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Original article

Predictors for individual patient antibiotic treatment effect in hospitalized community-acquired pneumonia patients

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ABSTRACT

Objective: Our objective was to identify clinical predictors of antibiotic treatment effects in hospitalized patients with community-acquired pneumonia (CAP) who were not in the intensive care unit (ICU).
Methods: Post-hoc analysis of three prospective cohorts (from the Netherlands and Spain) of adult patients with CAP admitted to a non-ICU ward having received either β-lactam monotherapy, β-lactam + macrolide, or a fluoroquinolone-based therapy as empirical antibiotic treatment. We evaluated candidate clinical predictors of treatment effects in multiple mixed-effects models by including interactions of the predictors with empirical antibiotic choice and using 30-day mortality, ICU admission and length of hospital stay as outcomes.
Results: Among 8562 patients, empirical treatment was β-lactam in 4399 (51.4%), fluoroquinolone in 3373 (39.4%), and β-lactam + macrolide in 790 (9.2%). Older age (interaction OR 1.67, 95% CI 1.23–2.29, p 0.034) and current smoking (interaction OR 2.36, 95% CI 1.34–4.17, p 0.046) were associated with lower effectiveness of fluoroquinolone on 30-day mortality. Older age was also associated with lower effectiveness of β-lactam + macrolide on length of hospital stay (interaction effect ratio 1.14, 95% CI 1.06–1.22, p 0.008).
Conclusions: Older age and smoking could influence the response to specific antibiotic regimens. The effect modification of age and smoking should be considered hypothesis generating to be evaluated in future trials. **A.F. Simonetti, Clin Microbiol Infect 2017;23:774.e1–774.e7**

Introduction

Community-acquired pneumonia (CAP) is a leading cause of hospitalization and death worldwide [1–3]. Although recent studies described a downward trend in 30-day mortality in hospitalized patients with CAP over the last 20 years [4,5], the reported hospital mortality in these patients remains high, ranging from 4% to 15% [4–7].

For patients with CAP admitted to a non-intensive-care-unit (non-ICU), international guidelines recommend either β-lactam monotherapy, β-lactam + macrolide combination therapy or respiratory fluoroquinolone monotherapy as empirical treatment [8–10]. However, the necessity for atypical coverage in non-severe CAP patients is uncertain because beneficial effects on mortality were only found in observational studies, not in randomized controlled trials [11,12]. Moreover, the use of macrolides and fluoroquinolones has been related to increased risks of antimicrobial resistance and adverse drug effects [13–17]. A limitation of the studies performed so far is that they compared interventions within the whole domain of hospitalized CAP (e.g. at the population level), lacking power for proper subgroup analyses.

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Despite important advancements in diagnostic testing, a causative pathogen is not detected in the majority of patients with CAP; and if detected there is often a delay of up to 48 hours [2]. Initial antibiotic treatment is therefore almost always empirical. However, CAP is a heterogeneous disease due to heterogeneity in both host and pathogen factors. Therefore, an individualized antibiotic treatment approach might prove beneficial.

The concept of individualized medicine, initially referred to the use of genomics in clinical care, has extended to recognizing the heterogeneity of each individual patient, particularly their risk factors for developing disease or having poor outcomes, and using this to inform treatment decisions. Biomarkers and clinical predictors have been widely studied in CAP in an attempt to predict the microbial aetiology [18,19] or clinical outcomes, such as early treatment failure or all-cause mortality [20–25]. Yet, predictors of pathogens are weak at best, and predictors of all-cause mortality do not inform the treating physician about the necessity to adjust empirical therapy. To pave the way for individualized medicine for CAP, it is necessary to take a further step and assess differences in treatment response based on multiple patient factors.

The objective of this study was to find candidate predictors at an individual patient level for effect modification of empirical antibiotic regimens (β-lactam, β-lactam + macrolide and fluoroquinolone) in patients with CAP hospitalized to non-ICU wards.

Patients and methods

Setting, study population and research design

This is a post-hoc analysis of three cohorts of hospitalized patients with CAP, two from the Netherlands and one from Spain [4,12,26]. The Dutch cohorts were from two large randomized clinical trials conducted in the Netherlands. All patients hospitalized for CAP from The Community-Acquired Pneumonia immunization Trial in Adults (CAPiTA), and all patients included in the Community-Acquired Pneumonia—Study on the Initial Treatment with Antibiotics of Lower Respiratory Tract Infections (CAP-START) were included.

