MAJOR ARTICLE

Usefulness of Procalcitonin as a Marker of Systemic Infection in Emergency Department Patients: A Prospective Study

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We prospectively evaluated serum procalcitonin concentrations in patients who presented to an emergency department (ED) with suspected infectious or inflammatory disease. Of 195 study patients, 68 had final diagnosis of systemic infection, and 24 of those 68 had elevated serum procalcitonin levels (>0.5 ng/mL). The procalcitonin level had a sensitivity of 0.35 and specificity of 0.99 for the diagnosis of systemic infection. In multivariate analysis, the procalcitonin level was the only independent variable associated with this diagnosis; in contrast, the C-reactive protein level was not. All patients with systemic infections who ultimately died had procalcitonin levels of >0.5 ng/mL at admission. Procalcitonin levels were significantly higher in patients who ultimately died of systemic infection than in patients who survived. The optimal procalcitonin threshold for the ED population may be lower than that proposed for critically ill patients. Determination of the procalcitonin level may be useful for screening and prognosis of more-severely ill ED patients.

Diagnosis of systemic infection is a routine challenge for emergency department (ED) physicians, who sometimes must decide on immediate treatment and dispatch patients to the appropriate hospital department. However, routine laboratory tests lack both sensitivity and specificity in correctly identifying which patients should receive antibiotics, and most confirmatory microbiological test results are not available for 24 h. The serum concentration of procalcitonin, the prohormone of calcitonin, increases rapidly in patients with systemic infections. High procalcitonin concentrations are both sensitive and specific for the diagnosis of sepsis. We evaluated the sensitivity, specificity, and predictive value of the procalcitonin level for identifying cases of systemic infection in patients attending an ED.

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PATIENTS AND METHODS

Patients were included if they presented to the ED during the period from 15 June through 31 August 2000 with suspected infectious or inflammatory disease, as indicated by a physician's order for a C-reactive protein (CRP) level determination. This broad inclusion criterion was chosen in order to include the highest possible proportion of patients with infectious diseases. Indeed, the number of patients for whom CRP levels are determined is large in our institution; it includes most patients with suspected infectious and inflammatory illnesses. Blood samples were obtained for routine tests (hemogram, CRP, and, if necessary, culture), and, for each patient, a serum sample was frozen for later determination of the procalcitonin level.

We recorded following data for each patient: sex, age, duration of symptoms, prior administration of antibiotics, systolic and diastolic blood pressure, pulse rate, body temperature, and suspected diagnosis. For patients admitted to the hospital after discharge from the ED, final diagnoses were recorded from medical files. Outpatients not admitted to the hospital after discharge from the ED were contacted by mail and/or telephone

to assess whether there had been a misdiagnosis or a complicated outcome. Pneumonia was defined as the presence of a new pulmonary infiltrate visible on a chest radiograph, temperature of ⩾38°C, and acute respiratory symptoms. Neither physicians in charge of inpatients nor physicians collecting data from outpatients knew the results of the procalcitonin testing.

Procalcitonin assay. Procalcitonin concentrations were measured in serum samples by use of an immunoluminometric assay (LUMItest PCT; Brahms Diagnostica). The detection limit of the assay was 0.08 ng/mL, and the functional sensitivity (interassay variation coefficient, 20%) was 0.33 ng/mL. The upper limit of normal was 0.5 ng/mL. All samples were tested in duplicate.

Statistical methods. Data were computed with SAS, release 6.12 (SAS Institute). All tests were 2-sided. $P < .05$ was considered significant. For univariate analysis, categorical variables were compared between case patients (those with systemic infection) and control patients (those with conditions other than systemic infection) with use of the χ^2 test. Quantitative variables were compared with use of Student's *t* test (for normally distributed variables, as determined by use of the Shapiro-Wilk test) or Wilcoxon rank-sum test (for nonnormally distributed variables).

