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Biomarkers kinetics in the assessment of ventilator-associated pneumonia response to antibiotics - results from the BioVAP study

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ABSTRACT

Purpose: Our aim was to evaluate the role of biomarker kinetics in the assessment of ventilator-associated pneumonia (VAP) response to antibiotics.
Materials and methods: We performed a prospective, multicenter, observational study to evaluate in 37 microbiologically documented VAP, the kinetics of C-reactive protein (CRP), procalcitonin (PCT), mid-region fragment of pro-adrenomedullin (MR-proADM). The kinetics of each variable, from day 1 to 6 of therapy, was assessed with a time dependent analysis comparing survivors and non-survivors.
Results: During the study period kinetics of CRP as well as its relative changes, CRP-ratio, was significantly different between survivors and non-survivors ($p = 0.026$ and $p = 0.005$, respectively). On day 4 of antibiotic therapy, CRP of survivors was 47% of the initial value while it was 96% in non-survivors. The kinetics of other studied variables did not distinguish between survivors and non-survivors. In survivors the bacterial load also decreased markedly. Adequate initial antibiotic therapy was associated with lower mortality ($p = 0.025$) and faster CRP decrease ($p = 0.029$).
Conclusions: C-reactive protein kinetics can be used to identify VAP patients with poor outcome as soon as four days after the initiation of treatment. **(Trial registration** - NCT02078999; registered 3 August 2012).
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1. Introduction

Ventilator-associated pneumonia (VAP) is the most common hospital-acquired infection (HAI) in the intensive care unit (ICU) [1]. In a recent large prospective observational study, 23% of the 2960 patients under invasive mechanical ventilation (MV) >48 h developed documented ventilator-associated lower respiratory tract infections, among which 12% were VAP [2].

Ventilator-associated pneumonia is an important complication of MV. It is associated with a longer duration of MV and length of stay, increased costs, as well as higher morbidity and attributable mortality [2,3]. But, other complications also happen in patients under MV like pulmonary edema, other HAIs, delirium, that also impact on outcomes.

Abbreviations: AUC, area under the curve; CFU, colony-forming units; CPIS, clinical pulmonary infection score; CRP, C-reactive protein; Dn, day and the "n" represents the day number; HAI, hospital-acquired infection; ICU, intensive care unit; IQR, interquartile range; MR-proADM, mid-regional proadrenomedulin; MV, mechanical ventilation; PCT, procalcitonin; QTA, quantitative tracheal aspirate; ROC, receiver operating characteristics curve; SAPS, simplified acute physiology score; SOFA, sequential organ failure assessment; VAP, ventilator associated pneumonia; VFD, ventilator free days; WCC, white cell count.

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Currently, the assessment of pneumonia response to antibiotic therapy relies on the resolution of the same criteria used in the diagnosis [4,5]. Bacterial eradication has been proposed as criteria of improvement [6], however these results were challenged [5]. Chest X-rays is also of limited value [7] and an initial deterioration is common [8].

Several studies have assessed the kinetics of procalcitonin (PCT) and C-reactive protein (CRP) in VAP after prescription of antibiotics as surrogate markers of clinical response [9-13]. Unfortunately almost all assessed only one biomarker.

The present analysis of the BioVAP study aimed to evaluate the kinetics of several biomarkers, namely CRP and PCT, as well as clinical variables in the assessment VAP response to antibiotic therapy in order to recognize, early in clinical course, VAP patients with poor outcome as well as to identify the individual patterns of CRP and PCT kinetics to antibiotics. Additionally, we also assessed the impact of the adequacy of antibiotic therapy on biomarkers' changes over time as well as on outcomes.

2. Materials and methods

The BioVAP study (**Bio**markers in the diagnosis and management of **V**entilator-**A**ssociated **P**neumonia) is a prospective, multicenter, observational study, designed to evaluate the additional information biomarkers can bring in the clinical decision making process of VAP at the bedside (NCT02078999) [14]. Local Institutional Ethics Committees approved the study design and written informed consent was obtained from all patients or their legally authorized surrogates in accordance with local requirements.

2.1. Study subjects

During the study period all patients admitted to the participating ICU were screened for inclusion if they were under MV for >72 h. A total of 211 included adult (>18 yrs) patients were divided into 3 groups: 1) non-infected, 2) pulmonary infection and 3) non-pulmonary infection (for details see Fig. 1 and electronic supplement material - ESM). For each patient, only the first ICU admission and the first VAP episode were included in the study.

