Journal of Critical Care 28 (2013) 970–974

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

Can we predict pneumococcal bacteremia in patients with severe community-acquired pneumonia?☆,☆☆

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ARTICLE INFO

Keywords:
Bacteremia
Biomarkers
Community-acquired pneumonia
Pneumococcus
Procalcitonin

ABSTRACT

Purpose: This study aimed to evaluate the role of biomarkers as markers of pneumococcal bacteremia in severe community-acquired pneumonia (SCAP).
Materials and Methods: A prospective, single-center, observational cohort study of 108 patients with SCAP admitted to the intensive care department of a university hospital in Portugal was conducted. Leucocytes, C-reactive protein (CRP), lactate, procalcitonin (PCT), D-dimer, brain natriuretic peptide (BNP), and cortisol were measured within 12 hours after the first antibiotic dose.
Results: Fifteen patients (14%) had bacteremic pneumococcal pneumonia (BPP). They had significantly higher levels of median CRP (301 [interquartile range, or IQR], 230-350] mg/L vs 201 [IQR, 103-299] mg/L; $P = .023$), PCT (40 [IQR, 25-102] ng/mL vs 8 [IQR, 2-26] ng/mL; $P < .001$), BNP (568 [IQR, 478-2841] pg/mL vs 407 [IQR, 175-989] pg/mL; $P = .027$), and lactate (5.5 [IQR, 4.5-9.8] mmol/L vs 3.1 [IQR, 1.9-6.2] mmol/L; $P = .009$) than did patients without BPP. The discriminatory power evaluated by the area under the receiver operating characteristic curve (aROC) for PCT (aROC, 0.79) was superior to lactate (aROC, 0.71), BNP (aROC, 0.67), and CRP (aROC, 0.70). At a cutoff point of 17 ng/mL, PCT showed a sensitivity of 87%, a specificity of 67%, a positive predictive value of 30% and a negative predictive value of 97%, as a marker of pneumococcal bacteremia.
Conclusions: In this cohort, significantly higher PCT, BNP, lactate, and CRP levels were found in BPP, and PCT presented the best ability to identify pneumococcal bacteremia. A PCT serum level lower than 17 ng/mL could identify patients with SCAP unlikely to have pneumococcal bacteremia.

1. Introduction

Community-acquired pneumonia (CAP) remains one of the leading causes of hospital admission and represents a burden to the health care system [1]. In recent decades, mortality among hospitalized patients with CAP has been reduced, but it remains elevated among patients admitted to the intensive care unit (ICU) [2-4].

Streptococcus pneumoniae is the leading pathogen, and approximately 20% of cases of pneumococcal pneumonia occur with bacteremia [5], leading to a mortality in the range of 15% to 36% [6-9].

Combination therapy, namely, the combination of a macrolide or a "respiratory" fluoroquinolone with a β-lactam, is advocated for the treatment for all patients with severe CAP [10-12]. This recommendation is supported mostly by retrospective and non-randomized studies [13-17] that showed a lower mortality rate with combination therapy, namely, in patients with pneumococcal bacteremia. Combination therapy is also associated with a better outcome in patients with septic shock [18] and in mechanically ventilated patients [19].

However, empiric use of combination therapy to all patients with severe CAP may lead to antibiotic overuse and resistance emergence, and in fact, avoiding the unnecessary use of antibiotics is the best way to reduce antibiotic pressure and decrease the emergence of antimicrobial resistance.

Whether it is possible to avoid using combination therapy in some patients with severe CAP remains an open question. Patients without

Abbreviations: CAP, community-acquired pneumonia; ICU, intensive care unit; COPD, chronic obstructive pulmonary disease; SAPS, Simplified Acute Physiology Score; PIRO, Predisposition, Insult, Response, Organ Failure; SOFA, Sepsis-related Organ Failure Assessment; PSI, Pneumonia Severity Index; WBC, leukocyte count; PCT, procalcitonin; CRP, C-reactive protein; BNP, Brain natriuretic peptide; SD, standard deviation; IQR, 25th to 75th interquartile range; ROC, receiver operating characteristics; aROC, area under the receiver operating characteristics curve; sTREM, soluble form of triggering receptor expressed on myeloid cells 1.

☆ Conflict of interest: The authors declare that they have no competing interests.

☆☆ Authors' contributions: All authors have made substantial contribution to the conception and design of the study as well as to the drafting, revising, and final approval of the version to be published. J.M.P. and A.T.P. performed statistical analysis.

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0883-9441/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.jcrc.2013.04.016

shock and without pneumococcal bacteremia would probably be the best candidates for monotherapy.

In addition, because early mortality accounts for more than half of deaths in patients with pneumococcal bacteremia, research efforts should be focused on the identification of early surrogate markers of the existence or inexistence of this type of infection [20].

The purpose of our study was to evaluate the role of biomarkers as markers of pneumococcal bacteremia in severe CAP.

2. Materials and methods

2.1. Study design

This was a single-center, observational, prospective cohort study of patients with severe CAP admitted to the intensive care department of a tertiary care university hospital in Portugal between December 2008 and January 2013. The study was approved by the local ethical committee. Despite its observational nature, written informed consent was obtained from every patient or patient representative before inclusion in the study.