For multivariate analysis, quantitative variables were assessed on the basis of the Systemic Inflammatory Response Syndrome (SIRS) definition [1], as follows: systolic arterial pressure, <90 mm Hg; pulse, >90 beats/min; rectal temperature, <36°C or >38°C; WBC count, <4000 cells/mm^3 or >12,000 cells/mm^3. Variables not included in the SIRS definition were assessed according to laboratory thresholds, as follows: creatinine level, >110 μmol/L; hemoglobin level, <120 mg/L; and platelet count, <100,000 cells/mm^3 (grade 2) or >100,000 and <150,000 cells/mm^3 (grade 1); CRP level, >4 mg/L; and procalcitonin level, >0.5 ng/mL). For age, we used the population median (42 years).

Variables with $P \leqslant .15$ were included in an unconditional logistic model to estimate ORs, compute 95% CIs, and perform likelihood-ratio tests. The diagnostic usefulness of procalcitonin level determination was investigated by means of receiver operating characteristic (ROC) analysis.

RESULTS

Patients. A total of 216 patients were referred to the ED with suspected infectious or inflammatory disease during the study period. Of these patients, 133 (62%) were admitted to the hospital, and the remaining 83 patients left the hospital after a consultation. Twenty-one outpatients (10%) were lost to follow-up and were excluded from further analysis. The major reason that patients were lost to follow-up was that a deliberately falsified address and telephone number given at reception to the ED. All patients lost to follow-up presented to the ED with benign illnesses or symptoms. Of the remaining 195 patients, 85 were women and 110 were men (mean age, 47 years; range, 16–98 years). Sixty-eight (35%) of these 195 patients received a final diagnosis of systemic infection (group I). This definition included but was not restricted to the following conditions: bacterial pneumonia, acute pyelonephritis, septicemia, cellulitis, acute prostatitis, peritonitis, and malaria. Final diagnoses for group I patients are summarized in table 1. The other 127 (65%) of the 195 patients had miscellaneous final diagnoses and were classified as having no systemic infection (group II). Forty-four (27%) of the 165 patients (18 in group I and 26 in group II) were receiving antibiotic treatment before admission to the ED. Information on antibiotic treatment was not available for 30 of 195 patients.

Procalcitonin levels. Figure 1 shows procalcitonin values for group I and group II. Twenty-four (35%) of 68 patients in group I and 1 (0.8%) of 127 patients in group II had procalcitonin levels of ⩾0.5 ng/mL (range, 0.5–98.5 ng/mL). With use of a cutoff point of 0.5 ng/mL, the procalcitonin level had an overall sensitivity 0.35, a specificity of 0.99, a positive likelihood ratio of 44.13, a negative likelihood ratio of 0.65, a positive predictive value (PPV) of 0.96 and a negative predictive value (NPV) of 0.74. For patients who were not receiving antibiotic therapy before admission to the ED, the sensitivity was 0.39 and the specificity was 1, and for patients who were receiving antibiotic therapy before admission to the ED, the sensitivity was 0.14 and the specificity was 1. The only group II patient with a procalcitonin level of >0.5 ng/mL (0.53 ng/mL) had acute ulcerative appendicitis. Forty-two of (62%) 68 group I patients and 15 (12%) of 127 group II patients had procalcitonin levels of ⩾0.2 ng/mL (sensitivity, 0.62; specificity, 0.88; PPV, 0.74; NPV, 0.81). Figure 2 presents the ROC curve of procalcitonin

Table 1. Final diagnoses for patients who were admitted to an emergency department with systemic bacterial infection (group I).

