Procalcitonin Kinetics as a Prognostic Marker of Ventilator-associated Pneumonia

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We investigated the value of procalcitonin kinetics as a prognostic marker during ventilator-associated pneumonia (VAP). This prospective, observational study was conducted in a medical intensive care unit in a university hospital. All consecutive patients with microbiologically proven VAP who survived 3 days after its diagnosis were included and grouped according to clinical outcome: favorable or unfavorable, defined as death, VAP recurrence, or extrapulmonary infection requiring antibiotics before Day 28. Serum procalcitonin levels were measured on Days 1, 3, and 7 for all patients. Among the 63 patients included, 38 had unfavorable outcomes. On Day 1, they were more critically ill than patients with a favorable outcome. Serum procalcitonin levels decreased during the clinical course of VAP but were significantly higher from Day 1 to Day 7 in patients with unfavorable outcomes. Multivariate analyses retained serum procalcitonin levels on Days 1, 3, and 7 as strong predictors of unfavorable outcome. Based on these data, procalcitonin could be a prognostic marker of outcome during VAP.

Keywords: procalcitonin; prognosis; ventilator-associated pneumonia

Ventilator-associated pneumonia (VAP) is the most frequent intensive care unit (ICU) nosocomially acquired infection in patients on mechanical ventilation (1–3) and is associated with prolonged hospital stay and higher ICU mortality (4, 5). Few data about VAP evolution after institution of appropriate antimicrobial therapy are available (6–10). Several studies showed that clinical and biologic parameters evolved differently for survivors and nonsurvivors or for patients with or without VAP recurrence, but the parameters chosen proved not to be predictive of outcome. The search continues for reliable prognostic markers that could rapidly (as of the first days of treatment) distinguish patients who will have favorable, as opposed to unfavorable, outcomes. Early identification of patients at high risk for death or VAP recurrence may provide an opportunity to change the treatment strategy to improve outcome.

Procalcitonin, the precursor molecule of calcitonin, is a 116–amino acid peptide that is devoid of known hormonal activity (11). Serum levels of procalcitonin are very low in healthy individuals. Despite little being known about the biologic properties of procalcitonin and its origin, procalcitonin levels rise during bacterial infections but not during viral infections or inflammatory reactions of noninfectious origin (11). Moreover, the procalcitonin level has been associated with prognosis during sepsis and septic shock (12). In pulmonary injury and pulmonary infection, the circulating concentrations of procalcitonin and other calcitonin precursors increase rapidly, probably in response to sepsis-related cytokine release from pulmonary neuroendocrine cells of the bronchial epithelium and/or mononuclear cells (13–15). Recently, Duflo and colleagues reported that serum procalcitonin could be used as a complementary diagnostic marker of VAP and, moreover, that its serum levels were higher in nonsurvivors than survivors (16). However, until now, the usefulness of procalcitonin as a prognostic marker during an episode of microbiologically proven VAP has not been evaluated. Therefore, we studied procalcitonin kinetics during the first week of VAP and tested the hypothesis that serum procalcitonin concentrations could serve as a novel marker of prognosis for patients with VAP. Some of the results of this study were previously reported in an abstract (17).

METHODS

Study Setting and Population

All consecutive patients who developed VAP after 48 hours or more of mechanical ventilation between February 2002 and April 2003 were included. Patients who were moribund (simplified acute physiology score II $\geqslant$ 65 points) or died during the first 3 days after VAP diagnosis were not included.

VAP was diagnosed when all the following criteria were met: (*1*) clinically suspected VAP, defined as a new and persistent pulmonary infiltrate on chest radiograph associated with at least one of the following: temperature of 38°C or more, leukocytosis of 10,000/mm^3 or more, and purulent tracheal secretions (for patients with acute respiratory distress syndrome, for whom the demonstration of radiologic deterioration was difficult, at least one of the three preceding criteria sufficed) and (*2*) significant growth (10^4 or more cfu/ml) of quantitative cultures of distal bronchoalveolar lavage fluid samples obtained by fiberoptic bronchoscopy (1).