Community-acquired pneumonia was diagnosed when, in addition to suggestive clinical features (eg, cough, fever, sputum production, and pleuritic chest pain), a demonstrable infiltrate by chest radiograph or computed tomographic scan was present [1]. *Severe CAP* was defined according to Infectious Diseases Society of America/American Thoracic Society criteria [10]. To be included into this study, patients with severe CAP had to be older than 18 years and have all biomarkers measured within 12 hours after the first antibiotic dose.

2.2. Data collection

The following parameters were collected at the moment or within the first 24 hours of ICU admission: age, sex, comorbidities, corticosteroids use, existence or development of septic shock and/or acute respiratory distress syndrome, and empiric antibiotic therapy. The duration of mechanical ventilation, length of hospital and ICU stay, and mortality (hospital and ICU) were recorded. Simplified Acute Physiology Score (SAPS) II [21], SAPS3 [22], Predisposition, Insult, Response, Organ Failure–CAP [23], Sepsis-related Organ Failure Assessment score [24], and Pneumonia Severity Index (PSI) [25] were calculated.

2.3. Microbiologic evaluation

At the point of inclusion into the study, 2 pairs of blood cultures were collected. Blood cultures were processed using an automated microbiology growth and detection system (BACTEC 9240 system, Beoton Dickinson, Sparks, MD). If there was bacterial growth, samples were gram stained and subcultured. A *bacteremic episode* was defined as growth of a typical organism for CAP in at least 1 of 4 collected blood cultures.

Tracheal aspirate was taken from every patient whenever possible to test for bacteria according to standard procedures. Representative sputum originating from the lower respiratory tract was validated by the criteria of more than 25 granulocytes and less than 10 epithelial cells per low-power field (total magnification $\times 100$).

Urine samples were collected and tested whenever possible for *Legionella pneumophila* and *S pneumoniae* with an antigen test. Real-time polymerase chain reaction was used to evaluate the presence of respiratory virus in nasopharyngeal swab and bronchoalveolar lavage, when clinically and epidemiologically indicated. Pleural fluid when available was also collected.

Identification of microorganisms and susceptibility testing was performed according to standard methods.

Severe CAP was considered microbiologically documented if at least 1 of the following criteria was met: (1) positive blood culture for a nonskin contaminant, (2) positive bacterial culture of pleural fluid samples, (3) positive urinary antigen for *L pneumophila* or *S pneumoniae*, (4) bacterial growth in cultures of bronchoalveolar lavage ($\geq 10^4$ colony-forming unit/mL) or tracheal aspirate (leukocytes >25 and epithelial cells <10 per high-power microscopic field), and (5) positive real-time polymerase chain reaction for respiratory virus in nasopharyngeal swab and bronchoalveolar lavage.

2.4. Biomarkers determination

Within 12 hours of the first antibiotic dose for a severe CAP episode, blood samples were taken for the determination of leukocyte count, lactate, procalcitonin (PCT), C-reactive protein (CRP), cortisol, D-dimer, and brain natriuretic peptide (BNP).

Leukocyte count was obtained using an automated blood counter Sysmex XE-5000 (Emilio de Azevedo Campos, Porto, Portugal). Serum CRP (Olympus AU5400 automated clinical chemistry analyzer; Beckman-Coulter, Izasa, Porto, Portugal), and D-dimers (STA Rack Evolution; Roche, Lisboa, Portugal) were measured by immunoturbidimetric assays. A chemiluminescent microparticle immunoassay was used for the quantitative determination of BNP (Architect i2000 automated analyzer; Abbott, Lisboa, Portugal). Cortisol was measured with an electrochemiluminescent immunoassay using a Cobas e411 automated analyzer (Roche). Serum levels of PCT were determined using a highly sensitive immunoassay (mini VIDAS, bioMérieux SA, Marcy l'Etoile, France) based on enzyme-linked fluorescent assay technique.

2.5. Statistical analysis

Discrete variables are described as counts (%) and continuous variables as the mean with SD or medians with 25th to 75th interquartile range (IQR), as appropriate. Categorical variables were compared using χ^2 or Fisher exact tests. Continuous variables with normal distribution were compared using the Student *t* test; otherwise, the nonparametric Mann-Whitney *U* test was performed.

Receiver operating characteristic (ROC) curves were generated to compare the overall predictive accuracy of biomarkers for pneumococcal bacteremia, and the area under the ROC curves (aROC) was calculated. Variables associated with pneumococcal bacteremia were defined if a 2-sided *P* value was .05 or less; 95% confidence intervals (CIs) were calculated. The level of significance was set at .05 for all the tests. PASW 18.0 software (Chicago, Ill) was used for the statistical analyses.

3. Results

3.1. Patients' characteristics and CAP etiology

The mean (SD) age of the overall cohort was 61 (16) years, and 63% were male. Mean (SD) PSI score was 153 (41), and 92.5% of patients were in high-risk PSI classes IV and V.

Severe CAP was microbiologically documented in 64 (59%) cases, and 6% were polymicrobial. As expected, *S pneumoniae* (n = 33) was the leading pathogen, followed by H1N1 (n = 7), *Staphylococcus aureus* (n = 5) and *L pneumophila* (n = 5). Table 1 details the prevalence of microorganisms isolated in this cohort. Positive blood cultures were documented in 23 patients (21%), and *S pneumoniae* was recovered from the blood in 15 (14%).

Table 2 shows global baseline characteristics on hospital admission and separated according to the presence or absence of pneumococcal bacteremia.

3.2. Empirical antibiotic therapy

Almost all patients (99%) received a combination of antibiotics, with one exception (fluoroquinolone plus β-lactam), a macrolide plus