Diagnosis	No. of patients (n = 68)
Pneumonia	18
Acute pyelonephritis	12
Cellulitis	12
Acute prostatitis	7
Malaria	6
Peritonitis	3
Bacterial arthritis	2
Cholangitis	2
Cholecystitis	1
Septic shock	1
Retroperitoneal abscess	1
Streptococcal infection	1
Latent syphilis	1
Prosthetic vascular infection	1

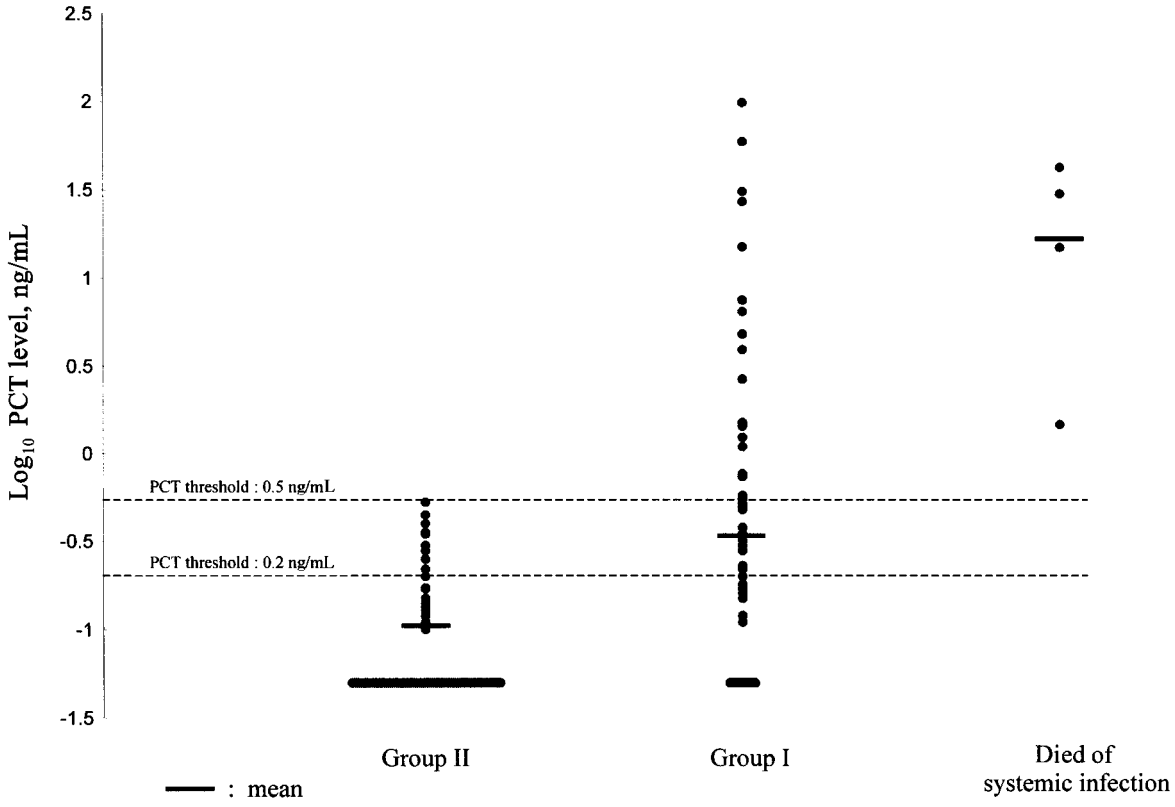

Figure 1. Procalcitonin (PCT) levels for 3 groups of patients. Group I comprised patients with systemic infection; group II comprised patients without systemic infection.

concentration for discrimination between patients in group I and patients in group II. The area under the ROC curve was 0.79.

For differentiation of bacterial pneumonia (18 patients) from bronchitis (11 patients), determination of the procalcitonin level had the following results: with use of a 0.5 ng/mL cutoff point, the sensitivity was 0.27, the specificity was 1, the PPV was 1 and the NPV was 0.46; with use of a 0.2 ng/mL cutoff point, the sensitivity was 0.44, the specificity was 1, the PPV was 1, and the NPV was 0.52. Similar results were found for the differentiation of acute pyelonephritis (12 patients) from cystitis (8 patients): with use of a 0.5 ng/mL cutoff point, the sensitivity was 0.25, the specificity was 1, the PPV was 1, and the NPV was 0.47; with use of a 0.2 ng/mL cutoff point, the sensitivity was 0.66, the specificity was 0.87, the PPV was 0.89, and the NPV was 0.63.

