Microbiogical data, but not procalcitonin improve the accuracy of the clinical pulmonary infection score

Boris Jung, Nathalie Embriaco, François Roux, Jean-Marie Forel, Didier Demory, Jérôme Allardet-Servent, Samir Jaber, Bernard La Scola, Laurent Papazian

Boris Jung
Nathalie Embriaco
François Roux
Jean-Marie Forel
Didier Demory
Jérôme Allardet-Servent
Samir Jaber
Bernard La Scola
Laurent Papazian

Microbiogical data, but not procalcitonin improve the accuracy of the clinical pulmonary infection score

B. Jung · S. Jaber
Intensive Care Unit,
Department of Anesthesiology
and Critical Care B (DAR B),
Centre Hospitalier Universitaire (CHU)
Montpellier, INSERM ERI 25,
Montpellier 34295, Cedex 5, France

N. Embriaco · J.-M. Forel · D. Demory ·
J. Allardet-Servent · L. Papazian (✉)
Medical Intensive Care Unit, Assistance
Publique-Hôpitaux de Marseille,
URMITE CNRS-UMR 6236,
Université de la Méditerranée,
Marseille, France
e-mail: laurent.papazian@ap-hm.fr
Tel.: +33-491-744948
Fax: +33-491-745435

F. Roux
Service central de Biophysique et de
Médecine Nucléaire, Nuclear Medicine,
Assistance Publique-Hôpitaux de Marseille,
Marseille, France

B. La Scola
Unité des Rickettsies, Faculté de Médecine,
Université de la Méditerranée,
Marseille, France

Abstract *Objective:* Early and adequate treatment of ventilator-associated pneumonia (VAP) is mandatory to improve the outcome. The aim of this study was to evaluate, in medical ICU patients, the respective and combined impact of the Clinical Pulmonary Infection Score (CPIS), broncho-alveolar lavage (BAL) gram staining, endotracheal aspirate and a biomarker (procalcitonin) for the early diagnosis of VAP. *Design:* Prospective, observational study *Setting:* A medical intensive care unit in a teaching hospital. *Patients:* Over an 8-month period, we prospectively included 57 patients suspected of having 86 episodes of VAP. *Intervention:* The day of suspicion, a BAL as well as alveolar and serum procalcitonin determinations and evaluation of CPIS were performed. *Measurements and main results:* Of 86 BAL performed, 48 were considered positive (cutoff of 10^4 cfu ml^{-1}). We found no differences in alveolar or serum procalcitonin between VAP and non-VAP patients. Including procalcitonin in the CPIS score did not increase its accuracy (55%) for the diagnosis of VAP. The best tests to predict VAP were modified CPIS (threshold at 6) combined with microbiological data. Indeed, both routinely twice weekly performed endotracheal aspiration at a threshold of 10^5 cfu ml^{-1} and BAL gram staining improved pre-test diagnostic accuracy of VAP (77 and 66%, respectively). *Conclusion:* This study showed that alveolar procalcitonin performed by BAL does not help the clinician to identify VAP. It confirmed that serum procalcitonin is not an accurate marker of VAP. In contrast, microbiological resources available at the time of VAP suspicion (BAL gram staining, last available endotracheal aspirate) combined or not with CPIS are helpful in distinguishing VAP diagnosed by BAL from patients with a negative BAL.

Keywords Ventilator-associated pneumonia · Procalcitonin · Clinical pulmonary infection score · Bronchoalveolar lavage · Endotracheal aspiration

Abbreviations

VAP	Ventilator-associated pneumonia
EA	Endotracheal aspiration
BAL	Broncho-alveolar lavage
FiO$_2$	Fraction of inspired oxygen
ICU	Intensive care unit
MCPIS	Modified clinical pulmonary infectious score
SAPS II	Simplified Acute Physiology Score
SOFA	Sequential Organ Failure Assessment Score
PTC	Protected telescoping catheter

Introduction

Ventilator-associated pneumonia (VAP) is the most frequent nosocomial infection in the intensive care unit (ICU) [1–4]. Although its attributable mortality remains debated, VAP is associated with increased lengths of ICU stay and mechanical ventilation [2, 4, 5]. It is then of interest to diagnose and to treat VAP adequately, as early as possible. The "clinical option" [1] is to treat every patient clinically suspected of VAP with broad-spectrum antibiotics, given clinical signs and positive endotracheal aspiration (non-quantitative culture). Indeed, any delay in treating severe sepsis results in increased mortality [6–8]. However, the "clinical option" [9–12] is poorly specific and may result in excessive antibiotic use and in increased prevalence of antibiotic resistance [13].

The "bacteriological option" [1] is based on the quantitative culture of a distal sample of alveolar fluid, which can be obtained with bronchoscopic [bronchoalveolar lavage (BAL) or protected specimen brush] or non-bronchoscopic methods (protected telescoping catheter, PTC). Although the introduction of antibiotics in this option is still based on clinical grounds and is sometimes difficult to perform in a 24-h workday, it improves the specificity of the diagnosis and allows more changes of antibiotic management [14].

Simple criteria allowing pneumonia to be confirmed or ruled out at an early stage of management would thus be clinically useful. An option combining clinical score and early bacteriological results may improve the sensitivity/specificity of VAP diagnosis [15]. Procalcitonin, the prohormone of calcitonin, is ubiquitously secreted in case of bacterial infection [16]. In case of suspected community-acquired pneumonia, procalcitonin assays serve to confirm the diagnosis but also to guide the duration of treatment [16–18]. In VAP, procalcitonin seems to be a strong indicator of recovery [19].

We therefore designed this prospective study to evaluate the respective and combined usefulness of the Clinical Pulmonary Infection Score (CPIS), BAL gram staining, endotracheal aspirate surveillance culture, and BAL and serum procalcitonin for ICU patients who were suspected of VAP. Our hypothesis was that combining clinical and microbiological parameters were the best tests to anticipate the diagnosis of VAP.