All patients were treated for 15 days, except for the 10 patients enrolled in the 8-day antibiotic arm of the PneumA Trial (four favorable and six unfavorable outcomes) (10) and the 25 patients enrolled after the end of the PneumA Trial who were treated for 6–10 days (15 favorable and 10 unfavorable outcomes). Pertinently, the empiric antibiotic regimen selected just after bronchoscopy (Day 1) was inappropriate for only three (4.8%) patients based on quantitative culture results.

Because no supplementary blood samples were drawn and investigations were considered part of routine clinical practice, no written informed consent was required, as confirmed by the Clinical Research Ethics Committee of the French Intensive Care Society, Paris, France. Patients or next of kin were informed of their inclusion in this study and could refuse to participate.

Baseline Assessment and Data Collection

Each patient's hospital chart was constituted prospectively, and the following data were recorded at ICU admission: age, sex, severity of underlying medical condition, stratified according to the criteria of McCabe and Jackson (18), simplified acute physiology score II (19), and reason for mechanical ventilation (20). In addition, the following parameters were recorded at ICU admission and on Days 1 (bronchoscopy), 3, and 7: presence or absence of organ dysfunction(s) and/or

(*Received in original form June 13, 2004; accepted in final form September 21, 2004*)

Supported in part by Brahms Diagnostica (Berlin, Germany).

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This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 171. pp 48–53, 2005
Originally Published in Press as DOI: 10.1164/rccm.200406-746OC on September 24, 2004
Internet address: www.atsjournals.org

TABLE 1. CLINICAL CHARACTERISTICS OF THE 63 PATIENTS WHO DEVELOPED VENTILATOR-ASSOCIATED PNEUMONIA*

Parameter	Overall Population n = 63	Unfavorable Outcome n = 38	Favorable Outcome n = 25
Age, yr	62 ± 14	64 ± 14	59 ± 14
Sex, male, n (%)	47 (75)	29 (76)	18 (72)
McCabe and Jackson score ⩾ 2, n (%)	21 (33)	14 (37)	7 (28)
SAPS II at admission	47 ± 16	48 ± 17	45 ± 15
Origin, n (%)			
Medical	27 (43)	16 (42)	11 (44)
Elective surgery	19 (30)	12 (31)	7 (28)
Emergency surgery	17 (27)	10 (27)	7 (28)
Reason for mechanical ventilation, n (%)			
Acute respiratory failure	26 (41)	17 (44)	9 (36)
Postoperative respiratory failure	32 (51)	20 (53)	12 (48)
Neurologic failure	4 (7)	1 (3)	3 (12)
Miscellaneous	1 (1)	0	1 (4)
Characteristics on Day 1†			
Duration of prior mechanical ventilation, d	12 ± 9	11 ± 8	13 ± 11
SAPS II	42 ± 12	45 ± 11	38 ± 13
Shock, n (%)	33 (52)	20 (53)	13 (52)
mCPIS‡	7.0 ± 1.5	7.2 ± 1.4	6.8 ± 1.6
Total duration of mechanical ventilation, d	35 ± 30	40 ± 34	24 ± 20
Patients still on mechanical ventilation on Day 7, n (%)	44 (70)	30 (79)	14 (56)
Duration of antibiotics, d	9.5 ± 2.8	9.5 ± 3.1	9.3 ± 2.5
mCPIS‡ on Day 3	6.4 ± 1.4	6.7 ± 1.3	6.0 ± 1.6
mCPIS‡ on Day 7	4.3 ± 1.8	4.5 ± 1.9	4.0 ± 1.5

Definition of abbreviations: mCPIS = modified clinical pulmonary infection score; SAPS = simplified acute physiology score.
* Plus–minus values are means ± SD.
† These values were obtained on the day of VAP diagnosis, that is, Day 1.
‡ mCPIS calculated as described by Luna and colleagues (7).

infection (21), sepsis-related organ failure assessment score (22), temperature, white blood cell (WBC) count, Pa_{O_2}/FI_{O_2}, serum C-reactive protein, radiologic score (23), and modified clinical pulmonary infection score (7) (*see* Table E1 in the online supplement).

