6 ng/mL) was both less sensitive and less specific than

Table 3. Sensitivity, specificity, and positive and negative predictive values of serum procalcitonin (PCT) assessment for the 9 cutoff values that separate the 10 deciles of PCT distribution.

PCT cutoff value, ng/mL	No. of cases under the cutoff value	Sensitivity, %	Specificity, %	Positive predictive value, %	Negative predictive value, %
0.07	15	100	10.6	14.3	100
0.12	33	100	23.4	16.3	100
0.18	48	100	34.0	18.4	100
0.30	64	95.2	44.7	20.4	98.4
0.40	82	95.2	57.4	25.0	98.8
0.55	97	85.7	66.7	27.7	96.9
0.90	115	76.2	78.0	34.0	95.7
2.00	129	52.4	84.4	33.3	92.2
6.20	146	23.8	92.2	31.3	89.0

the best CRP cutoff value (7.9 mg/L) for the diagnosis of infection in adult patients in the ICU. The AUROCC was also significantly lower for PCT than for CRP (0.66 vs. 0.78; $P < .05$) [14].

In our study, we did not evaluate the diagnostic utility of cytokine levels in comparison with PCT levels. However, neither IL-6 nor IL-8 appeared to contribute effectively to the diagnosis of sepsis in adults [12, 16, 20]. By contrast, in neonates with clinical suspicion of bacterial infection, PCT assessment performed less well than did IL-8 and the combination of IL-8 and CRP [21]. The lower reliability of PCT for the diagnosis of sepsis in critically ill neonates could be attributed to the physiologically increased PCT concentrations during the first 72 h of life [22].

Another question that can be addressed in our study is, how well does PCT assessment perform in the diagnosis of fever in patients with systemic inflammatory diseases? Eberhard et al. [23] compared PCT, CRP, and IL-6 levels in patients who were known to have a systemic autoimmune disease (systemic lupus erythematosus or systemic antineutrophilic-cytoplasmic antibody [ANCA]-associated vasculitis) and who were evaluated because of the onset of new symptoms. The final diagnosis was acute invasive infection (including both bacteremic and non-bacteremic infections) in a first group of 11 patients, whereas it was inflammatory relapse of the underlying disease in a second group of 42 patients. Mean PCT levels—but not mean CRP or IL-6 levels—increased significantly in the first group. By contrast, PCT levels remained at <0.5 ng/mL in all patients in the second group. This finding was confirmed by Schwenger et al. [24], who found that the PCT level was consistently <0.5 ng/mL in patients with active systemic lupus erythematosus or rheumatoid arthritis. The cutoff value was slightly higher (0.89 ng/mL) in patients with active ANCA-positive vasculitis. Likewise, in a few patients with active Wegener granulomatosis and

no concurrent infection, PCT levels have been as high as 3.3 ng/mL [25].

To our knowledge, no previous study has evaluated PCT levels in the initial diagnosis of inflammatory systemic disease. In our study, 2 patients who had been referred to the hospital for the diagnosis of acute fever eventually had a systemic vasculitis (systemic lupus erythematosus and Wegener's granulomatosis) diagnosed. No concurrent infection was diagnosed in either patient. PCT levels were <0.4 ng/mL in both patients. In contrast, serum CRP levels were 188 mg/L and 287 mg/L.

In summary, determination of the PCT level seems to be a reliable tool both for ruling out infection in patients with chronic inflammatory diseases and for distinguishing infections from systemic inflammatory diseases in the initial evaluation of patients presenting with acute fever. We have demonstrated that PCT findings are highly discriminative and can accurately predict bacteremia in patients hospitalized with a diagnosis of community-acquired fever, with 0.4 ng/mL as cutoff value. Therefore, we suggest that PCT measurement be included in the initial diagnosis strategy of such patients. We advocate that the PCT level be measured when the first blood sample is obtained for culture. If the PCT level turns out to be <0.4 ng/mL in the absence of clinical evidence of severity, antibiotic administration could be deferred until further diagnostic information becomes available, and no additional blood culture would be necessary. In these instances, CRP determination should be substituted for PCT determination.

In conclusion, we believe that such a strategy, when applied to the evaluation of patients with community-acquired fever, could help limit the number of blood cultures to be processed, as well as the number of antibiotic prescriptions, presumably resulting in both favorable economic and ecological effects, which remain to be evaluated.

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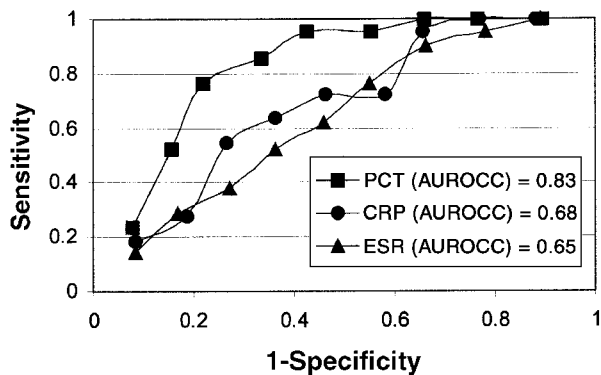


Figure 2. Area under the receiver operating characteristic curves (AUROCCs) of serum procalcitonin (PCT) level, C-reactive protein (CRP) level, and erythrocyte sedimentation rate (ESR) for the diagnosis of bacteremia.

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