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Atypical coverage in community-acquired pneumonia after outpatient beta-lactam monotherapy

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ABSTRACT

Introduction: In adults hospitalized with community-acquired pneumonia (CAP) after >48 h of outpatient beta-lactam monotherapy, coverage of atypical pathogens is recommended based on expert opinion.
Methods: In a post-hoc analysis of a large study of CAP treatment we included patients who received beta-lactam monotherapy for >48 h before hospitalization. Length of hospital stay (LOS), 30-day mortality, and number of treatment escalations were compared for those that continued beta-lactam monotherapy and those that received atypical coverage at admission.
Results: Of 179 patients (median age 66 years (IQR 50–78), 100 (56%) male), 131 (73%) received additional atypical coverage at admission. These patients were younger, had less comorbidities, and longer symptom duration, compared to those that continued beta-lactam monotherapy. In crude analysis, median (IQR) LOS was 6 (4–8) and 6 (4–9) days, mortality was 2% and 4%, and treatment escalations occurred in 8 (17%) and 11 (8%) patients without and with atypical coverage, respectively. Adjusted effect ratios for absence of atypical coverage on LOS, mortality, and treatment escalation were 0.77 (95% CI 0.61–0.97), 0.37 (0.04–3.67), and 2.75 (0.94–8.09), respectively.
Conclusion: In adults hospitalized with CAP after >48 h of outpatient beta-lactam monotherapy, not starting antibiotics with atypical coverage was associated with a trend towards more treatment escalations, without evidence of increased LOS or mortality.

1. Introduction

The optimal empirical antibiotic treatment of community-acquired pneumonia (CAP) consists of the narrowest possible antimicrobial spectrum without compromising patient outcome. However, CAP may have different etiological causes requiring different antibiotic therapies, which are unknown when starting empirical treatment. Therefore, physicians must balance all-inclusiveness (that will stimulate resistance development) and insufficient treatment (that may worsen patient outcome). Clinical parameters cannot predict the causative pathogen [1–3]. The most debated question is whether atypical pathogens, such as *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and *Legionella pneumophila* must be covered empirically in all patients hospitalized with CAP [4,5]. Empirical treatment guidelines are based on the clinical severity of infection, local distribution of pathogens and resistance patterns of bacteria causing CAP, and failure of antibiotics prior to hospitalization. As general practitioners mostly prescribe beta-lactam antibiotics for lower respiratory tract infections, previous receipt of such antibiotics is a frequent reason to include empirical treatment for atypical pathogens when hospitalization for CAP is needed [3]. Empirical atypical coverage can include tetracyclines, macrolides, or fluoroquinolones. This guideline recommendation is based mainly on expert consensus. In a retrospective study, though, clinical outcome was comparable for those receiving

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and not receiving empirical atypical coverage after pre-hospitalization exposure to beta-lactam antibiotics [6]. Yet, in that study data could not be adjusted for disease severity and microbiology. The question whether atypical coverage is needed in CAP patients hospitalized to non-ICU wards that received beta-lactam monotherapy before hospitalization, therefore, remains to be answered.

2. Methods

2.1. Patients and setting

Data were used from a cluster-randomized trial evaluating empirical antibiotic treatment strategies described previously [7,8]. In short, seven hospitals in the Netherlands were randomized to three alternating empirical antibiotic treatment strategies for CAP, beta-lactam monotherapy, beta-lactam plus macrolide therapy, and fluoroquinolone monotherapy, during consecutive periods of four months. All patients hospitalized to a non-intensive care unit (non-ICU) ward with a working diagnosis of CAP were eligible for inclusion. A working diagnosis of CAP was defined as the presence of at least two diagnostic clinical criteria (cough, production of purulent sputum or a change in the character of sputum, temperature >38 °C or <36.1 °C, auscultatory findings consistent with pneumonia, leucocytosis, C-reactive protein level more than 3 times the upper limit of the normal range, either of dyspnea, tachypnea, or hypoxemia, and new or increased infiltrate on chest radiography or CT scan) and in-hospital treatment with antibiotics for clinically suspected CAP as documented by the treating physician. Patients with two or more criteria and an obvious non-respiratory source of infection were not considered to have a working diagnosis of CAP, nor were patients who had recently been hospitalized (for >48 h in the previous 2 weeks) or who resided in long-term care facilities. Treating physicians were instructed to treat CAP patients according to the allocated strategy, but deviations were allowed for medical reasons. Physicians were also allowed to switch antibiotic treatment if medically indicated, e.g. if the causing pathogen was identified or if patients deteriorated or failed to improve. Patients were prospectively included in the study after providing informed consent for the purpose of data collection. The study was approved by the Institutional Review Board of the University Medical Center Utrecht, the Netherlands.