Follow-up, Definitions, and Outcome Measures

Recurrence was defined as a new VAP episode, that is, new clinical signs compatible with pneumonia, confirmed by significant ($\geqslant 10^4$ cfu/ml) growth in quantitative culture of new bronchoalveolar lavage fluid. It included persistent infection (the same pathogen responsible for episode 1), relapse (the same pathogen as episode 1 but after the end of antibiotic therapy), and superinfection (another pathogen, at any time).

Extreme vigilance for pneumonia recurrence was maintained throughout the study to detect any possible relapse or new episode of pulmonary infection, and fiberoptic bronchoscopy was performed before starting any new antibiotics as soon as a patient became febrile, had purulent tracheal secretions, a new pulmonary infiltrate, or progression of an existing infiltrate. Distal pulmonary secretions were also collected bronchoscopically when unexplained hemodynamic instability required higher vasopressor doses (> 30%) or their introduction, in the case of unexplained deterioration of blood gases, with more than 30% Pa_{O_2}/FI_{O_2} decrease, or when an intercurrent event imposed an urgent change of antibiotic therapy, regardless of the reason.

The primary outcome measurement was unfavorable outcome before Day 28, defined as at least one of the following: death, confirmed VAP recurrence, or extrapulmonary infection requiring antimicrobial treatment, whichever occurred first. Patients were grouped according to favorable or unfavorable outcome and were compared.

Procalcitonin Assay

For all patients, serum from blood drawn daily for routine biologic tests was collected on Days 1, 3, and 7 and was frozen for further analysis. An investigator blinded to clinical data used a time-resolved amplified cryptate emission technology on a Kryptor analyzer (Brahms Diagnostica, Berlin, Germany) to measure procalcitonin in 100 μl of serum.

Statistical Analyses

Data were compared as follows: continuous variables with Student's *t* test or the Mann-Whitney U test as appropriate, categoric variables with the chi-square test, and continuous variables over time with a factorial two-way analysis of variance. Procalcitonin was assessed as a prognostic marker at different times using receiver operating characteristics curves and their corresponding areas under the curves (24). To examine the univariate effects of patients' clinical characteristics and initial ICU events on unfavorable outcome, a logistic-regression model was used to test each characteristic. Significant continuous variables were categorized using the median as the threshold. Thereafter, multiple-logistic regressions using backward stepwise variable elimination (with variable exit threshold set at $p > 0.05$) were applied to the outcome of VAP on Days 1, 3, and 7. Risk factors with p values of 0.10 or less in our univariate analysis and factors previously reported in the literature (10, 25–27) to be strongly associated with unfavorable outcome were entered into the multivariate model. Interactions were tested in the model; variables strongly associated with an other(s) were not included in the multivariate analysis. StatView software (version 5.0; SAS Institute Inc., Cary, NC) was used for data processing and analyses. Significance was defined as p values less than 0.05. Additional details of the methods used are provided in the online supplement.

RESULTS

During the study period, among the 690 patients admitted to our ICU, 290 (42%) were ventilated for 48 hours or more. Although VAP was clinically suspected in 172 (59%) patients, it was microbiologically confirmed in only 69 (40%), and the 6 patients who died before Day 3 were not included in the analysis. Among the 63 patients enrolled in the study, 38 (60%) had unfavorable outcomes (14 deaths, 21 recurrences, and 3 documented extrapulmonary infections), with a mean time to unfavorable outcome of 16 ± 6 days. No patients had a concomitant extrapulmonary infection at the time of entry. Patients' characteristics at ICU admission and VAP Day 1 are shown in Table 1. There were no differences between groups at admission.

TABLE 2. ETIOLOGY OF THE FIRST EPISODE OF VENTILATOR-ASSOCIATED PNEUMONIA DOCUMENTED MICROBIOLOGICALLY IN BRONCHOSCOPIC SPECIMENS*

Microorganisms	Unfavorable Outcome (*n = 47*)	Favorable Outcome (*n = 29*)
Bacilli, n (%)	26 (55.3)	14 (48.3)
Pseudomonas aeruginosa	9 (19.1)	2 (6.9)
Acinetobacter baumannii	—	1 (3.4)
Escherichia coli	2 (4.3)	2 (6.9)
Enterobacter species	4 (8.5)	—
Proteus species	—	1 (3.4)
Serratia species	—	2 (6.9)
Klebsiella species	2 (4.3)	—
Citrobacter species	1 (2.1)	2 (6.9)
Moraxella species	—	1 (3.4)
Haemophilus species	5 (10.6)	2 (6.9)
Others	3 (6.4)	1 (3.4)
Cocci, n (%)	21 (44.7)	15 (51.7)
MSSA	4 (8.5)	4 (13.8)
MRSA	—	4 (13.8)
Coagulase-negative staphylococci	1 (2.1)	1 (3.4)
Streptococcus species	12 (25.5)	6 (20.7)
Neisseria species	3 (6.4)	—
Enterococcus species	1 (2.1)	—

Definition of abbreviations: MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *S. aureus*.

* Values are the numbers (%) of microorganisms isolated at significant concentrations from quantitative cultures of bronchoalveolar lavage ($\geq 10^4$ cfu/ml). Some patients had more than one pathogen. Not all percentages add up to 100 because of rounding.

At the time of VAP onset, patients whose outcome would be unfavorable were more critically ill than those with a subsequent favorable outcome, with significantly higher mean WBC counts and sepsis-related organ failure assessment scores and lower Pa_{O_2}/FI_{O_2} ratios.

Microorganisms considered responsible for VAP are listed in Table 2. The percentage of *Pseudomonas aeruginosa* infections in the unfavorable-outcome group was higher than that in the favorable-outcome group (19.1% vs. 6.9%, respectively) but was not significantly different ($p = 0.18$).

Characteristics of patients during VAP are reported in Table 1 and Figure 1. Although mean temperatures, the modified clinical pulmonary infection score, and organ dysfunction(s) and/or infection and sepsis-related organ failure assessment scores decreased from Day 1 to Day 7 in both groups, mean WBC counts, radiologic score, and Pa_{O_2}/FI_{O_2}ratios did not. On Day 7, patients whose outcomes would be unfavorable had mean temperatures and WBC counts similar to those with subsequent favorable outcomes, but their mean radiologic, organ dysfunction(s) and/or infection, and sepsis-related organ failure assessment scores were significantly higher, whereas their mean Pa_{O_2}/FI_{O_2} ratio was lower. The numbers of patients remaining on mechanical ventilation on Day 7 and the total numbers of days on mechanical ventilation were comparable for the two groups, but the percentage of patients who would have unfavorable outcomes and who were still on mechanical ventilation on Day 7 tended to be higher ($p = 0.09$). The mean duration of antimicrobial treatment was comparable for both groups (Table 1).

Serum procalcitonin and C-reactive protein concentrations decreased between Days 1 and 7 in both groups but were significantly higher in patients whose outcomes would be unfavorable than in those with subsequent favorable outcome (Figure 2). Similar results were obtained when patients were grouped in the three following categories: death, infection recurrence, and favorable outcome (Table E2 and Figures E1 and E2).

The ability to differentiate between patients whose outcomes would be unfavorable and those with subsequent favorable outcomes, based on procalcitonin concentrations on Days 1, 3, and 7, was assessed with receiver operating characteristics curve analysis (Figure 3). To predict unfavorable outcome, a procalcitonin cut-off value of 1 ng/ml on Day 1 had a sensitivity of 83% (95% confidence interval, 70–90%) and a specificity of 64% (95% confidence interval, 51–74%). A procalcitonin threshold of 1.5 ng/ml on Day 3 had a sensitivity of 74% (95% confidence interval, 62–83%) and a specificity of 84% (95% confidence interval, 74–91%), and a cut-off value of 0.5 ng/ml on Day 7 had a sensitivity of 90% (95% confidence interval, 80–96%) and a specificity of 88% (95% confidence interval, 77–94%).

Factors potentially associated with unfavorable outcome retained by multivariate analyses are reported in Table 3. As indicated, on Day 1, serum procalcitonin of more than 1 ng/ml was the strongest indicator of unfavorable outcome with an odds ratio of 12.3. On Day 3, a Pa_{O_2}/FI_{O_2} ratio of less than 210 mm Hg and serum procalcitonin of more than 1.5 ng/ml were even more strongly associated with unfavorable outcome. On Day 7, serum procalcitonin of more than 0.5 ng/ml was the strongest independent predictor of unfavorable outcome, with an odds ratio of 64.2.

DISCUSSION

We designed this study to test the hypothesis that procalcitonin could be a helpful marker of VAP prognosis. Although pulmonary and/or extrapulmonary superinfection could be more evocative of ongoing risks than VAP antimicrobial treatment failure, they are associated with poorer prognosis, and thus, we decided to pool them with other poor outcome events (death, persistent infection, and relapse). Our results showed that serum procalcitonin concentrations were higher in patients with unfavorable outcomes than in patients with favorable outcomes. Moreover, despite differences in the clinical presentations at VAP onset of the two groups, a serum procalcitonin threshold of more than 0.5 ng/ml on Day 7 was the strongest independent marker of unfavorable outcome. Other clinical or biologic factors, such as WBC counts or C-reactive protein, were not able to discriminate between patients whose outcomes would be unfavorable and those with subsequent favorable outcomes. Furthermore, procalcitonin levels were higher as early as Day 1 in patients whose outcomes would be unfavorable. This difference between the two groups early during the clinical course of VAP could be explained by the baseline characteristics of the patients; patients whose outcomes would be unfavorable were more critically ill than those with subsequent favorable outcomes, and more severe disease is known to be associated with high serum procalcitonin concentrations (12). However, despite significantly different procalcitonin levels for the two groups on Day 1 and Day 3, they overlapped, and the receiver operating characteristic values at these times were not sufficient to guide clinicians as to which clinical strategy they should adopt. On Day 7, the overlap of procalcitonin levels was small, and the area under the receiver operating characteristics curve was 0.9, leading us to postulate that serum procalcitonin on Day 7 could be useful in combination with clinical factors, such as Pa_{O_2}/FI_{O_2} and radiologic and sepsis-related organ failure assessment scores, to predict which patients are likely to fail.

Luna and colleagues showed that using serial measurements of modified clinical pulmonary infection score they could, by Day 3 after VAP diagnosis, differentiate between patients with poor clinical outcomes from those with good clinical outcomes (7). Notably, improvement of the modified clinical pulmonary infection score for survivors was due almost exclusively to im-

