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Effectiveness of and obstacles to antibiotic streamlining to amoxicillin monotherapy in bacteremic pneumococcal pneumonia

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ABSTRACT

Background: Antibiotic streamlining is pivotal to reduce the emergence of resistant bacteria. However, whether streamlining is frequently performed and safe in difficult situations, such as bacteremic pneumococcal pneumonia (BPP), has still to be assessed.
Methods: All adult patients admitted to Dijon Hospital (France) from 2005 to 2013 who had BPP without complications, and were alive on the third day were enrolled. Clinical, biological, radiological, microbiological and therapeutic data were recorded. A first analysis was conducted to assess factors associated with being on amoxicillin on the third day. A second analysis, adjusting for a propensity score, was performed to determine whether 30-day mortality was associated with streamlining to amoxicillin monotherapy.
Results: Of the 196 patients hospitalized for BPP, 161 were still alive on the third day and were included in the study. Treatment was streamlined to amoxicillin in 60 patients (37%). Factors associated with not streamlining were severe pneumonia (OR 3.11, 95%CI [1.23–7.87]) and a first-line antibiotic combination (OR 3.08, 95%CI [1.34–7.09]). By contrast, starting with amoxicillin monotherapy correlated inversely with the risk of subsequent treatment with antibiotics other than amoxicillin (OR 0.06, 95%CI [0.01–0.30]). The Cox model adjusted for the propensity-score analysis showed that streamlining to amoxicillin during BPP was not significantly associated with a higher risk of 30-day mortality (HR 0.38, 95%CI [0.08–1.87]).
Conclusions: Streamlining to amoxicillin is insufficiently implemented during BPP. This strategy is safe and potentially associated with ecological and economic benefits; therefore, it should be further encouraged, particularly when antibiotic combinations are started for severe pneumonia.

1. Introduction

The use of broad-spectrum antibiotics has significantly increased in outpatients in France [1], and is associated with the emergence of bacterial resistance. This is particularly true in severe community-acquired pneumonia (CAP), where *Streptococcus pneumoniae* (*S.p.*) remains the main causative agent [2], and even more so in hospital-acquired pneumonia (HAP), for which antibiotics with a significant ecological impact (such as cephalosporin, antipseudomonal β-lactam antibiotic, and quinolone) are increasingly used [3,4]. Antibiotic streamlining is needed to lower antibiotic pressure and thus the development of antimicrobial resistance [5]. Antibiotic streamlining generally refers to a reduction in the spectrum of administered antibiotics through the discontinuation of antibiotics or by switching to an agent with a narrower spectrum.

From this point of view, bacteremic pneumococcal pneumonia (BPP) is of particular interest. Firstly, it is more frequently observed in more severely ill patients or in the patients at higher risk of complications, thus leading to a more frequent empirical use of wide-spectrum antibiotics or combinations. Secondly, by offering the opportunity to both isolate the causative agent and assess its susceptibility to antibiotics, it provides valuable information to implement antibiotic streamlining towards narrower spectrum antibiotics, i.e., amoxicillin, which remains the treatment of reference, as the prevalence of penicillin resistance is relatively low in France and other countries [6].

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However, studies that focus on streamlining in BPP are scarce, and show that this strategy is not so common, being applied in 46% to 63% of patients [7–9]. This could be linked to the results of certain retrospective studies, which concluded that the use of antibiotic combinations (especially β-lactam-macrolide) could reduce mortality rates in pneumococcal pneumonia compared with monotherapy [10]. Lastly, conflicting effects of streamlining on outcome have been reported in studies in critically ill patients [7,11,12]. Nevertheless, this has to be weighed against the results of a recent meta-analysis, which indicated that antibiotic susceptibility testing (AST)-based streamlining in patients with bacteremia, severe sepsis and ventilator-acquired pneumonia was associated with a lower unadjusted mortality rate [13]. This was not observed in patients with other types of pneumonia [13]. However, there was no significant difference in mortality in the adjusted analysis and a non-significant trend towards increased mortality was found with the streamlining strategy when the analysis was restricted to only the three randomized controlled trials [13].

Thus, there is still some uncertainty about whether antibiotic streamlining is safe in pneumonia. As no new randomized controlled trials on this topic are likely to be conducted in the near future, observational studies assessing the safety of antibiotic streamlining after adjusting for confounding factors should be informative. In addition, the impact of streamlining to amoxicillin monotherapy in BPP has never been assessed.

The present study was therefore conducted to assess factors associated with not streamlining to amoxicillin monotherapy in BPP, and to determine the impact of streamlining on outcome in patients.