Results of univariate analysis comparing group I patients who had false-negative procalcitonin test results with those who had true-positive results are summarized in tables 2 and 3. Two variables were independently associated with a false-negative procalcitonin test result: age of <42 years (OR, 5.7; 95% CI, 1.3–33; $P = .03$) and a WBC count of <4000 and >12,000 cells/mm^3 (OR, 6.7; 95% CI, 1.7–31; $P = .008$). Two variables, duration of symptoms and previous receipt of antibiotic treatment, had values that did not show a statistically significant difference between patients with false-negative and patients with true-positive procalcitonin test results.

Diagnosis of systemic infection. Results of univariate analysis to identify variables associated with systemic infection are summarized in table 4. A procalcitonin level of >0.5 ng/mL and a temperature of >38°C were significantly associated with a diagnosis of systemic infection, whereas the CRP level was not. In multivariate analysis, the only variable associated with systemic infection was the procalcitonin level (OR, 43.5; 95% CI, 7.9–1000; $P = .0004$). Age, sex, systolic blood pressure of <90 mm Hg, pulse rate of >90 beats/min, body temperature of >38°C, WBC count of <4000 or >12,000 cells/mm^3, hemoglobin concentration, platelet count, CRP values, and creatinine concentration were not independently associated with the diagnosis of systemic bacterial infection.

Mortality rate. In group I, the 1-month mortality rate was 6.77% (4 of 59 patients), and in group II, it was 1.49% (2 of 134 patients). All group I patients who died had procalcitonin levels at admission that were >0.5 ng/mL (range, 1.47–42.2; figure 1). In group I, the mortality rate was 4.5% (2 of 44 patients) for patients who had not received prior antibiotic treatment and 5.5% (1 of 18 patients) for patients who received antibiotics before admission to the ED. The single group I patient who had prior antibiotic treatment and who died had