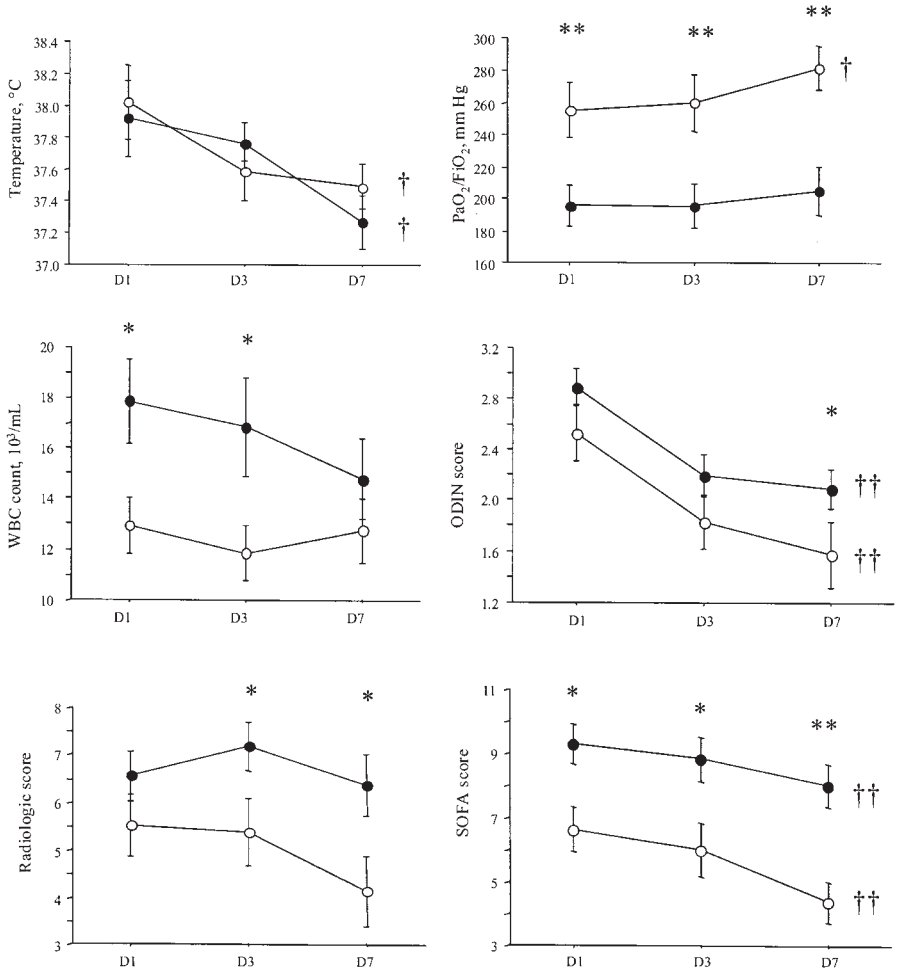

Figure 1. Kinetics of clinical parameters for patients with favorable (*open circles*) or unfavorable (*closed circles*) outcomes from Day 1 (D1) to Day 7 (D7). Results are expressed as means ± SEM. *$p < 0.05$ and **$p < 0.001$ for comparisons between groups. †$p < 0.05$ and ††$p < 0.0001$ on Day 7 versus Day 1. ODIN = organ dysfunction(s) and/or infection; SOFA = sepsis-related organ failure assessment; WBC = white blood cell count.

provement of the Pa_{O_2}/FI_{O_2} ratio and radiologic score (7). We found the same result; that is, Pa_{O_2}/FI_{O_2} was one of the two clinical factors that differed between groups on Day 7, whereas temperature, radiologic score, and WBC counts did not. In their study evaluating factors associated with VAP recurrence, Combes and colleagues found that the radiologic score and the presence of acute respiratory distress syndrome on Day 8 were associated with VAP recurrence, along with the persistence of fever and mechanical ventilation on Day 8 (8). However, the studies assessing the factors associated with either recurrence (8) or death (7) lacked a discriminatory marker of VAP prognosis.

Only a few other studies have investigated the abilities of biological markers to predict VAP prognosis. Froon and colleagues studied 42 patients with microbiologically proven VAP and found that bactericidal/permeability-increased protein (an inflammatory protein released by killed or activated neutrophils) and soluble E-selectin were higher early during the course of VAP in patients who would die, as compared with survivors (28). However, in that study, the authors showed that systemic levels of inflammatory mediators did not predict clinical severity or patient outcome better than daily simplified acute physiology score II (28). Duflo and colleagues evaluated markers of oxidative stress in the plasma and bronchoalveolar lavage samples of 36 patients with VAP and 42 patients without VAP (29). They found that thiobarbituric acid–reactive substances in bronchoalveolar lavage and plasma and alveolar concentrations of glutathione peroxidase were higher in patients with VAP than those without. However, that study failed to demonstrate a difference in plasma or bronchoalveolar lavage markers of oxidative stress between survivors and nonsurvivors (29). Moreover, in those two studies, the molecules studied are not routinely and easily assessed, whereas serum procalcitonin is easy to determine. It should be noted that the time-resolved amplified cryptate emission technology used in our study is not available worldwide, and the apparatus is expensive. Another already commercialized procalcitonin assay (based on luminometry) is available in many countries and, although less sensitive, could probably adequately obtain comparable results.

Procalcitonin, the precursor molecule of calcitonin, was initially described as a marker of bacterial infection in pediatric patients with meningitis (11). The results of recent investigations suggest that the procalcitonin concentration closely parallels the severity and evolution of infection (12, 30–32). Moreover, it seems to be useful as a prognostic marker during meningococcal disease in children (33) and as a guide to antimicrobial therapy in patients with lower respiratory tract infections (34). Only one study evaluated procalcitonin in 44 patients with VAP and 52 patients without. Those authors found that serum procalcitonin levels were higher in the patients with VAP and higher serum procalcitonin concentrations persisted during the clinical course of nonsurvivors (16). However, they did not evaluate serum procalcitonin as an independent prognostic marker during VAP.

