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Usefulness of procalcitonin for the diagnosis of ventilator-associated pneumonia

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Abstract *Objective:* To assess the predictive capacity for the diagnosis of ventilator-associated pneumonia (VAP) of serum procalcitonin levels before and on the day it is suspected. *Design and setting:* Single-center observational study in the intensive care unit of a teaching hospital. *Patients and participants:* Consecutive patients whose serum procalcitonin levels were available on the day that VAP was clinically suspected (day 1) and at some time within the preceding 5 days ("before"). *Measurements and results:* Serum procalcitonin levels were determined on day 1 and "before". Among the 73 suspected episodes VAP was confirmed by quantitative bronchoalveolar lavage cultures in 32 and refuted in 41. Respective median "before" procalcitonin levels were 1.89 ng/ml (interquartile range 0.18–6.01) and 2.14 (0.76–5.75) in patients with and without VAP, but their respective median day-1 procalcitonin levels did not differ: 1.07 ng/ml (0.39–6.57) vs. 1.40 (0.67–3.39). On day 1 a 0.5 ng/ml procalcitonin threshold had 72% sensitivity but only 24% specificity for diagnosing VAP. Between "before" and day 1, procalcitonin increased in 41% and 15% of patients with and without VAP, respectively. Thus a procalcitonin rise on day 1, compared to its "before" level, had 41% sensitivity and 85% specificity for diagnosing VAP, with respective positive and negative predictive values of 68% and 65%. *Conclusions:* Crude values and procalcitonin rise had poor diagnostic value for VAP in this particular setting and thus should not be used to initiate antibiotics when VAP is clinically suspected.

Keywords Ventilator-associated pneumonia · Procalcitonin · Diagnosis · Clinical pulmonary infection score

Introduction

How to diagnose ventilator-associated pneumonia (VAP) remains controversial [1, 2]. Although some data support the superiority of bronchoscopic techniques (here called invasive strategy) for diagnosing VAP [3, 4], this approach is not recognized worldwide and is often replaced by a clinical strategy, based on clinical variables (or the Clinical Pulmonary Infection Score, CPIS) and quantitative (or qualitative) cultures of endotracheal aspirates [5]. The invasive strategy is probably more difficult to implement everywhere, mainly because of the availability and mastery of the technique and economic considerations [1, 2]. Regardless of the strategy used the search continues for

reliable diagnostic markers that could rapidly and easily distinguish patients with VAP from those without. Prompt and specific identification of patients with true VAP might enable antibiotics to be initiated rapidly without their overuse.

Procalcitonin (PCT), one of the precursors of calcitonin, is upregulated during bacterial sepsis [6]. Its accuracy for diagnosing severe sepsis is now well recognized [7], making it a valuable marker for this diagnosis [8]. To our knowledge, only a few studies have evaluated the potential usefulness of PCT for diagnosing VAP in the intensive care unit (ICU) [9–12], and thus it remains unknown whether PCT can improve the management of ventilated patients with clinically suspected VAP. PCT is probably more difficult to use as a diagnostic marker in ICU patients than those admitted from the community, mainly because most of the former have already developed systemic inflammation response syndromes, multiorgan failure, and/or a previous infection, conditions known to raise the PCT level in the absence of active infection [13].

Therefore we conducted a prospective study to test the diagnostic value of PCT measured the day VAP was clinically suspected (day 1, D_1), using bronchoalveolar lavage (BAL) fluid cultures as the reference standard [1, 14]. Because we subsequently thought that PCT kinetics during the days preceding suspected VAP may be more informative than a single measurement obtained on D_1, the diagnostic value of PCT kinetics, using PCT values obtained within the 5 days preceding D_1, was also tested retrospectively.

Materials and methods

Study setting and population

Between January 2006 and June 2006 all consecutive patients who were clinically suspected of having developed VAP after 48 h of mechanical ventilation (MV) in our ICU, and for whom a PCT measurement had been obtained within the 5 days preceding D_1 ("before") were included. Clinical suspicion was defined as a new pulmonary infiltrate or progression of an existing infiltrate on chest radiography associated with at least one of the following: temperature 38.3°C or higher, white blood cell (WBC) count 10^9/l, and purulent tracheal secretions (in patients with acute respiratory distress syndrome, ARDS, in whom the demonstration of radiological deterioration is difficult, at least one of the three preceding criteria sufficed). VAP was also suspected when unexplained hemodynamic instability required higher vasopressor doses (increase of $> 30\%$) or their introduction; in the case of unexplained deterioration in blood gases, with less than 30% PaO_2/FIO_2 decrease; or when an intercurrent event imposed an urgent change in antibiotic therapy, regardless of the reason [1, 11].