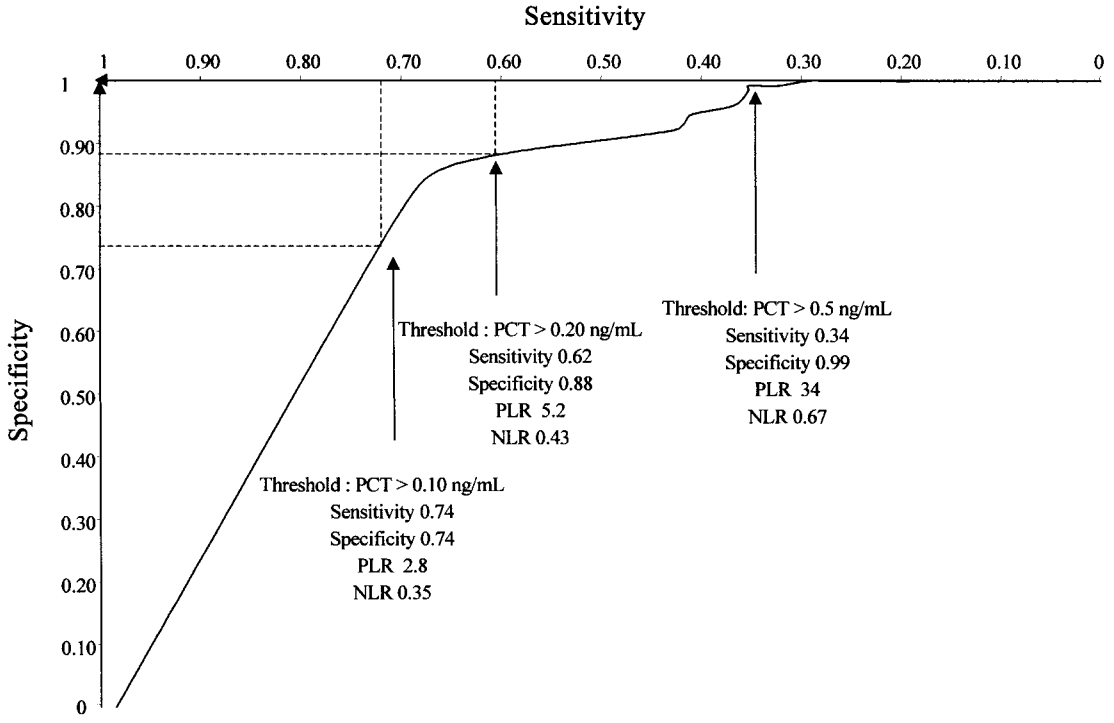

Figure 2. Receiver operating characteristic (ROC) curve of procalcitonin concentration (PCT) for discrimination between presence of systemic infection and absence of systemic infection. PLR, positive likelihood ratio; NLR, negative likelihood ratio.

a procalcitonin level of 42 ng/mL at admission to the ED. Procalcitonin levels at admission were significantly higher in patients who died of systemic infection than in those who survived (mean procalcitonin levels, 17.8 ng/mL vs. 1.5 ng/mL, respectively; $P < .001$). Patients with procalcitonin levels of >0.5 ng/mL were more likely to die of systemic infection within 1 month after admission (OR, 31.6; 95% CI, 2.9–1575; $P = .001$).

DISCUSSION

Etiologic diagnosis of febrile patients who present to an ED is complex and sometimes difficult. Physicians have to identify and often rapidly treat patients with systemic infection. Because most microbiological test results are not available for 24 h, a sensitive and specific marker of systemic infection would be useful. Although CRP level is a very sensitive marker of inflammation, it lacks specificity and so has limited utility in the ED [2]. In 1993, Assicot et al. [3] reported a correlation between a high serum level of procalcitonin and sepsis. Other studies have reported that the procalcitonin level has a high sensitivity and specificity for adult and pediatric bacterial meningitis and for the SIRS diagnosis in an intensive care unit [4–6]. To date, there are no data on routine procalcitonin level evaluation in the ED. Because the procalcitonin level exhibited promising sensitivity and specificity for diagnosis of systemic infection, we conducted a prospective study involving patients who presented to an ED with suspected infectious or inflammatory disease. We report that the procalcitonin level has excellent specificity (0.99) but a sensitivity of only 0.35 (with use of a cutoff point of 0.5 ng/mL) for the diagnosis of systemic infection. However, an elevated procalcitonin level was the only variable independently associated with the diagnosis of systemic infection. These contrasting results may have several explanations. First, patients in group I were identified on the basis of information in medical files, and this group of patients had heterogeneous infectious diseases with various degrees of gravity. Procalcitonin level determination has been reported to be particularly useful for critically ill patients with severe systemic inflammatory response, a population that is quite different from ours [7]. Indeed, group I patients with false-negative procalcitonin testing results were more likely to have a normal WBC count, which probably reflects a less severe systemic inflammatory response. Second, the procalcitonin thresholds suggested for the SIRS diagnosis in critically ill patients are much higher (5–10 ng/mL) than the thresholds used to differentiate viral from bacterial meningitis or pneumonia (0.2–1 ng/mL) [4, 5, 8, 9]. In our study, lowering the procalcitonin cutoff point to 0.2 ng/mL led to improved sensitivity (0.62) with persistent good specificity (0.88). The ED population in France is heterogeneous but is mostly comprised of patients who are not critically ill. Thus, the optimal procalcitonin threshold for

Table 2. Univariate analysis of quantitative variables at admission to the emergency department for patients in group I ($n = 68$), comparing patients who had false-negative procalcitonin test results with those who had true-positive results.