Some limitations of our study should be noted. First, our study population is relatively small, and these results have to be validated in a larger cohort of patients. Second, because of the specialization of our referral ICU in caring for patients with

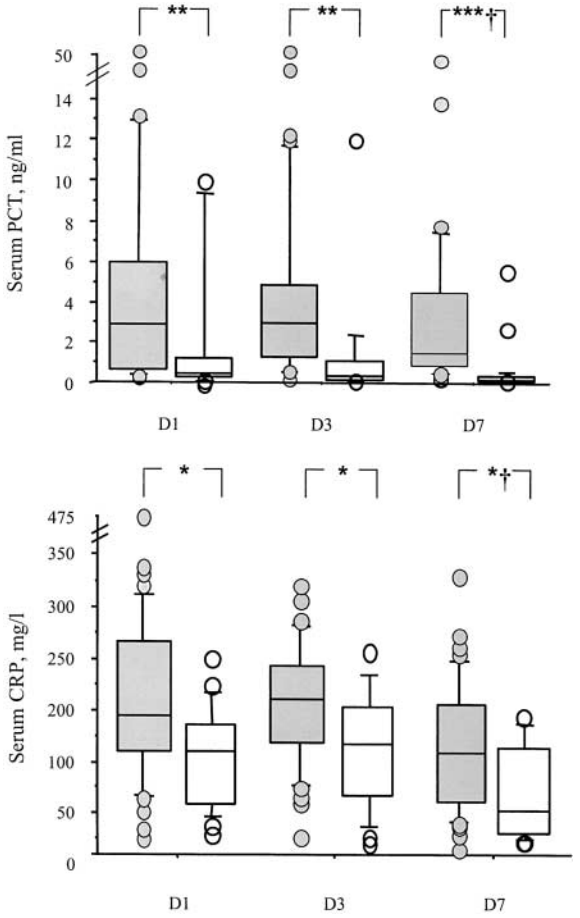

Figure 2. Kinetics of serum procalcitonin (*top*) and C-reactive protein (*bottom*) in patients with favorable (*open boxes*) or unfavorable (*closed boxes*) outcomes from Day 1 to Day 7. Box plots represent the 25th and 75th percentiles, with the *internal horizontal line* showing the median and *T bars* the 10th and 90th percentiles. *Circles* represent outliers. *$p < 0.05$, **$p < 0.001$, and ***$p < 0.0001$ for comparisons between groups; †$p < 0.05$ on Day 7 versus Day 1.

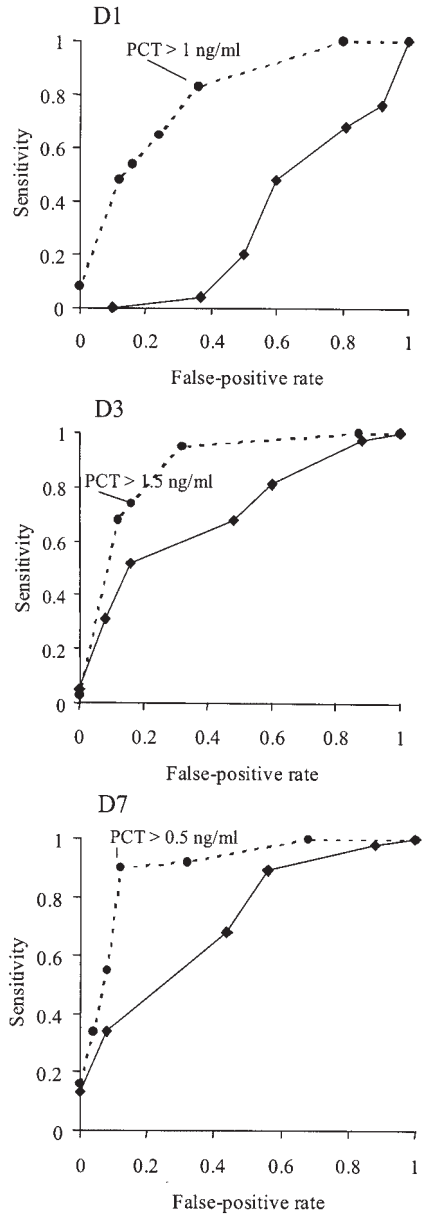

Figure 3. Receiver operating characteristics (ROC) curves of procalcitonin (PCT; *closed circles*) and C-reactive protein (CRP; *closed diamonds*) concentrations on Day 1 (D1), Day 3 (D3), and Day 7 (D7) to predict outcome. Areas under the ROC curves for procalcitonin and C-reactive protein were, respectively, 0.79 and 0.4 on Day 1, 0.87 and 0.69 on Day 3, and 0.90 and 0.66 on Day 7.