All these patients underwent fiberoptic bronchoscopy to collect distal pulmonary secretions and BAL fluids before any new antibiotics were started. After centrifugation total cells in an aliquot of the resuspended, original pooled fluid were counted. Cytocentrifuge preparations were made with a Cytospin 2 centrifuge (Shandon Southern Products, Cheshire, UK) and stained with a modified Wright-Giemsa stain (Diff-Quik, Baxter Diagnostic, Düdingen, Switzerland). Differential cell counts and the proportions of cells containing intracellular bacteria were determined, as previously described [14, 15]. VAP was diagnosed when the two following criteria were met: (a) clinically suspected VAP, as defined above, and (b) significant growth ($\geq 10^4$ cfu/ml) in quantitative cultures of distal BAL fluid samples obtained by fiberoptic bronchoscopy [1]. None of the patients receiving antibiotics on D_1 had had their antibiotic regimen modified during the preceding 3 days.

During the study period VAP was suspected 84 times in 46 patients. For 11 suspected episodes that occurred in five patients a "before" serum PCT measurement was not available, and they were not included in the analysis. However, taking into account these 11 episodes, for which D_1 PCT levels were available, did not change the results (data not shown). Among the 73 remaining suspected episodes VAP was diagnosed for 32 (44%) and refuted for 41 (66%). The clinical characteristics at ICU admission of the 41 patients included are shown in Table 1.

Table 1 Characteristics at ICU admission of the 41 patients included in the study

Age, median (years; IQR)	60 (50–71)
Sex: male	29 (71%)
McCabe and Jackson comorbidity score ≥ 2	27 (66%)
SAPS II, median (IQR)	54 (44–69)
SOFA score, median (IQR)	12 (7–15)
Admission category	
Medical	20 (49%)
Emergency surgery [a]	19 (46%)
Elective surgery [a]	2 (5%)
Reason for MV	
Acute respiratory failure	13 (32%)
Postoperative respiratory failure [b]	21 (51%)
Neurological	1 (2%)
Others	6 (15%)
Solid organ transplantation	3 (7%)
Corticosteroid use	14 (34%)
Renal failure [c]	24 (59%)
Total duration of MV, median (days; IQR)	22 (13–42)
ICU mortality	17 (41%)
Hospital mortality	22 (54%)

[a] All these patients were admitted to our ICU after recent cardiac surgery

[b] Acute lung injury, ARDS, pneumonia or multiorgan failure complicating cardiac surgery

[c] Defined as serum creatinine > 180 μmol/l or need for renal replacement therapy

Data analysis

The following data were recorded prospectively at admission: age, sex, category of admission (medical, elective or emergency surgery), severity of underlying medical conditions stratified according to the criteria of McCabe and Jackson [16], Simplified Acute Physiology Score (SAPS) II [17], and Sequential Organ-Failure Assessment (SOFA) score [18]. The following additional data were recorded on D_1 (also on the day of bronchoscopy): temperature, WBC count, PaO_2/FIO_2 ratio, radiological score [19], volume and aspect of tracheal secretions, and SOFA score.

PCT assay

It is our policy to measure PCT routinely, essentially as a prognostic marker [11]. We selected patients for whom a "before" serum PCT level had been determined. All these patients also had a PCT measurement on D_1, as part of their routine biological analyses. Patients were grouped according to their serum PCT level increase or decrease before D_1. All PCT concentrations were determined using time-resolved amplified cryptate emission technology on a Kryptor analyzer (Brahms Diagnostica, Berlin, Germany).

CPIS calculation

CPIS was calculated at baseline by one of the investigators independently of the treating physicians, based on the following five clinical and biological variables: body temperature, WBC count, tracheal secretion characteristics, oxygenation, and pulmonary radiography [20–22]. A modified CPIS (CPIS + PCT) was calculated by incorporating PCT kinetics as follows: serum PCT level increase between "before" and D_1, add 2 points; stable or decreased serum PCT level between "before" and D_1, 0 points. The addition of 2 points when PCT increased from "before" to D_1 and 0 otherwise was based on the results of a logistic-regression analysis, for which the dependent variable was the presence or absence of VAP and the independent variables the "classical" CPIS and PCT kinetics. The protocol was approved by our hospital's Committee for the Protection of Human Subjects. Informed consent was not obtained because this study did not modify existing diagnostic or therapeutic strategies. However, an information sheet describing the study was given to the patients or their relatives explaining that they were free to withdraw from the study at any time.