The Spanish (Bellvitge) cohort includes all patients with X-ray-confirmed CAP admitted via the emergency department of Bellvitge University Hospital. The Supplementary material (Table S1) shows the main characteristics of the three cohorts. For the purpose of this study, we only analysed patients who received β-lactam, β-lactam + macrolide or fluoroquinolone as empirical antibiotic treatment.

Data collection

Empirical antibiotic treatment was defined as the antibiotic treatment administered in the first calendar day of hospitalization (Dutch cohorts) or prospectively collected as a specific item in the data collection form (Bellvitge cohort), as the first antibiotic regimen administered to the patient after admission.

Data on clinical presentation, laboratory results, microbiological test results, antibiotic use and clinical outcome were retrieved from medical records. In the absence of notes in clinical records, the following variables were assumed to be absent/negative: pneumococcal or influenza vaccination, clinical symptoms (cough, purulent sputum, pleuritic chest pain, headache, gastrointestinal symptoms, chills), confusion, hypotension, tachycardia, positive urinary antigen for *Streptococcus pneumoniae*. Definitions of predictors and empirical antibiotic treatment are explained in the Supplementary material (Appendix S1).

All studies were approved by the Institutional Review Board in the participating hospitals and the informed consent covered the current analysis. To protect personal privacy, data were anonymized.

Outcomes

The primary outcome was all-cause mortality within 30 days after admission. The 30-day mortality was either assessed at a long-term follow-up visit (Bellvitge), from general practitioner medical records (Bellvitge, CAPiTA), or from the municipal records database (CAP-START). The secondary outcomes were ICU admission after the first day of hospitalization and length of hospital stay (LOS). All outcomes were measured and analysed at the individual patient level.

Predictors

Through an extensive search in PubMed we selected a list of candidate clinical predictors of treatment effects on CAP. These clinical predictors should be present and known at admission and associated either to specific CAP aetiology or to clinical outcome.

A complete list of the predictors chosen for the analysis and the correspondent bibliography are shown in the Supplementary material (Appendix S1).

In addition, the year of admission was included as a confounding variable, categorized in four periods of 5 years each, as follows: 1995–1999, 2000–2004, 2005–2009, 2010–2014.

Statistical analysis

Data are presented as percentages and numbers, means with SDs, medians with interquartile ranges (IQRs), or proportions with 95% CIs, as appropriate.

For binary outcomes we used mixed-effects logistic regression models—see the Supplementary material (Appendix S1) for details. To identify candidate predictors of treatment effects we applied a two-step approach. First, we estimated for each candidate predictor the interaction effect with antibiotic treatment in separate models, including the fixed effects, random effects, and the single interaction effect. Interaction variables with a two-sided $p < 0.10$ using the Wald test were included in the second step of our analysis. There we constructed a mixed-effects model including all selected interactions from the first step and all previously mentioned fixed and random effects. The p values of the second-step model were corrected for multiple testing using the Benjamini–Hochberg (BH) method [28]. Two-sided BH adjusted values of $p < 0.05$ were considered statistically significant. Associations are given as ORs with 95% CIs. Effect modifiers for the LOS were tested similarly with mixed-effects linear regression models, after log-transforming length of stay. The exponent of the regression coefficients was interpreted as the effect ratio, e.g. an effect ratio of 2 for factor *x* implies that a patient with *x* has an LOS twice that of a patient without *x*.

We performed sensitivity analyses including only patients with radiologically confirmed CAP and we performed analyses stratified per cohort. Assumptions of the models were tested visually by plotting residuals. Missing data on smoking habits (6.6% of missing data), pre-hospital antibiotic use (2.5%), living in a residential care home for the elderly (12.4%), serum sodium concentration (12.4%), leucocyte count (0.2%) and Pneumonia Severity Index (PSI) (0.1%) were imputed by multiple imputations (ten imputation data sets), assuming data missing at random. Descriptive statistics and multiple imputations were performed using the Statistical Package for the Social Sciences for Windows (Version SPSS 21.0.0.0). Mixed-effects models were performed with R (R Core Team, 2015), and the R-package lme4 (Bates, Maechler, Bolker, Walker 2015).

Results

A total of 8562 patients were included: 2184 (25.5%) from the CAPiTA cohort, 2154 (25.2%) from the CAP-START cohort and 4224