prolonged mechanical ventilation and severe disease and a high percentage of them had shock or other organ failures at the time of VAP, we have a very high unfavorable outcome rate (2, 6, 10). Hence, it is difficult to extrapolate our results to other ICU with different types of patients. However, Duflo and colleagues obtained similar results for their patients (16). Third, the high procalcitonin levels observed in patients whose VAP outcomes would be unfavorable could have been due to another infection, because this marker is not specific to pulmonary infection. However, we do not think this is likely because in our ICU we make every effort to exclude other causes of systemic infection in these patients, even when the diagnosis of VAP is clinically evident. In contrast to several previous studies (1–5, 9), we were unable to establish any significant relationship between *P. aeruginosa* infection and outcome, even though the percentage of VAP episodes caused by that organism was higher for patients with unfavorable than favorable outcomes. This lack of significance can probably be explained by the small number of patients concerned. Finally, our patients had spent an average of 12 days in the ICU before developing pneumonia, which might have contributed to the higher procalcitonin level.

In conclusion, the serum procalcitonin level may provide an early indication of VAP outcome. Further studies on a larger number of patients are required to delineate the role of this marker in early risk stratification.

Conflict of Interest Statement: C.-E.L. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; V.G. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; A.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; J.-L.T. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; S.B.A. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; M.B. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; C.G. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; J.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

TABLE 3. MULTIVARIATE LOGISTIC-REGRESSION ANALYSIS OF FACTORS USED TO DIFFERENTIATE BETWEEN PATIENTS WITH FAVORABLE OR UNFAVORABLE OUTCOMES

Factors Associated with Outcome	OR	95% CI	p Value
Day 1*			
$Pa_{O_2}/FI_{O_2} < 215$ mm Hg	3.6	1.1–12.1	0.04
Procalcitonin > 1 ng/ml	12.3	2.4–62.2	0.002
Day 3†			
$Pa_{O_2}/FI_{O_2} < 210$ mm Hg	25.9	3.9–173.2	0.0008
Procalcitonin > 1.5 ng/ml	24.6	4.6–122.3	< 0.0001
Day 7‡			
$Pa_{O_2}/FI_{O_2} < 235$ mm Hg	6.4	1.1–37.9	0.04
Procalcitonin > 0.5 ng/ml	64.2	11.1–375.5	< 0.0001

Definition of abbreviations: CI = confidence interval; OR = odds ratio.

* The following variables were entered into the model: age, McCabe and Jackson classification, duration of mechanical ventilation before ventilator-associated pneumonia onset, type(s) of pathogens responsible for ventilator-associated pneumonia, sepsis-related organ failure assessment score, white blood cell count, Pa_{O_2}/FI_{O_2} ratio, modified clinical pulmonary infection score, serum C-reactive protein, and procalcitonin on Day 1.

† The following variables were entered into the model: age, McCabe and Jackson classification, duration of mechanical ventilation before ventilator-associated pneumonia onset, type(s) of pathogens responsible for ventilator-associated pneumonia, sepsis-related organ failure assessment, and radiologic scores, white blood cell count, Pa_{O_2}/FI_{O_2} ratio, modified clinical pulmonary infection score, serum C-reactive protein, and procalcitonin on Day 3.

‡ The following variables were entered into the model: age, McCabe and Jackson classification, duration of mechanical ventilation before ventilator-associated pneumonia onset, type(s) of pathogens responsible for ventilator-associated pneumonia, sepsis-related organ failure assessment, and radiologic scores, Pa_{O_2}/FI_{O_2} ratio, modified clinical pulmonary infection score, serum C-reactive protein, and procalcitonin on Day 7.

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