Statistical analysis

Data are expressed as medians (with interquartile range, IQR) unless specified otherwise and were compared as follows: continuous variables with the Mann–Whitney *U*-test or Student's *t*-test, as appropriate; categorical variables with the χ^2 test or Kruskall–Wallis test, as appropriate. PCT and its kinetics, CPIS, and CPIS + PCT were evaluated as diagnostic tests for VAP with receiver operating characteristics (ROC) curves and their areas under the curves and compared to the predictive capacities of the CPIS and the modified CPIS + PCT, when PCT kinetic changes were taken into account, as specified above. Analyses were performed using StatView 5.0 and SPSS (SAS Institute, Cary, NC, USA) software. Statistical significance was defined as $p < 0.05$.

Results

The D_1 clinical characteristics of their 73 suspected VAP episodes in the 41 patients are reported in Table 2. Only the radiological score differed between patients with VAP and

Table 2 Clinical characteristics at the time VAP episodes were suspected

	Confirmed VAP $n = 32$	Refuted VAP $n = 41$
Antibiotics 15 days before	27 (84%)	39 (95%)
Previous infection	22 (69%)	32 (78%)
Postcardiac surgery	16 (50%)	24 (59%)
MV duration before VAP suspected (days)	17.0 ± 13.0	15.3 ± 12.4
Day 1		
Temperature, median (°C; IQR)	38.2 (37.2–38.7)	38.4 (37.7–38.5)
WBC count, median (10^9/l; IQR)	14.1 (10.1–17.9)	14.4 (10.8–20.1)
Radiological score, median (IQR)	5 (4–8)	7 (5–8)*
PaO_2/FIO_2 ratio, median (IQR)	180 (110–245)	150 (118–260)
SOFA score, median (IQR)	9 (6–14)	10 (7–14)
ARDS	15 (47%)	20 (49%)
Multiorgan failure	16 (50%)	36 (88%)
Serum PCT (ng/ml; IQR)		
"Before" day 1	1.89 (0.18–6.01)	2.14 (0.76–5.75)
Day1	1.07 (0.39–6.57)	1.40 (0.67–3.39)

* $p = 0.02$

those without, being significantly higher for the latter. "Before" PCT was 0.5 ng/ml or higher in 54 of the 73 episodes (74%), reflecting the fact that most of the patients had been admitted to the ICU for severe sepsis or septic shock or after cardiac surgery. Median serum PCT levels on D_1 did not differ between patients with and without VAP, even after adjustment to the "before" value using a covariance analysis (data not shown).

On D_1 no best PCT cutoff values for VAP diagnosis could be established. Using a threshold of 0.5 ng/ml yielded 72% sensitivity but only 24% specificity, which is explained by D_1 PCT of 0.5 ng/ml or higher in 31 of the 41 refuted-VAP episodes (Table 3, Fig. 1). The predictive ability of the D_1 PCT concentration to diagnose VAP using four different thresholds is reported in Table 3. Among the 41 refuted-VAP episodes the only extrapulmonary infections were one case of catheter-related *Pseudomonas aeruginosa* bloodstream infection and one of candidemia. Excluding these two patients did not change the results (data not shown).

Fig. 2 shows individual before to D_1 PCT kinetics, according to the presence or absence of VAP. PCT rose during this period in 41% and in 15% of patients with and without VAP, respectively ($p = 0.01$), giving a positive predictive value of 68% (95% CI 49–84) and a negative predictive value of 65% (95% CI 53–76; Table 3). Using a cutoff value of 1 ng/ml or higher to define the before to D_1 PCT increase, the positive predictive value for VAP diagnosis was 60% (95% CI 35–81); conversely, a PCT decline of 1 ng/ml or greater during that period had a positive predictive value for the absence of VAP of 61% (95% CI 44–76).

D_1 PCT rose in 6 of the 41 episodes for which VAP was refuted, among which two extrapulmonary infections were diagnosed (see above). Therefore, using PCT kinetics as a marker of pulmonary and extrapulmonary infections, serum PCT increase on D_1 compared to its "before" value had 42% sensitivity and 89% specificity, with 79% and 63% positive and negative predictive values, respectively. For the remaining four episodes, with PCT rises without infection, three were developing reversible multiorgan failure and one had severe ARDS.