Methods

This prospective study was performed in the medical ICU of Sainte-Marguerite University Hospital in Marseille, France, during an 8-month period. Because no supplementary blood samples were drawn and investigations (BAL) were considered part of routine clinical practice, no written informed consent was required, as confirmed by the Clinical Research Ethics Committee of the Institut Fédératif de Recherche 48, Marseille, France. Patients or their next of kin were informed of their inclusion in this study and could refuse to participate.

Study setting and population

All consecutive patients (18 years or older) who were ventilated 48 h or more were prospectively included if VAP was clinically suspected: presence of a new infiltrate or progression of a prior stable infiltrate on the chest radiograph in association with two of the four following criteria: fever >38°C or hypothermia <36°C; leukocytosis >10×10^9/l or <4×10^9/l; purulent tracheal secretions; decrease in the PaO$_2$/fraction of inspired oxygen (FiO$_2$) ratio [1]. Fiberoptic bronchoscopy examination was performed in each patient within 12 h of the suspicion of VAP.

Diagnosis of VAP

One of the investigators (NE, BJ, or LP) made daily rounds in the ICU to identify eligible patients, to determine the onset of VAP based on the diagnostic criteria described below, and to record relevant data from the medical records, bedside flow sheets, and the hospital's mainframe computer for reports of microbiological studies and bacterial antibiotic sensitivity profiles. When VAP was suspected, it is our routine care to perform fiberoptic bronchoscopy with BAL before any modification or introduction of new antibiotics.

All chest radiographs were analyzed prospectively by two (BJ, NE) of the investigators. The tip of the bronchoscope (Olympus BF P20 D, Olympus, New Hyde Park, NY) was introduced without any bronchial suctioning and was positioned in the most prominent radiographic infiltrate. The bronchoscope was wedged in the bronchial orifice of a lung segment, and BAL was performed by infusing three 50-ml aliquots of sterile 0.9% NaCl. The first aliquot, which was used as a bronchial wash, was discarded [20, 21], and subsequent aliquots were pooled, mixed, measured and then strained through cotton gauze to remove mucus. A gram stain of a cytocentrifuged layer was performed, and organisms were identified as gram negative bacilli and/or gram positive cocci. Bacterial identification and antibiotic susceptibility tests were performed using standard methods. Diagnosis of VAP was established when BAL quantitative culture grew with at least one microorganism at a concentration $\geq 10^4$ colony-forming units (cfu) ml^{-1} associated with clinical signs (all included in the CPIS) that could be related to VAP (Table 1; [22]). Viral and fungal pneumonias were excluded from the analysis. All episodes of bacterial VAP in a same patient were taken into account.

Table 1 Modified Clinical Pulmonary Infection Score, adapted from [22]

Parameter	Point
Temperature (°C)	
>36.5 and <38.4	0
>38.5 and <38.9	1
>39.0 or <36.0 2	2
Blood leukocytes per mm^3	
>4,000 and <11.000	0
<4,000 or >11,000	1
Tracheal secretions	
Few	0
Moderate	1
Large	2
Purulent	+1
Oxygenation PaO2/FIO2 (mmHg)	
>240 or presence of ARDS	0
<240 and absence of ARDS	2
Chest radiograph	0
No infiltrate	
Patchy or diffuse infiltrate	1
Localized infiltrate	2

Tracheal secretions were aspirated and evaluated (quality, quantity) by nurses. Oxygenation parameters were calculated on daily morning arterial blood gases. Chest radiographs were interpreted by two investigators (B. Jung, N. Embriaco)

Early onset VAP (≤5 days) was differentiated from late-onset pneumonia (>5 days after intubation and mechanical ventilation).

Baseline assessment and data collection

Each patient's hospital chart was constituted prospectively, and the following data were recorded on ICU admission: age, sex, severity of underlying medical condition stratified according to the criteria of McCabe and Jackson, Simplified Acute Physiology Score II (SAPS II) [23], Sepsis-related Organ Failure Assessment (SOFA) score [24], the presence of co-morbidities and reason for mechanical ventilation.

In addition, on the day of sampling, we collected SOFA score and the results of routine surveillance culture of endotracheal aspirate (EA) performed twice weekly (Tuesday and Friday morning) in all mechanically ventilated patients as previously described [25]. We also calculated the CPIS score modified by Luna (Table 1). We formulated the CPIS-EA score, which combined the CPIS score modified by Luna et al. (mCPIS) [22] and the quantitative culture of routinely performed endotracheal aspirate. No point was added to mCPIS when EA culture was <10^5 cfu ml^{-1}, and 2 points were added when EA culture was ≥10^5 cfu ml^{-1}. Total points for CPIS-EA score therefore varied from 1 to 12 points. We also formulated the CPIS-BAL gram score, which was a combination of mCPIS and direct examination of BAL fluid. No point was added when BAL fluid gram staining was negative, and 2 points were added when BAL fluid gram staining was positive. Total points for CPIS-BAL gram score also varied from 1 to 12 points.

Estimation of the probability of VAP

The probability of pneumonia using the clinical picture and the mCPIS was prospectively estimated by two ICU senior physicians at the time of sampling on a 0–100% scale. They were blinded to the definitive results of the BAL culture at that time. The potential improvement over this estimate that was provided by serum procalcitonin was assessed. Finally, the improvement in diagnostic accuracy was assessed after obtaining BAL direct examination results. This estimate was subsequently categorized as "very low" when the probability was scored less than 20%, "low" between 20 and 40%, "moderate" between 40 and 60%, high between 60 and 80%, and very high when between 80 and 100% [15]. Patients were classified as probably having a VAP according to the physicians' opinion when the combination of the two ICU physicians' evaluations was higher than 60%. Patients under this threshold were classified as probably not having VAP.

