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BRIEF REPORT

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Procalcitonin kinetics in the prognosis of severe community-acquired pneumonia

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Abstract *Objectives:* Procalcitonin (PCT) kinetics is a good prognosis marker in infectious diseases, but few studies of community-acquired pneumonia (CAP) have been performed in intensive care units (ICU). We analyzed the relationship between PCT kinetics and outcome in ICU patients with severe CAP. *Design and setting:* Prospective observational study in a 16-bed university hospital ICU. *Patients:* 100 critically ill patients with community-acquired pneumonia. *Measurements and results:* Median PCT was 5.2 ng/ml on day 1 and 2.9 ng/ml on day 3. It increased from day 1 to day 3 in non-survivors but decreased in survivors. In multivariate analysis four variables were associated with death: invasive ventilation (odds ratio 10–), multilobar involvement (5.6–), LOD score (6.9–), and PCT increase from day 1 to day 3 (4.5–). In intubated patients with a PCT level below 0.95 ng/ml on day 3 the survival rate was 95%. *Conclusion:* Increased PCT from day 1 to day 3 in severe CAP is a poor prognosis factor. A PCT level less than 0.95 ng/ml on day 3 in intubated patients is associated with a favorable outcome.

Keywords Community-acquired pneumonia · Procalcitonin · Prognosis

Introduction

Numerous recent studies have focused on procalcitonin (PCT) in infectious diseases diagnosis and prognosis, but its significance is still under debate. Pathophysiology understanding has recently improved. The PCT level increases 3 h after the beginning of an infectious syndrome and reaches a plateau 6–24 h later [1]. Expression is activated by the lipopolysaccharide (LPS) and the proinflammatory cytokines tumor necrosis factor α and interleukin 6, and parenchymal cells probably have a major role in PCT secretion in sepsis [2]. PCT has also a role in the severity of infections. One explanation has been proposed by Hoffman et al. [3] who found that PCT increased nitric oxide synthesis and migration of monocytes to the infected site when it was

associated with LPS, interferon γ, and tumor necrosis factor α.

PCT is a marker of infection with better sensitivity and specificity than C-reactive protein (CRP) [4]. Moreover, its measure is important for evaluation of patients' prognosis [5, 6, 7, 8]. However, some authors have not found such a relationship in community-acquired pneumonia (CAP) [9, 10]. In a study of 110 CAP patients in our intensive care unit (ICU) we noted a prognostic value of a PCT level with a cutoff of 2 ng/ml on admission but could not determine a cutoff value predicting mortality [11]. Several recent studies have underlined the interest of PCT kinetics in the evaluation of patients' prognosis [10, 12, 13]. We therefore examined PCT kinetics in hospitalized CAP patients in our ICU to evaluate its prognostic value.

Material and methods

All consecutive patients in the ICU of Tourcoing Hospital exhibiting CAP between November 2003 and March 2005 were prospectively included. A total of 120 patients met the inclusion criteria; of these, 20 were excluded (8 left the ICU, 8 died within 48 h of hospitalization, 4 failed to have PCT measured). Analysis was thus performed on 100 patients. Characteristics of patients on ICU admission are summarized Table 1. We collected the following variables on days 1 and 3: temperature, leukocyte and platelet counts, CRP, and PCT values, PaO_2/FIO_2ratio, and logistic organ dysfunction (LOD) score. Pneumonia was documented microbiologically in 55% of cases. The main agents were: *Streptococcus pneumoniae* ($n = 18$), *Staphylococcus aureus* ($n = 12$, with 2 resistant to methicillin), *Legionella pneumophila* ($n = 9$), *Haemophilus influenzae* ($n = 6$), *Escherichia coli* ($n = 4$), and other bacteria ($n = 6$). Twenty-three patients presented bacteremia: *S. pneumoniae* ($n = 11$), *S. aureus* ($n = 6$), *E. coli* ($n = 3$), and other pathogens ($n = 3$). Mortality rate in ICU was 30%. Patient mortality was evaluated at ICU discharge. More details about data collection, definitions, and statistical analysis are available in the Electronic Supplementary Material (ESM).