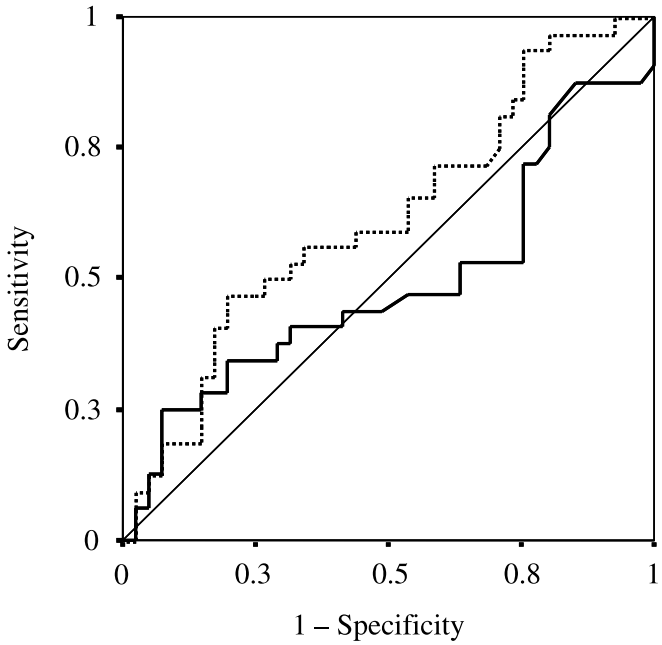

Fig. 1 ROC curves of day-1 PCT (*bold line*) and PCT increase (*dotted line*), with respective areas under the curves of 0.51 (95% CI 0.39–0.63) and 0.62 (95% CI 0.50–0.73)

CPIS predictive capacities on D_1 are shown in Table 3. Incorporation of PCT into the CPIS improved its sensitivity but lowered its specificity. The best parameter for VAP diagnosis was direct examination of cells collected during BAL. The ability to differentiate between patients with VAP and those without, based on D_1 PCT and PCT increase (Fig. 1) or CPIS and CPIS + PCT was assessed with ROC curve analyses. Areas under the ROC curves

Table 3 Predictive capacity to diagnose VAP episodes based on PCT kinetics and their incorporation into the CPIS (*PPV*, positive predictive value; *NPV*, negative predictive value; *PLR*, positive likelihood ratio; *NLR*, negative likelihood ratio)

	Sensitivity	Specificity	PPV	NPV	PLR	NLR
Day 1 PCT level						
≥ 0.5 ng/ml	72 (57–84)	24 (14–38)	43 (31–55)	53 (34–71)	0.95	1.17
≥ 1 ng/ml	53 (37–68)	37 (24–51)	40 (27–53)	50 (34–66)	0.84	1.27
≥ 1.5 ng/ml	44 (29–59)	51 (37–65)	41 (27–56)	54 (40–68)	0.90	1.09
≥ 2 ng/ml	41 (26–56)	61 (47–74)	45 (29–61)	57 (43–70)	1.05	0.97
PCT increased "before" D_1[a]						
= 0 ng/ml	41 (26–56)	85 (74–93)	68 (49–84)	65 (53–76)	2.73	0.69
≥ 0.5 ng/ml	26 (14–41)	86 (74–93)	57 (35–77)	61 (49–72)	1.86	0.86
≥ 1 ng/ml	19 (10–34)	90 (81–96)	60 (35–81)	60 (49–71)	1.90	0.9
CPIS > 5	59 (41–76)	73 (57–86)	63 (47–77)	70 (56–81)	2.19	0.56
CPIS + PCT > 5	72 (57–84)	63 (49–76)	61 (46–74)	74 (60–85)	1.95	0.44
Direct examination of BAL cells	94 (84–98)	98 (91–99)	97 (89–99)	95 (87–99)	47	0.06

[a] "Before" to D_1 differences were calculated with the following formula: PCT D_1 – "before"