Procalcitonin assay

For all patients, serum collected from blood drawn the day of suspicion of VAP was frozen for further analysis. BAL samples for procalcitonin determination were centrifuged (1,500 rpm, 10 min), and supernatants were immediately stored at −80°C until measurements. An investigator blinded to clinical data used TRACE (time-resolved amplified cryptate emission) technology on a Kryptor analyzer (Brahms Diagnostica, Berlin, Germany). The Kryptor analyzer detection limit in 100 μl of both serum and alveolar fluid was 0.019 ng ml^{-1}, and sensitivity (interassay variation coefficient, 20%) was 0.06 ng ml^{-1}. The 95th percentile reference was 0.064 ng ml^{-1}.

Statistical analysis

Data are expressed as mean ± SD for normally distributed data and median with interquartile range (IQR) for non-normally distributed data. Continuous variables were compared using Student's t test for normally distributed variables and the Mann-Withney rank-sum test for non-normally distributed variables. The chi-square test or Fisher's exact test was used to compare categorical variables. To evaluate the amount of procalcitonin in BAL and blood, we individualized two groups of patients: patients with a suspicion of VAP but a negative BAL, and patients with a confirmed VAP (BAL positive).

Results

Patient population

Over an 8-month period, 86 BAL procedures for suspicion of VAP were performed in 57 prospectively included consecutive patients. The clinical characteristics of the 57 patients are reported in Table 2. One episode of VAP was suspected in 35 patients, two episodes were suspected in 17 patients, three episodes in 3 patients and four episodes in 2 patients.

While a VAP was clinically suspected in 86 cases, it was bacteriologically confirmed by BAL culture results in 48 cases (56%). Fourteen of these 48 episodes were classified as early onset. Characteristics of the patients at the time of BAL are reported in Table 3. Patients were

Table 2 Characteristics of the patients on ICU admission

Characteristics	
n	57
Age (years, mean ± SD]	61 ± 17
Men (%)	39 (68)
ICU diagnostic category [*n* (%)]	
Medical	56 (98)
Surgical	1 (2)
Provenance [*n* (%)]	
Home	16 (28)
Medical or surgical ward	35 (61)
Referral from another ICU	6 (11)
Reason for mechanical ventilation [*n* (%)]	
Respiratory failure (all)	45 (79)
Acute respiratory failure with hemodynamic failure	25 (44)
Acute respiratory failure without hemodynamic failure	12 (21)
Acute on chronic respiratory insufficiency	8 (14)
Extra-pulmonary sepsis or septic shock	5 (9)
Hemodynamic failure (excluding septic shock)	2 (3)
Neurologic failure	5 (9)
Comorbidities [*n* (%)]	
Chronic respiratory disease	20 (35)
Diabetes mellitus	13 (23)
NYHA class 4	1 (2)
Cirrhosis	0 (0)
Metastatic cancer	5 (9)
Hematologic malignancy	1 (2)
Dialysis-dependent end-stage renal disease	3 (5)
Solid organ transplant	5 (9)
AIDS	3 (5)
McCabe and Jackson comorbidity score [*n* (%)]	
Nonfatal disease	22 (39)
Ultimately fatal disease	25 (44)
Rapidly fatal disease	10 (17)
SOFA score (mean ± SD)	8 ± 3.5
SAPS II score (mean ± SD)	47 ± 18
Length of mechanical ventilation [days, median (IQR)]	19 (8.5–30)
ICU length of stay [days, median (IQR)]	20 (10–29.5)
ICU mortality [*n* (%)]	23 (40)

ICU intensive care unit, *SAPS II* Simplified Acute Physiology Score [23], *SOFA score* sequential organ failure assessment score [24]

already on antibiotics in 36 of the 86 cases (42%) when BAL samples were obtained. In only six cases had antibiotic change occurred in the preceding 3 days. Fifty-four microorganisms were considered responsible for VAP. Forty-one (85%) were gram negative bacilli (*P. aeruginosa* in 37% of the cases and *Klebsiella sp.* or *Enterobacter sp.* in 17 and 10% of the cases, respectively). Thirteen gram positive cocci were isolated (11 methicillin-susceptible *S. aureus*, 1 methicillin-resistant *S. aureus* and 1 coagulase negative *Staphylococcus*). There was no difference for length of mechanical ventilation after the first suspicion of VAP according to the result of BAL (22 [13–30] days and 13 [7–25] in the VAP group and in the no VAP group, respectively). Among the 38 patients considered not to have VAP, antibiotics were discontinued when BAL culture was available in 13 cases (34%), never introduced in 8 cases (21%), continued for extrapulmonary superinfection in 12 cases (32%) and stopped because of dying patients in 5 cases (13%) (none because of identified VAP).

Operative indices of the tested criteria of VAP

As shown in Table 4, the diagnostic accuracy of the mCPIS ≥5 was only 58% [95% confidence interval (CI) 48–68] with a sensitivity of 75% and a poor specificity. Gram stains of BAL specimens were positive in only 19 of 48 (40%) confirmed VAPs and in 4 of 38 (10.5%) non-confirmed VAPs. Serum and BAL procalcitonin had poor diagnostic accuracy because of the very low specificity for reduced thresholds and the rapid decline in sensitivity while increasing threshold (Fig. 1).

Combining mCPIS with either a positive direct examination of the BAL (mCPIS-BAL-gram) using a threshold of 6 or a previous EA culture $\geq 10^5$ cfu ml^{-1} (mCPIS-EA) improved specificity from 37% for mCPIS to 61% for the two combined indices ($P = 0.001$), while sensitivity remained acceptable (71% and 83%, respectively) (Table 4).

Diagnostic accuracy of mCPIS-EA at a threshold of 6 was higher than that of the combination of mCPIS ≥5 with a serum procalcitonin level of at least 0.2 ng ml^{-1} ($P = 0.026$), but did not differ from mCPIS-BAL-gram ($P = 0.25$). Finally, mCPIS-EA and mCPIS-BAL-gram areas under the ROC curves were significantly larger than the areas of both serum ($P = 0.001$ and $P = 0.002$, respectively) and BAL procalcitonin levels ($P = 0.001$ for both) (Fig. 2). There was no difference between gram negative and gram positive VAP regarding alveolar or serum procalcitonin concentrations (data not shown).

The probability of pneumonia was estimated by physicians at the time of sampling (blinded to the definitive results of BAL culture) according to the clinical picture with the modified CPIS with an accuracy of 57% (49 of 86 VAP suspicions). This diagnostic

Table 3 Characteristics of patients the day of BAL

	VAP ($n = 48$)	No VAP ($n = 38$)	*P* value
Demographic characteristics			
ICU length of stay [days, median (IQR)]	12.5 (3–22)	3.5 (2–9)	0.006
Duration of mechanical ventilation [days, median (IQR)]	12 (4–27.5)	3 (2–15)	0.01
SOFA score (mean ± SD)	6.0 ± 3.5	6.8 ± 3.9	0.24
Septic shock/severe sepsis [n (%)]	23 (48)	22 (58)	0.48
ARDS [n (%)]	28 (58)	21 (55)	0.95
Physiological variables			
Temperature (°C, mean ± SD)	37.9 ± 1.2	37.8 ± 1.4	0.63
White blood cells count (giga/l, mean ± SD)	14.2 ± 8.5	14.0 ± 8.7	0.72
PaO2/FiO2 (mmHg, mean ± SD]	208 ± 85	199 ± 79	0.81
Purulent tracheal secretions [n (%)]	23 (48)	9 (24)	0.04
New chest radiograph infiltrate [n (%)]	41 (85)	32 (84)	0.88
mCPIS [median (IQR)]	6 (4.5–7.5)	5 (4–7)	0.05
Plasma procalcitonin [ng ml^{-1}, median (IQR)]	0.55 [0.20–2.7]	1.13 [0.30–3.50]	0.67
Alveolar procalcitonin [ng ml^{-1}, median (IQR)]	0.05 [0.03–0.07]	0.05 [0.04–0.08]	0.24
Antibiotic therapy and infection parameters			
Ongoing antibiotics [n (%)]	22 (46)	14 (37)	0.54
Antibiotics within 7 days [n (%)]	33 (69)	22 (58)	0.42
Antibiotic prescription within 3 months [n (%)]	45 (94)	25 (66)	0.002
Antibiotic change within the preceding 3 days [n (%)]	2 (4)	4 (11)	0.40
EA $\geq 10^5$ prior BAL [n (%)]	31 (65)	5 (13)	0.001
Bacteremia within 24 h of BAL [n (%)]	15 (31)	4 (10)	0.04

ARDS acute respiratory distress syndrome, *BAL* bronchoalveolar lavage, *EA* endotracheal aspirate, *ICU* intensive care unit, *mCPIS* Modified Clinical Pulmonary Infection Score, *VAP* ventilator-associated pneumonia

Table 4 Operative characteristics for the diagnostic markers of VAP in patients presenting a suspicion of VAP

	Sensitivity [CI (%)]	Specificity [CI (%)]	PPV [CI (%)]	NPV [CI (%)]	Accuracy [CI (%)]
mCPIS					
≥4	94 (87–100)	24 (10–38)	61 (50–72)	75 (50–99)	63 (53–73)
≥5	75 (63–87)	37 (22–52)	60 (48–72)	54 (35–73)	58 (48–68)
≥6	58 (44–72)	66 (51–81)	68 (54–72)	56 (44–77)	62 (52–72)
Clinical suspicion including mCPIS	31	89	79	51	57
BAL-gram	40 (26–54)	90 (80–100)	83 (68–98)	54 (42–66)	62 (52–72)
EA $\geq 10^5$	67 (54–80)	90 (80–100)	89 (79–99)	68 (55–81)	77 (68–87)
Serum PCT (ng ml^{-1})					
≥0.1	94 (87–100)	8 (0–16)	56 (45–67)	50 (10–90)	56 (46–66)
≥0.3	67 (54–80)	26.5 (12.5–40.5)	53 (40–66)	38.5 (19–57)	49 (38–60)
≥0.5	54 (40–68)	39 (24–54)	53 (39–67)	40.5 (24–56)	48 (37–59)
Alveolar PCT (ng ml^{-1})					
≥0.03	86 (76–96)	9 (3–15)	55 (43–67)	33 (8–58)	53 (42–54)
≥0.05	50 (35–65)	47 (36–58)	55 (40–70)	42 (26–58)	49 (38–60)
Clinical suspicion including mCPIS and serum PCT ≥ 0.2 ng mL^{-1}	40	74	66	49	55
mCPIS-EA $\geq 10^5$					
≥5	90 (82–98)	34 (19–48)	63 (52–72)	72 (51–93)	65 (55–65)
≥6	83 (72–94)	61 (46–76)	73 (61–85)	74 (59–89)	73 (64–82)
≥7	67 (54–80)	68 (53–83)	73 (60–86)	62 (47–77)	67 (57–77)
mCPIS-BAL-gram					
≥5	83 (72–94)	37 (22–52)	63 (51–75)	64 (44–84)	63 (53–73)
≥6	71 (58–84)	61 (53–69)	69 (56–82)	62 (46–78)	66 (56–76)
≥7	58 (44–72)	66 (51–81)	68 (54–82)	56 (42–70)	62 (52–72)