2. Patients and methods

2.1. Study design

All adult patients hospitalized for BPP (either community-acquired or healthcare-related) in several wards of Dijon University Hospital between January 1st 2005 and March 31st 2013 were included in a prospective cohort (French National Hospital Clinical Research Program [PHRC] 2004/37). Data were collected via standardized report forms. This cohort was completed retrospectively by adding patients hospitalized for BPP in the same hospital during the same period, who had not been included in the prospective cohort study for logistical reasons.

The study was conducted in accordance with the Declaration of Helsinki and National standards. The collection of nominative data was approved by the national authority for the protection of privacy and personal data and by the local ethics committee (Comité de protection des personnes Est I).

2.2. Inclusion and non-inclusion criteria

To be included in the present study, patients had to meet the following criteria: (1) aged over 18 years; (2) positive blood cultures for *S. pneumoniae*; and (3) diagnosed with pneumonia, defined as an acute illness (<10 days of symptoms) with the presence of a new pulmonary infiltrate on chest radiograph at the time of hospitalization, plus either a new or increased cough with or without sputum production, or an abnormal temperature (<35.6 °C or >37.8 °C), or an abnormal serum leukocyte count: i.e., leukocytosis (leukocyte count $\geq 10 \cdot 10^6$/L), left shift, or leukopenia (leukocyte count $<4 \cdot 10^6$/L).

Patients who died during the first 3 days were not included, nor were those with missing data and those for whom concomitant meningitis, endocarditis, spondylitis or arthritis was discovered during the first 3 days after hospital admission.

Healthcare-associated pneumonia (HCAP), HAP, and CAP were defined according to the guidelines of the American Thoracic Society/Infectious Diseases Society of America [4,14]. HCAP corresponded to any of the following: hospitalization for ≥2 days in the preceding 90 days; residence in a nursing home; home infusion therapy; long-term dialysis within 30 days; and home wound care. HAP was defined as pneumonia that occurred 48 hours or more after admission and that was not incubating at the time of admission.

2.3. Study variables

Demographic data, medical history, initial clinical presentation, and biological findings (first 24 hours), antibiotic treatment, microbiological culture results, and outcome were all recorded. To evaluate disease severity, clinical and biological data were collected for the first 24 hours to calculate the Pneumonia Severity Index (PSI) score as defined by Fine et al [15]. The PSI scores were classified as low (class I to III) and high (class IV to V) [15]. The following therapeutic data were recorded: mechanical ventilation and admission to an intensive care unit (ICU). Immunosuppression included human immunodeficiency virus seropositivity; daily administration of corticosteroids (at least 5 mg per day of prednisone or an equivalent drug); immunosuppressive therapy; chemotherapy for an underlying malignancy during the 6 months before hospital admission; and primary or secondary hypogammaglobulinemia, hypocomplementemia, and splenectomy [16].

The susceptibility of bacterial strains to antibiotics was assessed according to the 2016 European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints [17]. Minimal inhibitory concentrations (MICs) above 0.5 mg/L for penicillin G and amoxicillin defined non-susceptibility.

Antibiotic treatments were assessed throughout the follow-up of the patients, with special attention paid to the third and seventh days.

2.4. Judgment criterion/outcome

Streamlining was defined as either changing an initially appropriate antimicrobial therapy (or discontinuing an antimicrobial combination) to amoxicillin monotherapy (also called de-escalation), or continuing either intravenous or oral amoxicillin monotherapy, according to the microbial culture results, on the third day after the blood culture was received at the Microbiology Department.

Thirty-day mortality was reported as the proportion of patients who died within 30 days after hospitalization. Follow-up was recorded as the number of days from the date the blood sample was received at the Microbiology Department to death or to the 30-day censoring point.

2.5. Statistical analysis

Continuous variables were expressed as medians (interquartile ranges [IQR]), and categorical variables as frequencies (percentages). Continuous data were compared using the Mann–Whitney U–test, and categorical data were compared using the χ^2 test (and Fisher's exact test when appropriate). Forward stepwise logistic regression was used for the multivariate analysis, which included all the variables with $P \leq 0.250$ in the univariate analysis. The model fit was evaluated with the Hosmer-Lemeshow goodness-of-fit test.

The cumulative probability of not streamlining to amoxicillin monotherapy was compared between patients with a low and high PSI score using the Kaplan-Meier method and the log-rank test.

A propensity score, containing all variables significantly associated with the type of antibiotic treatment on day 3, was then calculated to compare 30-day mortality between patients who were streamlined to amoxicillin and those who were not. The propensity score was estimated by first using patient age and sex and then variables with $P < 0.250$ selected in the logistic regression model: