Diagnostic and prognostic value of procalcitonin in patients with septic shock

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Objective: **To determine whether procalcitonin is a reliable diagnostic and prognostic marker in septic shock compared with nonseptic shock.**

Design: **Prospective controlled trial.**

Setting: **Intensive care unit of the Avicenne Teaching Hospital, Bobigny, France.**

Patients: **All patients admitted to our intensive care unit over a 12-month period with clinical evidence of shock.**

Interventions: **None.**

Measurements and Main Results: **Echocardiography or pulmonary artery flotation catheter measurements were used to assess hemodynamics, and multiple specimens were obtained for microbiological studies. Standard criteria were used to diagnose septic shock. Serum concentrations of procalcitonin, C-reactive protein, and lactate were determined on the day of shock onset (day 1) and on days 3, 7, and 10. Seventy-five patients were included, 62 in the septic shock group and 13 in the cardiogenic shock group. Serum procalcitonin on day 1 was significantly higher in patients with than without septic shock (median, 14 [0.3–767] ng/mL vs. 1 [0.5–36] ng/mL, $p < .01$). A cutoff value of 1 ng/mL had 95% sensitivity and 54% specificity for separating patients with and without sepsis. C-reactive protein failed to discriminate between these two groups. Among patients with sepsis, procalcitonin concentrations were significantly higher in those who died than in the survivors, at all four measurement time points (median, 16 [0.15–767] ng/mL vs. 6 [0.2–123] ng/mL, $p = .045$ on day 1; 6.5 [0.3–135] ng/mL vs. 1.05 [0.11–53] ng/mL, $p = .02$ on day 10). A cutoff value of 6 ng/mL on day 1 separated patients who died from those who survived with 87.5% sensitivity and 45% specificity. C-reactive protein was not helpful for predicting mortality. Serum lactate was a nonspecific prognostic marker.**

Conclusions: **These data indicate that procalcitonin may be a valuable early diagnostic and prognostic marker in patients with septic shock. (Crit Care Med 2004; 32:1166–1169)**

Key Words: procalcitonin; diagnosis; prognosis; septic shock; mortality.

Septic shock is a leading cause of mortality in intensive care units (ICUs). Despite recent advances in the understanding of pathogenic mechanisms involved in septic shock, mortality rates have remained remarkably stable over the past two decades, ranging from 50% to 60% (1).

Early specific antibiotic treatment combined with adequate hemodynamic support has a major impact on the outcome (2–6). However, severe sepsis leading up to septic shock can be difficult to differentiate from systemic inflammation without infection. Many features occur in both conditions, including changes in body temperature, leukocytosis, and tachycardia. Furthermore, microbiological evidence of infection is often missing in patients with septic shock, at least at the early phase (7). Mediators such as proinflammatory cytokines and C-reactive protein (CRP) are released both in septic shock and in many noninfectious inflammatory diseases. These factors conspire to delay the diagnosis of septic shock, thus potentially depriving patients of early antibiotic treatment and compromising outcomes. A test capable of improving the early diagnosis of septic shock would therefore be expected to improve outcomes by increasing the proportion of patients who receive early appropriate treatment.

Procalcitonin, one of the calcitonin precursors described >20 yrs ago, gained new interest in the early 1990s (8–10). Actually, procalcitonin production increases more in septic shock than in other inflammatory conditions and seems to correlate with patient outcome (11–17).

The aim of this study was to confirm the diagnostic value of procalcitonin and to further evaluate its prognostic interest in septic shock.

PATIENTS AND METHODS

Patients. All patients with clinical evidence of shock were prospectively enrolled in this single-center study performed in the ICU of a teaching hospital. Immediately after inclusion, hemodynamic measurements were obtained in all patients either via a pulmonary artery flotation catheter or by echocardiography. Microbiological studies were done on blood samples and on other specimens as clinically indicated.