BAL-gram direct examination of bronchoalveolar lavage, *EA* endotracheal aspirate, *mCPIS* Modified Clinical Pulmonary Infection Score, *PCT* procalcitonin, *CI* 95% confidence interval

performance was not improved by the addition of the serum procalcitonin result [accuracy 55% (47 of 86)]. When the clinical picture including modified CPIS and procalcitonin was combined with direct examination of BAL, it significantly improved the diagnostic performance (accuracy of 79%, 68 of 86 VAP suspicions; $P = 0.003$ vs. clinical picture with modified CPIS, $P = 0.001$ vs. clinical picture with modified CPIS, and serum procalcitonin). However, the diagnostic accuracy of the association of clinical picture with modified CPIS, serum procalcitonin and direct examination of BAL was similar to that of the last routinely performed endotracheal aspirate at a threshold of 10^5 cfu ml^{-1} (77%). When clinicians evaluated the risk of VAP with clinical picture with the mCPIS, 23 suspicions among 86 (27%) were classified as at intermediate risk (40–60%). Fifteen of these 23 patients (65%) were treated immediately after the BAL procedure because of their hemodynamic status and/or respiratory status and/or an impaired immune status.

Discussion

The main result of this study is that addition of microbiological data (direct BAL examination or culture results of a recent endotracheal aspirate) to the clinical suspicion rather than serum or alveolar PCT values is more helpful in the increasing accuracy of the early diagnosis of VAP.

In 2008, diagnosis of VAP remains a challenge for intensivists [26, 27]. The microbiological techniques require 24–48 h for complete analysis, which can be too long for the sickest patients, but could also result in overprescription of broad-spectrum antibiotics while waiting for final microbiological results. Those considerations have led some investigators to test the accuracy of biomarkers to determine whether patients need antibiotics [16, 17, 28]. Procalcitonin, the prohormone of calcitonin, is a specific biomarker of bacterial infection [29, 30]. Its secretion is ubiquitous in case of sepsis, and its level in blood is increased by community-acquired pneumonia [16–18]. However, few studies have evaluated its usefulness in diagnosing VAP [19, 28, 31–34].

Our study shows that on the day of suspicion of VAP, neither the serum nor BAL level of procalcitonin is a reliable biomarker of VAP. Our results are similar to those reported by Gibot et al. [31], who showed that the blood level of procalcitonin was not different in VAP patients as compared with patients without pneumonia. More recently, two studies reported that the crude value of plasma procalcitonin the day of the VAP suspicion had poor diagnostic value for VAP [33, 34]. However, none of these three studies evaluated the diagnostic value of alveolar levels of procalcitonin [31, 33, 34]. Duflo et al.

reported that using mini-BAL, the procalcitonin alveolar level was not different in patients presenting or not a VAP at day 0, 3 and 6 after the onset of the suspicion [31, 33, 34]. We found similar results using BAL and a more recent fully automated homogeneous sandwich immunoassay (TRACE® technology, Kryptor® analyzer).

The secretion of procalcitonin in response to sepsis seems to be initiated by adherent monocytes that act as a trigger during this initial period [35]. After a short crosstalk time between adherent monocytes and tissues, cells of the tissue start to produce procalcitonin [35, 36]. Although adherent monocytes seem to be the cornerstone of the ubiquitous secretion of procalcitonin, the pathway of its excretion to the serum compartment and its apparently poor secretion to tissue compartment are not clearly understood. Moreover, previous studies reported that procalcitonin was rarely elevated in cerebrospinal fluid [37], in ascites [38] or in synovial fluid [39] during localized infection. Regarding our results and those of Duflo et al. [28], alveolar procalcitonin assay cannot be recommended as a guide for diagnosis of VAP (Fig. 1b). In addition, serum assay as a single value the day of the
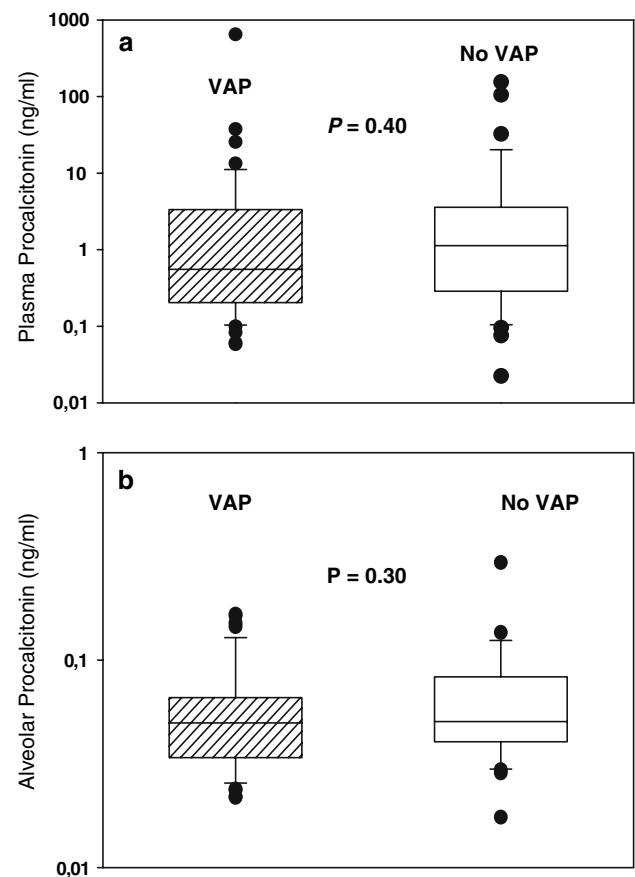
Fig. 1 Procalcitonin in the diagnosis of ventilator-associated pneumonia. No significant difference in plasma (Fig. 1a) or alveolar procalcitonin (Fig. 1b) was observed among groups

suspicion of VAP does not appear to be a reliable marker of pneumonia (Fig. 1a) [28, 31, 33, 34].

In the present study, the diagnostic accuracy of the mCPIS ≥ 5 was only 58% with a sensitivity of 75% and a poor specificity (Table 4). Our results are similar to those of other studies [40, 41] demonstrating that mCPIS has a higher sensitivity but a lower specificity than BAL.

Combining a CPIS ≥ 5 with a serum procalcitonin level of at least 0.2 ng ml^{-1} did not strongly increase the diagnostic accuracy (57%) or the other operative indices (sensitivity of 65%, specificity of 47%, predictive positive value of 61% and negative predictive value of 51%) (Fig. 2). In contrast with a recently published paper [15], but like others [26, 42], the sensitivity of gram staining of BAL as an independent parameter was low. In our clinical practice, the introduction of new antibiotics is not guided by the BAL gram staining, but is targeted on the previous EA culture result and then adapted when the final BAL culture is available [25, 43]. Combining clinical score such as CPIS and routine surveillance of airway colonization improved VAP diagnosis. Diagnostic accuracy of mCPIS-EA at a threshold of 6 was higher than that of the combination of mCPIS ≥ 5 with a serum procalcitonin level of at least 0.2 ng ml^{-1} ($P = 0.026$), but we observed no difference between mCPIS-EA and mCPIS-direct examination of the BAL. Indeed, combining mCPIS with direct examination of the BAL improved specificity and sensitivity. This latter result is similar to those in other studies [15, 44]. The results also agree with previous studies by our team, where we reported 95% of adequate initial antibiotic therapy for VAP when it was guided by the last systematically, twice-weekly performed quantitative endotracheal aspiration [25] and 85% when it was guided by only once weekly EA [43]. Furthermore, these findings are reinforced by those of Depuydt et al. [45], who showed that systematic surveillance cultures help to predict pathogens responsible for VAP.

Study limitations

Our study presents several limitations. Firstly, 40 to 50 percent of patients were already on antibiotic therapy the day of sampling, which may have decreased the sensitivity of BAL sampling. However, this phenomenon, if it existed, must be marginal in our study because less than 10 percent had newly (less than 72 h) introduced antibiotics [46, 47]. It should be pointed out that there is no gold standard for the routine diagnosis of VAP. Secondly, this was a single center study performed with TRACE technology, which has not been developed to analyze procalcitonin in body fluids, but in blood. Thirdly, we did not evaluate the interest of repeated determinations of procalcitonin or CPIS score, although it has been shown that monitoring the kinetics improves the specificity of those tests in some studies [48] but not in others [33, 40, 41]. However, the aim of our study was to evaluate the combination of clinical scores and biomarkers to anticipate the diagnosis of VAP and not to follow the treatment and/or to anticipate the prognosis in patients presenting a VAP. Finally, we did not evaluate other biomarkers, such as CRP or sTREM-1, as proposed by Gibot and co-workers [31].
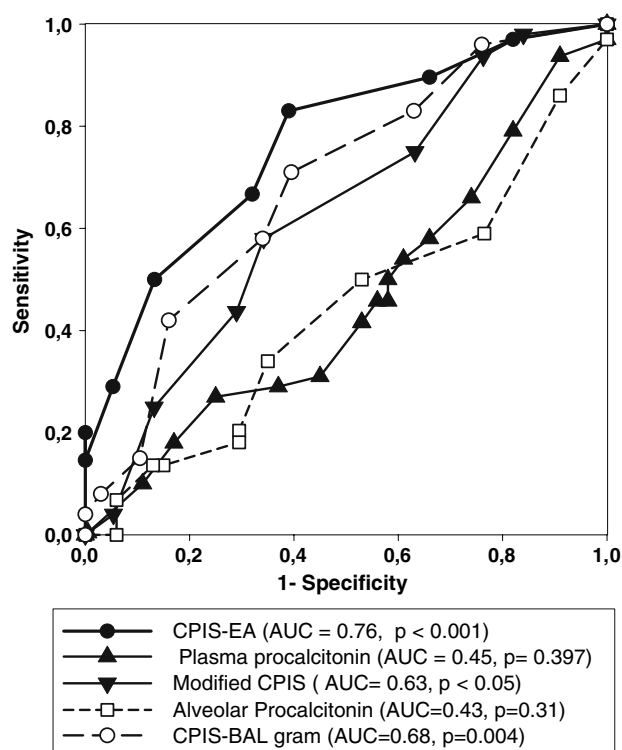
Fig. 2 Receiver-operating characteristics of modified CPIS, alveolar and plasma procalcitonin, modified CPIS combined with both BAL gram staining (CPIS-BAL gram) and endotracheal aspirate (CPIS-EA). Modified CPIS combined with both the results of gram staining and endotracheal aspirate have the best area under the ROC curve to predict a VAP episode

Legend:
— ●— CPIS-EA (AUC = 0.76, p < 0.001)
— ▲— Plasma procalcitonin (AUC = 0.45, p = 0.397)
— ▼— Modified CPIS (AUC= 0.63, p < 0.05)
-- □-- Alveolar Procalcitonin (AUC=0.43, p=0.31)
— ○— CPIS-BAL gram (AUC=0.68, p=0.004)

Conclusions

The present study showed that microbiological resources (the last available endotracheal aspirate or direct examination performed on BAL at the moment of suspicion of VAP) combined with CPIS are helpful in distinguishing VAP diagnosed by BAL from patients with a negative BAL.

In contrast, a single value of serum procalcitonin is not an accurate marker of VAP. Alveolar procalcitonin, even using the TRACE technique, does not help clinicians to identify VAP.