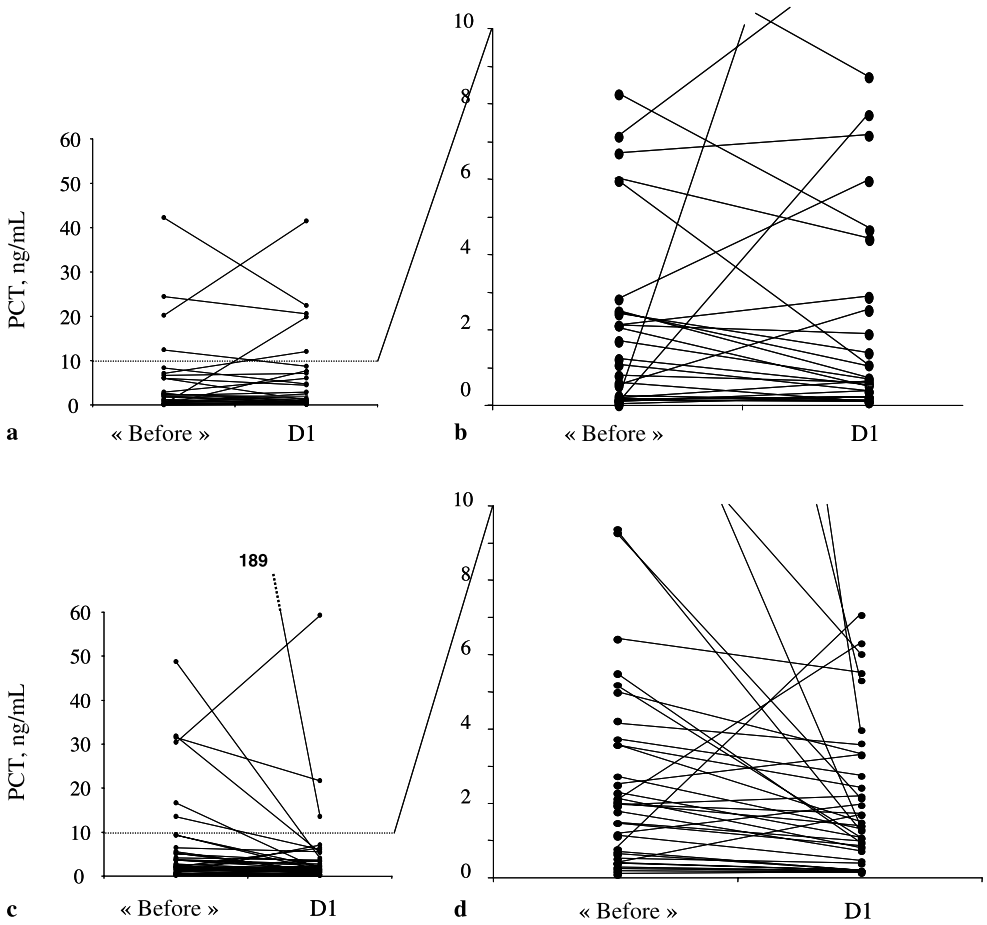

Fig. 2 Individual values and kinetics of serum PCT concentrations in the 32 confirmed (**a**) and the 41 refuted-VAP episodes (**c**) "before" and the day (D_1) VAP was clinically suspected, and the respective magnifications of their PCT values = 10 ng/ml (**b**, **d**)

were 0.68 (95% CI 0.56–0.78) for CPIS and 0.69 (95% CI 0.57–0.79) for CPIS + PCT. Subgroup analyses are available in the Electronic Supplementary Material.

Discussion

The results of this study demonstrate that PCT is a poor marker for VAP diagnosis in this population. Neither its D_1 level nor its kinetics had significant predictive capacity to diagnose VAP. Moreover, its combined use with CPIS did not improve the ability to identify patients with VAP from those without. The best parameter was direct examination of BAL cells, looking for intracellular bacteria. However, the positive predictive value of a serum PCT increase for pulmonary or extrapulmonary infection was 79%, justifying the immediate administration of antibiotics to those patients.

Only few data are available concerning PCT accuracy for VAP diagnosis, and published reports yield contradictory information. The results of three studies showed that PCT levels were higher in patients with VAP than those without [9, 23, 24], but these findings were refuted in another [10]. In two other studies testing PCT as a marker of VAP prognosis serum PCT levels varied widely at the time of diagnosis, ranging from 0.6 to 50 ng/ml in the first [11] and from 0.08 to 21.68 ng/ml in the other [12]. PCT cutoff values which are useful in the emergency department [25, 26] may be of only limited value in the ICU setting. Most ICU patients had preexisting condition(s) known to increase serum PCT concentrations (cardiac surgery, ARDS, multiorgan failure and/or a previously documenter bacterial infection), explaining the high PCT levels and their inability to discriminate among patients with or without a new VAP episode [27]. Furthermore, inflammation probably contributes little to VAP, as opposed to the severe underlying systemic inflammatory response syndrome associated in all critically ill intubated patients.