2.2. Definitions

Diagnosis of VAP was made in patients under MV for at least 48 h according to standard criteria (for details see ESM) [15,16]. The thresholds used for diagnosis of pneumonia were $\geq 10^5$ colony-forming units (CFU)/ml on a quantitative tracheal aspirate (QTA) and/or $\geq 10^4$ CFU/ml on a bronchoalveolar lavage (BAL). All patients had a QTA at the day of VAP diagnosis and BAL was also performed in $N = 31$. Empiric antibiotic therapy was started according to the American Thoracic Society or to the Hospital Clínic of Barcelona guidelines of VAP treatment [8,17]. Analysis of the bacterial load considered the logarithm of CFU/ml count only from QTA (logQTA) [12].

According to the BioVAP protocol, in all patients, a QTA was performed at ICU admission and subsequently twice weekly (Mondays–Thursdays or Tuesdays–Fridays). It was acceptable to adjust empiric antibiotic therapy according to QTA previous findings, as well as, the prevalent ICU microflora in each participating centre.

Antibiotic therapy was classified as adequate if in the empiric therapy prescribed by the onset of VAP, at least one antibiotic covers all pathogens isolated as determined by the sensitivity pattern. Antibiotics were changed according to the isolated pathogen and the antimicrobial susceptibility testing.

2.3. Data collection and management

Data collection included demographic data and comorbid diseases (for data management see ESM). The Simplified Acute Physiology Score (SAPS) II [18] was calculated from the worst values within the first 24 h after ICU admission. Organ dysfunctions were evaluated at ICU admission and during the duration of MV according to the Sequential Organ Failure Assessment (SOFA) score [19]. Ventilator-free days (VFD) at day 28 were calculated as follows: VFD = 0 if death < 28 days; VFD = (28-number of days with MV in the first 28 days); VFD = 0 if MV > 28 days.

Day 1 (D1) was considered the day of VAP diagnosis and antibiotic prescription. Patients were closely monitored during the first 6 days of antibiotic therapy (for definitions see ESM). In all VAP patients a QTA was obtained at D3 and D5 of antibiotic therapy. Patients were followed up till death or ICU discharge as well as hospital discharge.

Several clinical variables were collected daily, namely CRP, PCT, mid-regional proadrenomedulin (MR-proADM), simplified Clinical Pulmonary Infection Score (CPIS) [20,21], and SOFA score. We also calculated the relative CRP and PCT changes, CRP-ratio and PCT-ratio, in relation to D1 concentrations, respectively. From D1 onwards the CRP-ratio and PCT-ratio was calculated dividing that particular day concentration by the D1 value.

Ventilator-associated pneumonia patients were divided in 4 groups according to their individual patterns of CRP-ratio kinetics [11]: fast response – when CRP-ratio at D4 was <0.4 of D1 CRP; slow response – characterized by a continuous and slow decreased of CRP-ratio; non-response – when CRP-ratio remained always ≥0.8 of the initial value; biphasic response – characterized by an initial CRP-ratio decrease to levels <0.8 of the D1 CRP, followed by a secondary rise to values ≥0.8. The same criteria were used to classify VAP patients according to their individual pattern of PCT-ratio kinetics.

For the present analysis, we assessed biomarker kinetics, namely CRP, PCT, MR-proADM, as well as temperature, WCC, bacterial load, VFD, CPIS and SOFA in VAP patients during the first 6 days of antibiotic therapy comparing ICU survivors and non-survivors.

3. Statistical analysis

Continuous variables were expressed as mean and standard deviation (SD) or median and interquartile range (IQR) if the distribution was clearly asymmetric. Comparisons between groups were performed with two-tailed unpaired Student's *t*-test, paired Student's *t*-test and One-Way ANOVA or Mann-Whitney *U* test, Wilcoxon Signed Ranks test and Kruskal Wallis *H* test for continuous variables according to data distribution. Fisher's exact test and Chi-square test were used to carry out comparisons between categorical variables as appropriate.

Time-dependent analysis of different variables from D1 to D6 of MV was performed with General Linear Models univariate repeated measures analysis using a split-plot design approach.

Receiver operating characteristics curves (ROC) of the studied variables were plotted to assess ability to evaluate prognosis of VAP. The accuracy of these variables was assessed calculating its area under the curve (AUC), assessment of the best cut-off value, sensitivity and specificity calculation.

Data were analyzed using PASW Statistics v.20.0 for MAC (SPSS, Chicago, IL). All statistics were two-tailed and significance level was set at 0.05.

4. Results

During the study period, 37 out of 211 MV patients developed VAP with microbiological confirmation (31 from the non-infected group, 5 from the pulmonary infections group, 1 from the non-pulmonary infections group; 17 VAP/1000 ventilator-days). Demographic characteristics of the VAP patients are shown in Table 1.

At D1, CRP, PCT, temperature, WCC, CPIS and SOFA of survivors and non-survivors were not statistically different (Table 2). Only MR-proADM was significantly higher in non-survivors (Table 2).

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