The current analysis was restricted to patients receiving beta-lactam monotherapy as the last antibiotic treatment for >48 h prior to hospitalization. As these data were available per calendar day, we defined “>48 h” as three or more calendar days. Patients with two or more antibiotic-free calendar days between the end of outpatient antibiotic treatment and the day of hospitalization were not included, as we considered them not part of the study domain.

Patients were divided into two groups: those receiving and those not receiving atypical coverage at the time of hospitalization. As data on antibiotic treatment was available per calendar day, beta-lactam monotherapy was defined as receiving beta-lactams on the first calendar day of admission, and not receiving other antibiotics. If coverage of atypical pathogens was initiated on the second admission day, group assignment was based on the timing and rationales for treatment assignment provided in the medical records. E.g. if patients were hospitalized in the evening, a beta-lactam could be administered before midnight and a macrolide or fluoroquinolone was given the next morning, but this was already planned at the ER; such patients were classified as receiving empirical atypical coverage. However, if patients switched to atypical coverage the next calendar day based on new clinical or microbiological information, the empiric treatment was classified as no atypical coverage. All treatment episodes consisting of beta-lactam monotherapy (penicillin, amoxicillin (with or without clavulanic acid), cephalosporins, and carbapenems) were classified as absence of atypical coverage. Atypical coverage was categorized as receipt of a fluoroquinolone, macrolide, or tetracycline, or any combination of these with a beta-lactam. The decision to cover atypical pathogens was made by the treating physician.

2.2. Data collection

Data were collected from the medical records by trained research nurses and included demographics, comorbidities, severity indicators, laboratory results, antibiotic consumption, complications, and duration of hospitalizations. For assessment of disease severity we used the pneumonia severity index (PSI), a score consisting of 20 variables, and the CURB-65 score consisting of confusion, urea, respiratory rate, blood pressure, and age > 65 years; both scores developed to predict 30-day mortality [9,10]. The microbiological diagnostics were according to standard care practices and not dictated by protocol. Routine microbiological tests consisted of blood and sputum cultures and pneumococcal and legionella urinary antigen tests. Other tests including serology or polymerase chain reaction (PCR) tests of respiratory samples were requested at the discretion of the treating physician. Antibiotic treatment before admission was derived from the medical records or, if not documented, the patient was inquired by trained research nurses. Mortality status up to day 90 after admission was recorded from the medical charts. If in doubt, the mortality status of patients were checked electronically in the municipal personal records database except in one hospital,. In this hospital without electronic access to this database, research nurses contacted the general practitioner of each patient with an unknown status. In the Netherlands, every inhabitant is registered with a single general practitioner, who is routinely informed about important medical affairs.

2.3. Outcomes

The primary outcome was length of hospital stay (LOS) in days. Secondary outcome measures were all-cause 30-day mortality and treatment escalations. Treatment escalation was defined as antibiotic change for clinical deterioration/lack of improvement, or an identified pathogen not covered by the empirical treatment.

2.4. Statistical analysis

Common descriptive statistics were used to compare the two groups and differences were tested using the chi-squared or Fisher's exact test for proportions and Student's t-test or Mann–Whitney U test for continuous variables, as appropriate. Differences in LOS were analyzed using a linear regression model with log-transformed LOS as the outcome. The exponential of the effect estimate is reported, which represents the relative change in LOS for patients continuing beta-lactam monotherapy compared to those receiving atypical coverage. All-cause 30-day mortality and treatment escalations were analyzed using a logistic regression model. Estimates are reported with 95% confidence intervals (CI) and a two-sided p-value <0.05 was considered statistically significant.

3. Results

Of 2283 patients included in the CAP-START study, 749 (32.8%) received any antibiotic prior to hospitalization and 179 (7.8%) received beta-lactam monotherapy prior to hospitalization for >48 h (Fig. 1). The median age was 66 years (interquartile range