References

1. Official Statement of the American Thoracic Society, the Infectious Diseases Society of America (2005) Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 171:388–416
2. Bregeon F, Ciais V, Carret V, Gregoire R, Saux P, Gainnier M, Thirion X, Drancourt M, Auffray JP, Papazian L (2001) Is ventilator-associated pneumonia an independent risk factor for death? Anesthesiology 94:554–560
3. Fagon JY, Chastre J, Hance AJ, Montravers P, Novara A, Gibert C (1993) Nosocomial pneumonia in ventilated patients: a cohort study evaluating attributable mortality and hospital stay. Am J Med 94:281–288
4. Papazian L, Bregeon F, Thirion X, Gregoire R, Saux P, Denis JP, Perin G, Charrel J, Dumon JF, Affray JP, Gouin F (1996) Effect of ventilator-associated pneumonia on mortality and morbidity. Am J Respir Crit Care Med 154:91–97
5. Rello J, Ollendorf DA, Oster G, Vera-Llonch M, Bellm L, Redman R, Kollef MH (2002) Epidemiology and outcomes of ventilator-associated pneumonia in a large US database. Chest 122:2115–2121
6. Ibrahim EH, Sherman G, Ward S, Fraser VJ, Kollef MH (2000) The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. Chest 118:146–155
7. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, Suppes R, Feinstein D, Zanotti L, Taiberg L, Gurka D, Kumar A, Cheang M (2006) Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 34:1589–1596
8. Leone M, Bourgoin A, Cambon S, Dubuc M, Albanese J, Martin C (2003) Empirical antimicrobial therapy of septic shock patients: adequacy and impact on the outcome. Crit Care Med 31:462–467
9. The Canadian Critical Care Group (2006) A randomized trial of diagnostic techniques for ventilator-associated pneumonia. N Engl J Med 355:2619–2630
10. Croce MA, Swanson JM, Magnotti LJ, Claridge JA, Weinberg JA, Wood GC, Boucher BA, Fabian TC (2006) The futility of the clinical pulmonary infection score in trauma patients. J Trauma 60:523–527 (discussion 527–528)
11. Pugin J, Auckenthaler R, Mili N, Janssens JP, Lew PD, Suter PM (1991) Diagnosis of ventilator-associated pneumonia by bacteriologic analysis of bronchoscopic and nonbronchoscopic "blind" bronchoalveolar lavage fluid. Am Rev Respir Dis 143:1121–1129
12. Singh N, Rogers P, Atwood CW, Wagener MM, Yu VL (2000) Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. A proposed solution for indiscriminate antibiotic prescription. Am J Respir Crit Care Med 162:505–511
13. Fagon JY, Chastre J, Wolff M, Gervais C, Parer-Aubas S, Stephan F, Similowski T, Mercat A, Diehl JL, Sollet JP, Tenaillon A (2000) Invasive and noninvasive strategies for management of suspected ventilator-associated pneumonia. A randomized trial. Ann Intern Med 132:621–630
14. Luyt CE, Combes A, Nieszkowska A, Reynaud C, Tonnellier M, Trouillet JL, Chastre J (2007) Does invasive diagnosis of nosocomial pneumonia during off-hours delay treatment? Intensive Care Med 33:734–737
15. Fartoukh M, Maitre B, Honore S, Cerf C, Zahar JR, Brun-Buisson C (2003) Diagnosing pneumonia during mechanical ventilation: the clinical pulmonary infection score revisited. Am J Respir Crit Care Med 168:173–179
16. Christ-Crain M, Stolz D, Bingisser R, Muller C, Miedinger D, Huber PR, Zimmerli W, Harbarth S, Tamm M, Muller B (2006) Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: a randomized trial. Am J Respir Crit Care Med 1:84–93
17. Christ-Crain M, Jaccard-Stolz D, Bingisser R, Gencay MM, Huber PR, Tamm M, Muller B (2004) Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. Lancet 363:600–607
18. Stolz D, Christ-Crain M, Bingisser R, Leuppi J, Miedinger D, Muller C, Huber P, Muller B, Tamm M (2007) Antibiotic treatment of exacerbations of COPD: a randomized, controlled trial comparing procalcitonin-guidance with standard therapy. Chest 131:9–19
19. Luyt CE, Guerin V, Combes A, Trouillet JL, Ayed SB, Bernard M, Gibert C, Chastre J (2005) Procalcitonin kinetics as a prognostic marker of ventilator-associated pneumonia. Am J Respir Crit Care Med 171:48–53
20. Baldesi O, Michel F, Guervilly C, Embriaco N, Granfond A, La Scola B, Portugal H, Papazian L (2009) Bacterial ventilator-associated pneumonia: bronchoalveolar lavage results are not influenced by dilution. Intensive Care Med 35:1210–1215
21. Torres A, El-Ebiary M (2000) Bronchoscopic BAL in the diagnosis of ventilator-associated pneumonia. Chest 117:198S–202S
22. Luna CM, Blanzaco D, Niederman MS, Matarucco W, Baredes NC, Desmery P, Palizas F, Menga G, Rios F, Apezteguia C (2003) Resolution of ventilator-associated pneumonia: prospective evaluation of the clinical pulmonary infection score as an early clinical predictor of outcome. Crit Care Med 31:676–682
23. Le Gall JR, Lemeshow S, Saulnier F (1993) A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA 270:2957–2963
24. Vincent JL, de Mendonca A, Cantraine F, Moreno R, Takala J, Suter PM, Sprung CL, Colardyn F, Blecher S (1998) Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. Crit Care Med 26:1793–1800
25. Michel F, Franceschini B, Berger P, Arnal JM, Gainnier M, Sainty JM, Papazian L (2005) Early antibiotic treatment for BAL-confirmed ventilator-associated pneumonia: a role for routine endotracheal aspirate cultures. Chest 127:589–597

26. Klompas M (2007) Does this patient have ventilator-associated pneumonia? JAMA 297:1583–1593

27. Rea-Neto A, Youssef N, Tuche F, Brunkhorst F, Ranieri M, Reinhart K, Sakr Y (2008) Diagnosis of ventilator-associated pneumonia: a systematic review of the literature. Crit Care 12:R56

