

The Future Diagnostic Role of Procalcitonin Levels: The Need for Improved Sensitivity

SIR—We agree with Chirouze et al. [1] that the measurement of procalcitonin (PCT) levels is very useful for evaluating the presence and extent of systemic infection in adult patients with acute fever. Nevertheless, there are several issues raised by their findings that require clarification.

It would be helpful if Chirouze et al. [1] would have provided more details about the reported wide range of PCT levels (0.05–87 ng/mL) in the nonbacteremic subjects. Many of the nonbacteremic subjects (e.g., those with viral and skin infections) would be expected to have low PCT levels. In addition, did the patients who received previous antibiotic treatment have relatively low levels of PCT? What was the PCT level in patients with “transient bacteremia”?

With regard to the evaluation of low levels of serum PCT, it must be recognized that the PCT levels reported in most pub-

lished clinical studies, including that of Chirouze et al. [1], were measured by an assay that was unable to reliably measure levels of <300 pg/mL. The importance of such sensitivity was shown in a study of patients in an intensive care unit in which 2 different assays were used in parallel [2]. Therefore, because any claim that a negative predictive value has been established must be based on the results of an appropriately discriminating assay, the cutoff value of 400 pg/mL suggested by Chirouze et al. [1] was not clinically valid. To illustrate this point further, figure 1 shows the range of PCT levels, as determined by a sensitive assay (0.005 ng/mL), in healthy subjects and in patients in an intensive care unit [3] with various degrees of inflammation but without infection (i.e., systemic inflammatory response syndrome [SIRS] 1–4). Clearly, PCT levels can span a wide range of concentrations before reaching the levels detected by the commonly used commercial assay used by Chirouze et al. [1].

The role of serum PCT measurement (which is more appropriately termed “calcitonin precursor measurement” [4]) in the diagnosis of various inflammatory and infectious illnesses is evolving, as Chirouze et al. [1] suggested in their article. However, the time has arrived to apply sensitive assays that can distinguish between PCT levels in healthy individuals, nonbacteremic patients with escalating SIRS, and bacteremic patients [5, 6]. Until this is done, the reliance on PCT assays with poor low-level sensitivity to predict the absence of bacteremia in adult patients with acute fever is problematic.

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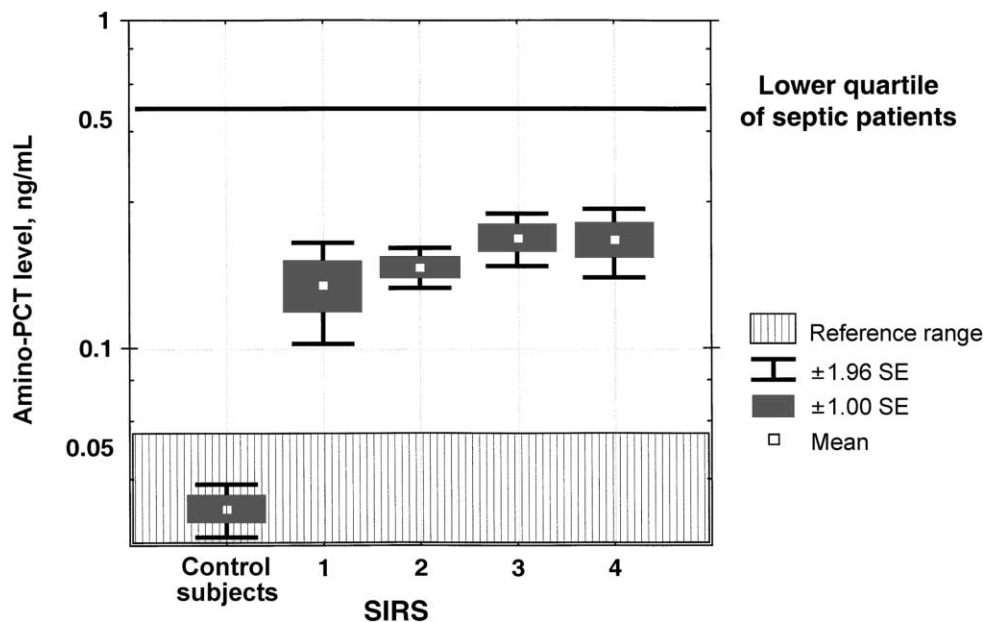


Figure 1. An assay more sensitive than that used by Chirouze et al. [1] was used to measure the level of procalcitonin (PCT) and calcitonin precursors in 101 patients admitted to a medical intensive care unit [3]. This assay can reliably detect low levels of PCT and calcitonin precursors in healthy persons (i.e., control subjects). As illustrated, levels of PCT and calcitonin precursors in the control subjects were significantly lower than those in nonbacteremic patients in a medical intensive care unit who had various degrees of systemic inflammatory response syndrome (SIRS; degrees 1–4 in severity) diagnosed ($P = .001$ between control subjects and the SIRS groups listed; there was no significant difference between the SIRS groups). There is considerable separation of the latter patients from those with sepsis (horizontal line).