Data Collection. For all patients, the following variables were collected: age, gender, Simplified Acute Physiology Score II and Acute Physiology and Chronic Health Evaluation II score, lengths of mechanical ventilation and ICU stay, type of shock, and vital status at ICU discharge. In the patients with septic shock, available data on the primary site

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Table 1. General characteristics of the study patients

	Septic Shock	Nonseptic Shock	*p* Value
No.	62	13	
M/F	44/18	7/6	NS
Age, yrs, mean ± SD	59 ± 14	66 ± 13	NS
Admission SAPS II, mean ± SD	69 ± 23.5	65 ± 25	NS
Admission APACHE II, mean ± SD	33 ± 11	28 ± 11	NS
Length of mechanical ventilation, days, mean ± SD (range)	13 ± 17 (1–75)	8 ± 12 (1–44)	NS
Length of ICU stay, days, mean ± SD (range)	16 ± 19 (1–87)	14 ± 14.5 (3–46)	NS

M, male; F, female; NS, not significant; SAPS, Simplified Acute Physiology Score; APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit.

of infection and causative microorganisms were recorded.

Blood Sample Collection and Assays. Blood was collected on the first day of shock in all patients and on days 3, 7, and 10 in patients who were still in the ICU at those time points. The serum was separated, stored at −70°C, and used subsequently for assaying procalcitonin, CRP, and lactate. Procalcitonin was measured using an immunoluminometric assay (LUMItest PCT, gift from Brahms Diagnostica, GMBH, Berlin, Germany) on a Berilux Analyzer 250 (Behring Diagnostics, Marburg, Germany). The detection limit was 0.08 ng/mL, and the intra-assay coefficients of variation at low and high concentrations were 12% and 5%, respectively. The normal serum procalcitonin concentration with this assay is <0.5 ng/mL. CRP was measured using a nephelometric assay (Dade-Behring, SA Paris, France) with a detection limit of 0.2 mg/L and intra-assay coefficients of variation at low and high concentrations of 3.3% and 2%, respectively. The normal value is <6 mg/L. Serum lactate was determined enzymatically (LAC Vitros Slides) on a Vitros 950 (Ortho-Clinical-Diagnostics, Rochester, NY). Normal values range from 0.7 to 2 mM/L.

To assess the diagnostic value of procalcitonin, we compared serum concentrations on day 1 between the groups with and without septic shock. In the group with sepsis, we compared the variations in procalcitonin concentrations from day 1 to day 10 between the patients who survived and those who died, to evaluate the prognostic information provided by procalcitonin.

Similar comparisons were performed for CRP and lactate, and the results were compared with those obtained with procalcitonin.

Definitions. Septic shock was defined as infection, either documented microbiologically or strongly suspected, combined with Bone's criteria (18).

Cardiogenic shock was defined as presence of any of the following: systolic blood pressure <90 mm Hg; >40-mm Hg decrease in systolic blood pressure in a hypertensive patient; or need for vasopressor therapy to maintain blood pressure combined with a cardiac index <2.2 $L \cdot min^{-1} \cdot m^{-2}$ with a pulmonary artery occlusion pressure >14 mm Hg or a left ventricular ejection fraction <40%. Hypovolemic shock was defined as a need for intravenous crystalloids or colloids or blood transfusion to maintain blood pressure.

According to these criteria, patients were classified as having either septic shock or nonseptic shock.

Statistics. Data were analyzed using nonparametric tests (Mann-Whitney U test, Wilcoxon test, and Fisher's exact test). Results are expressed as mean ± SD except for procalcitonin and CRP concentrations, which are reported as medians (ranges). All *p* values were two-tailed, and $p < .05$ was considered significant. Statistical calculations were done with the Statistical Program for the Social Sciences, version 8.0 (SPSS, Chicago, IL).

RESULTS

Patients. Over a 12-month period, 75 patients were included in the study, of whom 62 were classified as having septic shock and 13 nonseptic shock. Overall mortality rate was 66.7% with no significant difference between the two groups (65% and 77% in the patients with and without septic shock, respectively; $p = .6$). Table 1 reports the main characteristics of our study patients.

Diagnostic Value of Procalcitonin. Serum procalcitonin concentrations on day 1 were significantly higher in the patients with than without septic shock. A cutoff value of 1 ng/mL had 95% sensitivity and 54% specificity for separating patients with and without septic shock. Positive predictive value and negative predictive value were 91% and 70%, respectively. Serum CRP and lactate concentrations were similar in the two groups (Table 2).