28. Duflo F, Debon R, Monneret G, Bienvenu J, Chassard D, Allaouchiche B (2002) Alveolar and serum procalcitonin: diagnostic and prognostic value in ventilator-associated pneumonia. Anesthesiology 96:74–79

29. Simon L, Gauvin F, Amre DK, Saint-Louis P, Lacroix J (2004) Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis. Clin Infect Dis 39:206–217

30. Uzzan B, Cohen R, Nicolas P, Cucherat M, Perret GY (2006) Procalcitonin as a diagnostic test for sepsis in critically ill adults and after surgery or trauma: a systematic review and meta-analysis. Crit Care Med 34:1996–2003

31. Gibot S, Cravoisy A, Levy B, Bene MC, Faure G, Bollaert PE (2004) Soluble triggering receptor expressed on myeloid cells and the diagnosis of pneumonia. N Engl J Med 350:451–458

32. Oppert M, Reinicke A, Muller C, Barckow D, Frei U, Eckardt KU (2002) Elevations in procalcitonin but not C-reactive protein are associated with pneumonia after cardiopulmonary resuscitation. Resuscitation 53:167–170

33. Luyt CE, Combes A, Reynaud C, Hekimian G, Nieszkowska A, Tonnellier M, Aubry A, Trouillet JL, Bernard M, Chastre J (2008) Usefulness of procalcitonin for the diagnosis of ventilator-associated pneumonia. Intensive Care Med 34:1434–1440

34. Pelosi P, Barassi A, Severgnini P, Gomiero B, Finazzi S, Merlini G, Melzi d'Eril G, Chiaranda M, Niederman MS (2008) Prognostic role of clinical and laboratory criteria to identify early VAP in brain injury. Chest 134:101–108

35. Linscheid P, Seboek D, Schaer DJ, Zulewski H, Keller U, Muller B (2004) Expression and secretion of procalcitonin and calcitonin gene-related peptide by adherent monocytes and by macrophage-activated adipocytes. Crit Care Med 32:1715–1721

36. Wiedermann FJ, Kaneider N, Egger P, Tiefenthaler W, Wiedermann CJ, Lindner KH, Schobersberger W (2002) Migration of human monocytes in response to procalcitonin. Crit Care Med 30:1112–1117

37. Shimetani N, Shimetani K, Mori M (2001) Levels of three inflammation markers, C-reactive protein, serum amyloid A protein and procalcitonin, in the serum and cerebrospinal fluid of patients with meningitis. Scand J Clin Lab Invest 61:567–574

38. Viallon A, Zeni F, Pouzet V, Lambert C, Quenet S, Aubert G, Guyomarch S, Tardy B, Bertrand JC (2000) Serum and ascitic procalcitonin levels in cirrhotic patients with spontaneous bacterial peritonitis: diagnostic value and relationship to pro-inflammatory cytokines. Intensive Care Med 26:1082–1088

39. Martinot M, Sordet C, Soubrier M, Puechal X, Saraux A, Liote F, Guggenbuhl P, Legre V, Jaulhac B, Maillefert JF, Zeisel M, Coumaros G, Sibilia J (2005) Diagnostic value of serum and synovial procalcitonin in acute arthritis: a prospective study of 42 patients. Clin Exp Rheumatol 23:303–310

40. Luyt CE, Chastre J, Fagon JY (2004) Value of the clinical pulmonary infection score for the identification and management of ventilator-associated pneumonia. Intensive Care Med 30:844–852

41. Schurink CA, Van Nieuwenhoven CA, Jacobs JA, Rozenberg-Arska M, Joore HC, Buskens E, Hoepelman AI, Bonten MJ (2004) Clinical pulmonary infection score for ventilator-associated pneumonia: accuracy and inter-observer variability. Intensive Care Med 30:217–224

42. Papazian L, Autillo-Touati A, Thomas P, Bregeon F, Garbe L, Saux P, Seite R, Gouin F (1997) Diagnosis of ventilator-associated pneumonia: an evaluation of direct examination and presence of intracellular organisms. Anesthesiology 87:268–276

43. Jung B, Sebbane M, Chanques G, Courouble P, Verzilli D, Perrigault PF, Jean-Pierre H, Eledjam JJ, Jaber S (2009) Previous endotracheal aspirate allows guiding the initial treatment of ventilator-associated pneumonia. Intensive Care Med 35:101–107

44. Veinstein A, Brun-Buisson C, Derrode N, Alvarez A, Pinsard M, Robert R, Blot F (2006) Validation of an algorithm based on direct examination of specimens in suspected ventilator-associated pneumonia. Intensive Care Med 32:676–683

45. Depuydt P, Benoit D, Vogelaers D, Decruyenaere J, Vandijck D, Claeys G, Verschraegen G, Blot S (2007) Systematic surveillance cultures as a tool to predict involvement of multidrug antibiotic resistant bacteria in ventilator-associated pneumonia. Intensive Care Med 34:675–682

46. Timsit JF, Misset B, Renaud B, Goldstein FW, Carlet J (1995) Effect of previous antimicrobial therapy on the accuracy of the main procedures used to diagnose nosocomial pneumonia in patients who are using ventilation. Chest 108:1036–1040

47. Torres A, Fabregas N, Ewig S, de la Bellacasa JP, Bauer TT, Ramirez J (2000) Sampling methods for ventilator-associated pneumonia: validation using different histologic and microbiological references. Crit Care Med 28:2799–2804

48. Ramirez P, Garcia MA, Ferrer M, Aznar J, Valencia M, Sauquillo JM, Menendez R, Asenjo MA, Torres A (2007) Sequential measurements of procalcitonin in diagnosing ventilator-associated pneumonia. Eur Respir J 31:356–362