Table 1 Patients' characteristics at admission

Age (years)	62.9±15.1
SAPS II	45.8±16.8
LOD score	6±3.2
PaO_2/FIO_2	171±89.2
Gender: M/F	64/36
McCabe: 1/2/3	8/54/38
Immunosupression	18
Corticotherapy	7
Malignancy	7
Others	4
Radiographic chest infiltrate	
Unilobar	56
Multilobar	44
Bilateral	32
Aspiration	15
Septic shock	40
Bacteremia	23
Ventilation	
Invasive	65
Noninvasive	15
Oxygenotherapy	20

Categorical variables are expressed as frequencies and continuous variables as means with standard deviation when the distribution was normal; when it was not normal, they are expressed in medians and interquartile range (IQR). Comparisons between groups were performed using the χ^2 test or Fisher's exact test for categorical parameters. Continuous variables were analyzed using Wilcoxon's test. To determine the factors associated with mortality we carried out two multivariate analyses: logistic regression analysis and χ^2 automatic interaction and detection (CHAID).

Results

Median PCT was 5.2 ng/ml (IQR 0.9–19.9) on day 1 and 2.9 ng/ml (0.6–10.5) on day 3. Median CRP was 192 mg/l (IQR 91–317) on day 1 was and 143 mg/l (72–245) on day 3. Median PCT was higher on day 1 in ICU nonsurvivors (6.4 ng/ml, IQR 1.4–37) than in survivors (4.5 ng/ml, < 0.5–14; $p = 0.03$); median PCT on day 3 in nonsurvivors was 8.2 ng/ml (2.9–53) and in survivors 1.6 ng/ml (< 0.5–7.6; $p < 0.001$). Analysis of PCT kinetics showed an increase in nonsurvivors and a decrease in survivors ($p = 0.01$; Fig. 1). PCT increased from day 1 to day 3 in

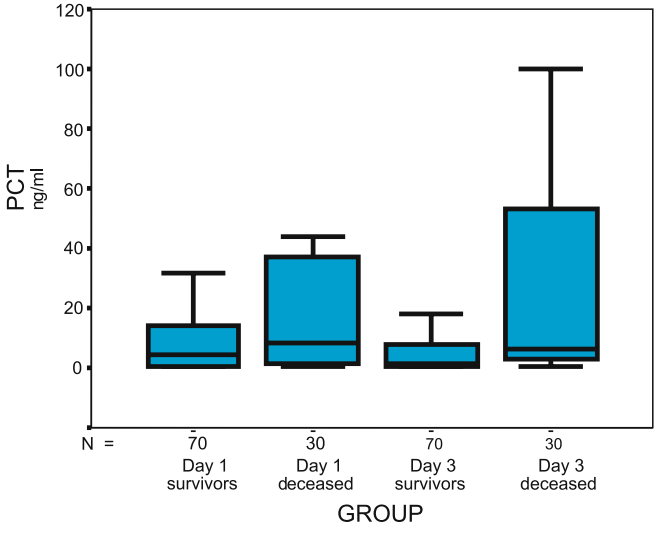

Fig. 1 Box plot of procalcitonin (*PCT*) levels on days 1 and 3 in survivors and nonsurvivors; $p = 0.03$ survivors' vs. nonsurvivors' PCT value on day 1, $p < 0.001$ survivors' vs. nonsurvivors' PCT value on day 3, $p = 0.01$ survivors' vs. nonsurvivors' PCT change from day 1 to day 3

17 of 30 nonsurvivors patients and decreased in 62 of 70 survivors. PCT decreased from day 1 to day 3 with regard to mortality, with 89% specificity, 82% predictive negative value, 56% sensitivity, and 71% predictive positive value. Variations in CRP were not statistically significant (increase in 9 of 30 deceased patients and in 26 of 70 survivors; $p = 0.6$).