Procalcitonin concentrations were similarly elevated in patients with Gram-negative and in those with Gram-positive infections ($p = .91$) and were elevated as well in patients with candidemia.

Prognostic Value of Procalcitonin. Among patients with septic shock, those who died in the ICU had significantly higher procalcitonin concentrations than those who were alive at ICU discharge, at all the assay time points (Table 3). As early as day 1, a cutoff value of 6 ng/mL predicted death with 87.5% sensitivity and 45% specificity. Among patients with cardiogenic shock, those who died also had higher procalcitonin concentrations although differences did not reach significance (Table 4). Lactate concentrations were associated with vital status at ICU discharge, whereas CRP was not (Table 5).

Microbiology. Among the 62 patients with septic shock, 47 (76%) had microbiological evidence of infection and 32 (52%) had positive blood cultures. The main sites of infection were the lung (19%), urinary tract (9.5%), and gastrointestinal tract (6.5%). Recovered organisms were Gram-negative bacteria in 24 (24 of 62, 39%) patients, Gram-positive bacteria in 22 (22 of 62, 35.5%) patients, and yeasts in two (two of 62, 3%) patients. In 14 (14/62, 22.5%) patients, more than one organism was recovered (Table 6).

DISCUSSION

In our study, serum procalcitonin concentrations were significantly higher in the patients with than without septic shock. Among the patients with septic shock, they were significantly higher in those who died. Interestingly, serum procalcitonin concentrations were not significantly different between the patients with Gram-positive and those with Gram-negative infections. Moreover, serum procalcitonin concentrations were increased in the two patients with candidemia. These results suggest that procalcitonin may be reliable both as a diagnostic and as a prognostic marker in patients with septic shock of bacterial origin. Whether fungal infections, namely candidemias, induce an increase in procalcitonin remains unclear (19, 20). In this study, procalcitonin was increased.

Table 2. Diagnostic value of procalcitonin (PCT), C-reactive protein (CRP), and lactate on day 1 of septic shock

	Septic Shock	Nonseptic Shock	*p* Value
PCT, ng/mL	14 (0.3–767)	1 (0.15–36)	.0003
CRP, mg/L	122 (6–444)	68 (3–134)	NS
Lactate, mmol/L	2.4 (0.5–18)	3.2 (1–25)	NS

NS, not significant.

Table 3. Prognostic value of procalcitonin (ng/mL) in septic shock

	Patients Who Died	Patients Who Survived	*p* Value
D1	16 (0.15–767)	6 (0.2–123)	.045
D3	14 (0.2–300)	3 (0.2–52)	.03
D7	15 (0.9–197)	1.1 (0.14–49)	.003
D10	6.5 (0.3–135)	1.05 (0.11–53)	.02

Data are expressed as median (range). Blood samples for procalcitonin assays were taken on the first (D1), third (D3), sixth (D7), and tenth (D10) days of shock.

Table 4. Prognostic value of procalcitonin (ng/mL) in cardiogenic shock

	Patients Who Died	Patients Who Survived	*p* Value
D1	2 (0.15–36)	1 (0.2–9)	NS
D3	4 (0.4–23)	0.25 (0.2–32)	NS
D7	3 (2.2–5.6)	0.17 (0.14–0.26)	NS
D10	4.5 (1.1–6.4)	0.13 (0.11–0.15)	NS

Data are expressed as median (range). Blood samples for procalcitonin assays were taken on the first (D1), third (D3), sixth (D7), and tenth (D10) days of shock.

Table 5. Prognostic value of C-reactive protein (CRP, mg/L) and lactate in patients with septic shock

	Patients Who Died	Patients Who Survived	*p* Value
CRP			
D1	126 (3–444)	81 (6–261)	NS
D3	154 (51–416)	190 (71–296)	NS
D7	185 (12–286)	148 (13–184)	NS
D10	96 (46–146)	58 (2–150)	NS
Lactate			
D1	4 (0.5–25)	1.7 (1–4.6)	0.0001
D3	2.3 (0.7–16)	1.4 (0.3–2.7)	0.0006
D7	1.9 (0.7–7)	1.4 (0.9–4)	NS
D10	2 (1–5)	1.15 (0.6–5)	.04

NS, not significant.