This reasoning led us to hypothesize that PCT kinetics would be more informative than a single measurement. However, we were unable to demonstrate its usefulness as a diagnostic marker. It is probably inescapable that patients requiring prolonged MV, not only those admitted to the ICU after complicated cardiac surgery, have already developed a systemic inflammation response syndrome, multiorgan failure(s), and/or a previous infection before their ICU admission or during their stay. Unfortunately all these

conditions are known to raise PCT levels in the absence of infection. Only 7 of the 73 episodes in this study (10%) had no risk factors for increased PCT levels.

Pneumonia is sometimes a compartmentalized infection, with local cytokine production without systemic release [28, 29]. Thus as for other localized infections PCT can be synthesized locally without systemic release, explaining its low serum level or apparent before to D_1 decrease in patients with true pulmonary infections [30]. It is also known that a time lag of 24–48 h can exist between bacterial infection onset and peak PCT release, perhaps explaining why the PCT level could be "apparently low" on D_1 [31]. Our PCT determinations and their timing may simply have "missed" this peak in some patients with true infections.

Some limitations of our study should be noted. First, this study was conducted in patients with late-onset VAP, most of whom had received antibiotics during the 15 days preceding D_1. Thus it is difficult to extrapolate our observations to patients with early onset VAP who had not received such prior antimicrobial treatment. However, a recent study showed that serum PCT levels could be relevant for early onset VAP diagnosis [24]. Second, our referral ICU is specialized in caring for critically ill patients after cardiac surgery, conditions which are known to increase serum PCT concentrations. In our study 51% of the patients were admitted after cardiac surgery. Hence it is difficult to project our findings onto other ICU with different types of patients. Perhaps PCT predictive capacity would be a better marker in subsets of patients with early onset infection and no other known causes of PCT increase. Third, because of our study design, "before" PCT levels were not available for 11 patients, which may have changed the results.

Fourth, although our results remained unchanged when only the 30 episodes with a "before" PCT determined within 2 days prior to VAP suspicion were considered, we cannot exclude that, for some infected patients, serum PCT levels determined on the eve of D_1 might have been even lower (reflecting continued regression of preexisting conditions), and thus their increased D_1 values would have yielded more meaningful kinetics and hence better predictive capacity. Moreover, this possibility combined with the known time lag between infection onset and increased circulating PCT levels may explain why some patients with true VAP had apparently decreased PCT concentrations on D_1. A better design to test the usefulness of PCT kinetics would have been to prospectively follow PCT concentrations every day to determine whether a rise following an initial progressive decline could help diagnose VAP. However, such a design would have been very difficult to implement, as it would have rendered daily PCT determinations obligatory for all ventilated patients admitted to the ICU until suspicion of VAP, death, or discharge. Moreover, such a strategy would have imposed an unrealistic workload on day-to-day ICU practice and its high economic cost could not be justified.

Finally, the diagnosis of pneumonia in patients on MV and isolation of the causative agents of these patients' pneumonia are often difficult. To overcome these difficulties we chose an invasive strategy for the present study systematically performing fiberoptic bronchoscopy to collect BAL from each patient clinically suspected of having developed VAP, taking great care to obtain specimens of distal pulmonary secretions before any modifications could be made of existing antimicrobial treatment, if any. Although we cannot exclude the possibility that pneumonia was incorrectly diagnosed in some patients included in our study, it is unlikely that many cases of true pneumonia could have been missed by our diagnostic protocol. Indeed, a heightened clinical suspicion of VAP was maintained throughout the study period for all enrolled patients and specifically those with ARDS, from whom bronchoscopic samples were obtained as soon as they became febrile and/or deteriorated clinically, even when no progression of lung infiltration could be ascertained. On the other hand, it can be argued that pneumonia was overdiagnosed in our patients because bronchoscopic techniques may give rise to a few false-positive results despite the universal recognition of these methods as highly specific. However, we think that this hypothesis is unlikely because most patients who developed VAP had clinical features highly compatible with pneumonia at the time of infection onset.

Based on our findings, PCT and its kinetics cannot be used as a diagnostic marker for VAP, and thus cannot be a surrogate for initiating antibiotics, except for patients with increased serum PCT levels. However, as for community-acquired pneumonia [26, 32], the predictive capacity of PCT kinetics—to shorten the duration of antimicrobial therapy or to stop antibiotics in the absence of nosocomial VAP—remains to be determined.

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