Variable	No. (%) of patients with available data	Mean value ± SD, by test result		P[a]
		True positive ($n = 24$)	False negative ($n = 44$)	
Patient age, years	67 (98.5)	64 ± 20	46 ± 39	<.001
Systolic blood pressure, mm Hg	52 (76.5)	119 ± 39	134 ± 19	.04[b]
Diastolic blood pressure, mm Hg	50 (73.5)	72 ± 22	74 ± 12	.2[b]
Pulse rate, beats/min	50 (73.5)	99 ± 21	93 ± 18	.3
Body temperature, °C	59 (86.8)	38.4 ± 1.3	38.6 ± 1.1	.6
Duration of symptoms, days	48 (67.6)	4 ± 3.9	6.9 ± 11.6	.6[b]
Hemoglobin level, mg/L	68 (100)	131 ± 19	135 ± 16	.4
Platelet count, cells/mm^3	68 (100)	247,200 ± 141,800	217,900 ± 88,500	.6[b]
Urea level	63 (92.6)	7.1 ± 7.9	5.7 ± 25.8	.25[b]
Creatinine concentration, mM	63 (92.6)	83 ± 39	90 ± 55	.6[b]
C-reactive protein level, mg/L	63 (92.6)	85 ± 110	89 ± 148	.9

[a] Student's t test, except as noted.
[b] Wilcoxon rank-sum test.

the ED population could be nearer to 0.2 ng/mL than to 0.5 ng/mL.

Another argument that suggests use of a lower procalcitonin threshold for the ED population concerns procalcitonin kinetics. Procalcitonin levels are detected 3 h after synthesis induction, and the half-life of procalcitonin is ~20–24 h [10, 11]. Most patients admitted to the hospital because of infectious diseases do so through the ED and then are transferred, several hours later, to the infectious diseases department or the intensive care unit. Procalcitonin levels in blood samples obtained from patients in the ED reflect the earliest biological inflammatory response and may be only slightly elevated. Finally, although the number of patients who had received antibiotic therapy before determination of the procalcitonin level was not significantly different between group I patients with false-negative procalcitonin test results and those with true-positive results, the sensitivity of the procalcitonin level was much lower for patients who had received antibiotics than for patients who had not (sensitivity, 0.14 vs. 0.39, respectively). This probably indicates that the antibiotics were rapidly effective against bacterial infection and, therefore, dramatically reduced the procalcitonin level, as has been reported in a pediatric population [3]. In our study, prior receipt of antibiotic treatment was not significantly associated with survival. However, because the infectious diseases entities studied were heterogeneous and because of the low mortality rate, no definitive conclusions could be drawn.

We report that the procalcitonin level has low sensitivity for the diagnosis of community-acquired pneumonia or acute pyelonephritis. Previous studies of community-acquired pneumonia reported that the highest procalcitonin concentrations were in patients with pneumonia due to classic bacterial pathogens, rather than in patients with atypical or viral pneumonia [8, 12]. We can not exclude the possibility that several of the cases of pneumonia in our study were of atypical or viral etiology. Furthermore, distinguishing pneumonia from other causes of respiratory syndromes, such as acute bronchitis and upper respiratory tract infections, is sometimes difficult [13]. Despite the

Table 3. Univariate analysis of qualitative variables at admission to the emergency department for patients in group I, comparing patients who had false-negative procalcitonin test results with patients who had true-positive results.

Variable	Patients with available data ($n = 68$)	Test result		P	OR (95% CI)
		True positive ($n = 24$)	False negative ($n = 44$)		
Previously received antibiotic treatment	62 (91.2)	4/21 (19)	14/41 (34)	.2	2.2 (0.5–9.7)
Ratio of men to women	68 (100)	2.4	1.6	.4	1.5 (0.5–5.1)
WBC count <4000 or >12,000/mm^3	68 (100)	13/24 (54.2)	11/44 (25)	.02	0.28 (0.8–0.92)

NOTE. Data are no. (%) of patients, no. of patients/no. of patients with available data (%), or ratio.