Data are expressed as median (range). Blood samples for measurement of CRP and lactate were taken on the first (D1), third (D3), sixth (D7), and tenth (D10) days of shock.

Routine use of procalcitonin as a diagnostic and monitoring tool may improve the management and, consequently, the survival of patients with septic shock.

Table 6. Microbiology

	No.
Gram-positive bacteria	
Staphylococcus aureus	11
S. epidermidis[a]	18
Streptococcus pneumoniae	5
S. faecalis	3
Gram-negative bacteria	
Pseudomonas aeruginosa	13
Escherichia coli	10
Klebsiella species	6
Proteus mirabilis	4
Acinetobacter baumanii	2
Serratia species	2
Citrobacter species	2
Haemophilus inflenzae	2
Yeasts	
Candida albicans	2

[a]Considered as responsible for infection in three cases, associated with other pathogens in 15 cases.

Yet, no conclusion could be drawn since there were only two candidemias. This issue needs further investigation.

Previous studies have provided convincing evidence that procalcitonin is useful for the diagnosis of septic shock (12–14, 21, 22). Procalcitonin is markedly increased in patients with severe systemic infection but is either normal or only moderately increased in those with systemic inflammatory response syndrome triggered by viral infections or noninfectious disorders such as burns or acute biliary pancreatitis or cardiogenic shock (23). In addition, contrary to proinflammatory cytokines and CRP, procalcitonin discriminates between patients with sepsis or severe sepsis and those with septic shock (12–14). In these studies, however, the diagnostic cutoff value was high (5 ng/mL). We found a considerably lower cutoff value (1 ng/mL) to be highly sensitive for the early diagnosis of septic shock. Interestingly, most septic shock patients in our study were admitted for medical reasons. Two other recent studies evaluating the diagnostic interest of procalcitonin in medical septic shock patients found cutoff values similar to ours (24, 25). In contrast, procalcitonin values up to 8 ng/mL have been reported in patients with a normal postoperative course (26). Thus, the best cutoff value for the diagnosis of septic shock has still to be determined but may differ depending on whether medical or surgical patients are considered. The poor specificity of procalcitonin in our study was due to six (six of 13, 46%) patients without infection having high procalcitonin concentrations. Procalcitonin concentration elevation in patients without infection is probably ascribable to translocation of bacteria across the gut wall altered by congestion or ischemia, as indicated by the recent finding of high serum procalcitonin concentrations in patients with cardiogenic shock (27, 28). Conversely, three patients with infection had low procalcitonin serum concentrations, 0.3, 0.4,

and 0.44 ng/mL, respectively. Low procalcitonin concentrations in patients with septic shock have been reported previously but are rather unusual (10). All three patients with low procalcitonin in our study had positive microbiological studies and received antibiotics. Two had low prothrombin concentrations (<50%) indicating liver failure before the onset of shock, and the third may have had liver function impairment related to alcohol abuse. Thus, the low procalcitonin concentrations in these three patients may be ascribable to dysfunction of the liver, which is one of the sites involved in procalcitonin production (29, 30, 31). The low sensitivity of the assay used for procalcitonin measurement may also be an explanation. In this study, we also found evidence that procalcitonin may be an early prognostic marker in patients with septic shock. As early as the first day of shock, values >6 ng/mL were 87.5% sensitive and 45% specific for death. Earlier studies found that procalcitonin serum concentrations were correlated with disease severity and mortality rate. However, cutoff values determined so far were much lower than ours (1.1 and 1.6 vs. 6 ng/mL), probably reflecting differences in patient severity but also emphasizing the need for further evaluation (14–17, 24).

Serum procalcitonin concentrations were >6 ng/mL in 12 patients with septic shock who survived. Thus, the specificity of high procalcitonin concentrations for mortality was poor. However, failure of high serum procalcitonin concentrations to decrease under treatment in patients with septic shock may prove useful as an alarm signal indicating that treatment reappraisal may be in order to improve effectiveness.

CONCLUSIONS

Routine use of procalcitonin as a diagnostic and monitoring tool may improve the management and, consequently, the survival of patients with septic shock. In addition, the prognosis of septic shock patients can be assessed by a single determination of procalcitonin on day 1. However, procalcitonin concentrations should be interpreted with the knowledge that sensitivity and specificity are imperfect.

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