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Procalcitonin: What Should Be Its Role in the Clinical Management of Febrile Patients Admitted to the Hospital?

SIR—I read with interest the article by Chirouze et al. [1]. In their study, measurement of serum procalcitonin (PCT) levels helped differentiate bacteremic from nonbacteremic infectious episodes in 165 acutely febrile patients admitted to the hospital. On the basis of their findings, Chirouze et al. [1] advocated routine measurement of serum PCT levels as guidance to determine whether or not to perform multiple blood cultures for and administer empirical antibiotic therapy to such patients.

To offer such broad advice regarding the clinical management of febrile patients on the basis of one study is, however, premature. For instance, the association of bacteremia at admission to the hospital

with the subsequent morbidity and in-hospital death of patients with an acute infection is not strong enough to justify withholding empirical antibiotic treatment to patients with low PCT levels. In a study of 464 adult febrile patients admitted to the hospital, 90 patients had bacteremia and 33 patients died [2]. Of the patients who died, only 10 were bacteremic at admission (relative risk of in-hospital death due to bacteremia, 1.9; 95% CI, 0.9–4.2) [2]. The circulating concentration of proinflammatory microbial components, rather than the presence of whole, culturable bacterial cells, appeared relevant to the prediction of the course of disease. For example, of 48 patients who had gram-negative bacteremia—most cases of which were due to pyelonephritis—7 (29%) of the 24 patients with endotoxemia (endotoxin concentration [as determined by *Limulus amoebocyte lysate* assay], >5 pg/mL) died, whereas 0 of the 24 patients without endotoxemia died ($P < .01$) [2]. Thus, the clinical condition of the patient and the likely source of infection, rather than knowledge of the presence or absence of bacteremia, will dictate the administration of empirical antibiotic therapy to, for example, patients with pyelonephritis, erysipelas, cholangitis, and so on. Finally, the use of serum PCT levels as guidance for clinical management is premature because I could not confirm the very high negative predictive value of low PCT levels for determining the absence of bacteremia in acutely febrile patients.

I prospectively examined the association between circulating levels of various markers of infection in and clinical findings and hospital outcome for adult febrile patients who were included in previous studies in which I participated [2, 3]. The PCT levels of 381 patients (median age, 62 years; 59% male) were measured and compared with the results of microbiological analyses to validate the findings of Chirouze et al. [1]. PCT levels were measured in a single run by use of an immunoluminometric assay (Brahms Diag-

nostica). The lower limit of detection of the assay was 0.1 ng/mL. For 66 (17%) of 381 patients, blood cultures were positive for bacteremia; gram-positive microorganisms were grown in 35 cultures, gram-negative microorganisms were grown in 28 cultures, and mixed growth occurred in 3 cultures. Using the PCT cutoff value of 0.4 ng/mL suggested by Chirouze et al. [1], clinicians would have missed 10 (15%) of 66 episodes of bacteremia. Of note, none of the 10 bacteremic patients with PCT levels of <0.4 ng/mL had severe liver disease, which was a suggested reason that this PCT cutoff value was not noted among bacteremic patients [1]. Alternate cutoff values did not improve the association between low levels of PCT and the absence of bacteremia (table 1); the negative predictive values were 88%–94% for the different PCT cutoff values analyzed. The negative predictive value of measurement of low PCT levels for the detection of endotoxemia was even lower (<80%), although there was a trend toward an association between a positive predictive value of the measurement of low PCT levels and detection of endotoxemia ($\chi^2 = .06$). In one of the studies reported earlier, I and colleagues [3] described a prediction model of hospital outcome that reflected a real-life encounter between physicians and a febrile patient at admission to the hospital. We reported that clinical data (e.g., patient age, underlying disease, and recent history with respect to the febrile episode) outweighed the predictive value of laboratory markers like cytokine and PCT levels [3].

High levels of circulating markers of infection (e.g., cytokines, C-reactive protein, and PCT) and a high erythrocyte sedimentation rate are generally associated with the severity of the inflammatory response and any adverse outcomes, and, thus, they may be useful for the stratification of patients in clinical studies. However, when compared with the value of clinical judgment, the predictive value of measuring these markers at admission to identify patients who have an infection,