Table 4. Univariate analysis of variables at admission to the emergency department, comparing the entire study group, group I (patients with systemic infection), and group II (patients with no systemic infection).

Variable	No. (%) of patients with available data	Mean value ± SD, by patient group			P[a]
		All (n = 195)	Group II (n = 127)	Group I (n = 68)	
Procalcitonin level, ng/mL	195 (100)	1.9 ± 9.5	0.09 ± 0.09	5.3 ± 15.6	<.001[b]
Age, years	193 (98.9)	47 ± 22	44 ± 21	52 ± 21	.01
Systolic blood pressure, mm Hg	148 (75.8)	130 ± 25	130 ± 23	129 ± 27	.8
Diastolic blood pressure, mm Hg	146 (74.8)	77 ± 45	80 ± 55	73 ± 15	.4[b]
Pulse rate, beats/minute	144 (73.8)	91 ± 1.6	89 ± 19	95 ± 19	.08
Body temperature, °C	156 (80)	38 ± 0.08	37.7 ± 0.9	38.6 ± 1.1	<.001[b]
Duration of symptoms, days	132 (67.6)	6.3 ± 17	6.5 ± 20	5.9 ± 10	.3[b]
Hemoglobin level, mg/L	194 (99.4)	132 ± 17	131 ± 17	133 ± 17	.3
Platelet count, cells/mm^3	194 (99.4)	218,000 ± 97,000	268,300 ± 890,000	155,200 ± 110,000	.2[b]
Urea level, mg/L	184 (94.3)	6 ± 0.4	5.9 ± 4.4	6.2 ± 6.3	.7[b]
Creatinine concentration, mM	185 (94.8)	88 ± 43	89 ± 40	87 ± 49	.8
C-reactive protein level, mg/L	184 (94.3)	82 ± 114	80 ± 102	88 ± 135	.9

[a] Student's t test, except as noted.
[b] Wilcoxon rank-sum test.

strict definition we used, the number of cases of pneumonia may have been overestimated in the population who presented with respiratory illnesses. Although acute pyelonephritis can result in septic shock with bacteremia, most cases are self-limited focal kidney infections that probably do not induce procalcitonin synthesis. Similarly, 4 of 5 patients with confirmed appendicitis had procalcitonin levels of <0.2 ng/mL at admission to the ED; the fifth patient, who had ulcerative appendicitis, had a procalcitonin level of 0.53 ng/mL.

Our data are in accordance with those in previous studies that have reported elevated procalcitonin levels in patients with malaria [14, 15]. The 2 group I patients with nonbacterial infections had malaria, and 1 of these 2 patients had shock (procalcitonin level, 59 ng/mL). All 6 of the patients who presented with malaria during the study period had detectable procalcitonin levels (range, 0.12–59 ng/mL).

Finally, the procalcitonin level best correlated with prognosis for patients with systemic infection: all group I patients who died had a procalcitonin level of >1 ng/mL at admission to the ED. Furthermore, patients with procalcitonin levels of >0.5 ng/mL at admission were more likely to die of systemic infection. Massive induction of procalcitonin synthesis indicates a severe systemic inflammation response to a systemic nonviral infection and an increased risk of fatal outcome [16, 17].

Determination of procalcitonin levels may be useful in the ED to identify patients with severe systemic nonviral infections. Because of the low sensitivity but excellent specificity and PPV for this test, an elevated procalcitonin concentration indicates ongoing and potentially severe systemic infection with an increased risk of fatal outcome, whereas normal values do not exclude the possibility of an infectious process in its beginning stages. Determination of the optimal procalcitonin threshold for the ED population is crucial, and this threshold may be lower than that proposed for critically ill patients. The prognosis value of the procalcitonin level may be useful for screening ED patients with more-sever infections. Further studies are needed to refine the place of procalcitonin level determination among the biological tools used in the ED.

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