Multivariate analysis revealed only four variables with an independent risk factor of mortality: invasive ventilation on admission (odds ratio, OR, 9.988, 95% confidence interval, IC, 2.18–45.65; $p = 0.003$), chest radiographic involvement of more than one lobe (OR 5.64, 95% CI 1.85–17.18; $p = 0.002$), PCT increase (OR 4.539, 95% CI 1.31–15.75; $p = 0.017$), and LOD score increase from day 1 to day 3 (OR 6.874, 95% CI 1.22–38.81; $p = 0.029$). (See ESM S.T1 and S.T2 related to univariate and multivariate analysis.)

Multivariate analysis using the CHAID method showed the two most significant variables in patients' prognosis to be the need of invasive ventilation on ICU admission and PCT level on day 3. Mortality was 9% in nonintubated patients, and 42% in intubated patients. In the later group mortality was 5% in patients with day 3 PCT level below 0.95 ng/ml and 57% in those with day 3 PCT level above 0.95 ng/ml.

Discussion

Our results confirm the relevance of PCT level on days 1 and 3 in severe CAP. An increase within the first 48- h of hospitalization appears as an independent risk factor of mortality, and a level below 0.95 ng/ml on day 3 is an early predictor of favorable outcome in intubated patients.

PCT level on admission in patients suffering from sepsis or septic shock is usually considered a better prognostic marker than the other inflammatory markers [14, 15, 16]. Nevertheless, its sensitivity is too low to determine a cutoff admission value distinguishing patients who will survive and who will die. Recently the focus has been put upon PCT kinetics. A relationship between PCT variations and outcome during hospitalization have been well established in sepsis and septic shock [8, 12, 13].

Few data on PCT and CAP are available in the literature. A study of 96 hospitalized CAP patients found no correlation between admission PCT level and hospital mortality, but the overall mortality was low. On the other hand, PCT value was correlated with Acute Physiology and Chronic Health Evaluation II score, and PCT decreased on day 3 and day 6 for all patients [17]. Polzin et al. [9] noted that PCT increase was often below the 0.5 ng/ml cutoff value in patients presenting a lower respiratory tract infection (CAP, nosocomial pneumonia, and chronic bronchitis exacerbation) excepted in patients who died. The study by Brunkhorst et al. [10] has been the only one to evaluate the prognostic value of PCT in CAP and nosocomial pneumonia hospitalized in ICU. Day 1 PCT level was not predictive of outcome although an increase between days 3 and 5 was associated with death; this factor was not statistically significant in multivariate analysis.

In our previous study [11] PCT level on ICU admission in CAP patients was a prognostic marker. We found that PCT level was higher in the case of bacteremia and initial septic shock, in patients who develop sepsis-related complications during their stay, and in patients who die in ICU. Our current study focused on PCT kinetics. We observed that a PCT decrease during the first 2 days of ICU stay is a good indicator of outcome, and that a PCT increase is an independent risk factor of mortality with an odds ratio greater than 4.

An interesting result is the high probability of survival (95%) in intubated patients with day 3 PCT level less than 0.95 ng/ml. PCT appears to be an early mortality marker in patients who otherwise at that time present with unpredictable outcomes (pneumonia in the early phase of treatment when clinical, biological and radiological abnormalities are not yet corrected). The only patient who died in this group was an elderly woman who remained in the ICU several weeks without any possibility of ventilator weaning and died of a cause unrelated to pneumonia. Our results suggest a particularly simple prognosis algorithm, but this must be confirmed by validation through a larger cohort.

Our study has several limitations. Our results are limited by our PCT measuring technique which used a 0.5 ng/ml detection level, and this threshold is not specific enough to eliminate a bacterial infection. A major problem is the lack of a universally accepted "gold standard" for the diagnosis of pneumonia. Our patients presented with the clinical, biological, and radiological criteria required to assess the diagnosis of pneumonia. Bacteriological samples were negative in 45% of them, a figure that is common in this setting [18], and therefore we do not think this lack of documentation can cast doubt upon our results.

Thus, in conclusion our findings confirm the value of measuring PCT for the evaluation of ICU hospitalized patients with severe CAP. A PCT decrease is highly predictive of survival while a PCT increase is an independent risk factor of mortality. More specifically, in intubated patients a day 3 PCT value less than 0.95 ng/ml is associated with 95% survival probability.

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