Sequential administration of beta-lactams and macrolides on the outcomes of hospitalized patients with community-acquired pneumonia (CAP)

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ABSTRACT

Introduction
Guidelines for CAP recommend administration of beta-lactam plus macrolides since this combination decreases mortality. Explanations for decreased mortality include: 1) macrolides are effective against atypical pathogens and 2) macrolides act as anti-inflammatory agents. In patients with meningitis, the anti-inflammatory agent (steroids) are administered before the use of beta-lactam antibiotics to improve clinical outcomes. Data on the clinical outcomes of patients with CAP are lacking regarding the effect of macrolides when given before or after beta-lactams.

Objective
The objective of this study was to compare clinical outcomes when macrolides are used before or after administration of beta-lactams.

Methods
This was a secondary data analysis of the Community-Acquired Pneumonia Organization (CAPO) International Cohort Study database. Patients receiving a combination of beta-lactams plus macrolides for empiric therapy were included. Patients given beta-lactams and macrolides within 1 hour or more than 24 hours apart were excluded.

Results
A total of 555 patients were included, 63 with a macrolide first and 492 with a beta-lactam first. The adjusted percent in-hospital mortality was 1% for patients receiving a macrolide first and 8% for patients receiving a beta-lactam first (P=0.158).

Conclusions
These data suggest that, although not statistically significant, there is a clinically relevant decrease in in-hospital mortality if a macrolide is given before a beta-lactam. Since macrolides may decrease mortality only when given prior to beta-lactam antibiotics, their activity is likely due to anti-inflammatory effects as opposed to coverage of atypical pathogens.

INTRODUCTION

Even though we currently have newer broad-spectrum antibiotics and better treatment regimens, the mortality rate from pneumonia remains high (12%) (1). Appropriate antibiotic regimen is crucial for the outcome of hospitalized patients with CAP. According to the American Thoracic society 2007 guidelines, recommended empiric antibiotics for CAP according to the setting are as follows, for inpatients, non-ICU treatment [beta-lactam plus a macrolide or a respiratory fluoroquinolone], for inpatients, ICU treatment [beta-lactam plus either a macrolide or a respiratory fluoroquinolone] and if Pseudomonas is a consideration [an antipneumococcal, antipseudomonal b-lactam (piperacillin- tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin or the above b-lactam plus an aminoglycoside and azithromycin] (2).

The most commonly used antimicrobial regimen is a beta-lactam antibiotic in combination with a macrolide. Beta-lactams act on the bacterial cell wall causing bacteriolysis while macrolides act at the level of bacterial ribosome and also have anti-inflammatory effect according to the literature (3). Data from other serious infection like meningitis showed that the administration of anti-inflammatory drugs such as steroids before the beta-lactams reduced mortality in this population (4). Current recommendations for the treatment of CAP do not specify any particular order in which these antibiotics should be given. Data on clinical outcomes of patients with CAP are lacking regarding the impact of macrolides when given before or after beta-lactams.

The objective of this study was to compare clinical outcomes when macrolides are used before or after administration of beta-lactams.

METHODS

-Study design and Study population
This was a secondary analysis of patients enrolled in the Community-Acquired Pneumonia Organization (CAPO) international cohort study. Data were collected between 2001 and 2014. In each participating center, non-consecutive medical records of hospitalized patients with the diagnosis of CAP were reviewed. A sample of the data collection form is available at the study website (www.caposite.com). Validation of data quality was performed at the study center before the case was entered in to the CAPO database. Institutional Review Board approval was obtained by each participating center.

-Study definitions:
CAP: Diagnosis of CAP required the presence of criterion A, B, and C:

A. New pulmonary infiltrate on imaging (CT scan or chest x-ray) at the time of admission to the hospital.
B. Signs and Symptoms of CAP (at least one of the following)
    1. New or increased cough (per the patient)
    2. Fever >37.8°C (100.0°F) or hypothermia <35.6°C (96.0°F).
    3. Changes in WBC (leukocytosis >11,000 cells/mm^3, left shift > 10% band forms/microliter, or leukopenia < 4,000 cells/mm^3
C. Working diagnosis of CAP at the time of hospital admission with antimicrobial therapy given within 24 hours of admission.

METHODS

-Study Groups: Patients were classified in two study groups based on whether macrolide was given before or after the administration of beta-lactam antibiotics. This is shown in figure 1.

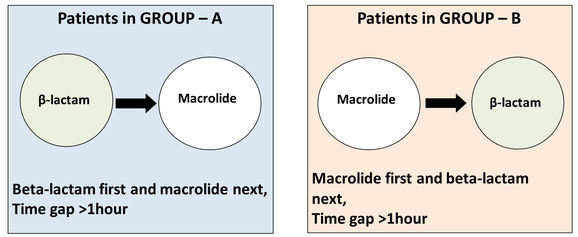

Figure 1. Study Groups

-Study outcomes:
Time to clinical stability (TCS): A patient was defined as clinically stable the day that the following four criteria were met: a) improved cough and shortness of breath, b) lack of fever for at least 8 hours, c) improving leukocytosis (decreased at least 10% from the previous day), and d) tolerating oral intake with adequate gastrointestinal absorption. Patients were evaluated daily within the first 7 days of hospitalization to determine the day when clinical stability was reached.
Length of stay (LOS): defined in days and calculated for each patient as the day of discharge minus the day of admission. Patients hospitalized for more than 14 days were censored at 15 days in an effort to capture LOS data related only to bacterial CAP.
In-hospital mortality: defined as death by any cause during hospitalization.

-Statistical analysis: Baseline categorical explanatory variables were summarized as frequencies and percentages and differences between both groups of patients were analyzed using a chi-square test or Fisher's exact test when appropriate and warranted. Continuous variables were summarized as frequencies and interquartile range and differences between groups were analyzed by Wilcoxon-Mann-Whitney test. TCS and LOS were analyzed with the Kaplan-Meier method, and log-rank tests were applied to evaluate differences between both groups of patients. P-values ≤ 0.05 were considered statistically significant.
To define the adjusted association between macrolide vs. beta-lactam timing on the risk of in-hospital mortality, a log-binomial regression model was used. The model included a restricted cubic spline of the pneumonia severity index for adjustment of disease severity. The predicted risk of in-hospital mortality was then plotted against the time differential in hours between the administrations of the macrolide to the time of the beta-lactam.

RESULTS

- A total of 555 patients were included, 63 with a macrolide first and 492 with a beta-lactam first.
- Patients' characteristics are shown in Table 1.
- Time to Clinical Stability for both study groups is shown in Figure 2.
- Length of Stay for both study groups is shown in Figure 3.
- The adjusted percent in-hospital mortality for both study groups is shown in Figure 4.

Table 1. Patients' characteristics

Variable	Macrolide first	Macrolide second	p-value
Demographics			
Age , Median (IQR)	72 (23)	73 (25)	0.559
Sex, male(%)	50 (79)	296 (60)	0.003
Nursing home resident, n (%)	3 (5)	31 (6)	0.786
Comorbid Conditions			
Congestive Heart Failure, n (%)	16 (25)	90 (18)	0.176
COPD, n (%)	17 (27)	144 (29)	0.77
Diabetes, n (%)	19 (30)	103 (21)	0.107
HIV, n (%)	0 (0)	13 (3)	0.38
Chronic Renal Failure, n (%)	7 (11)	64 (13)	0.841
Liver Disease, n (%)	1 (2)	44 (9)	0.047
Neoplastic Disease, n (%)	9 (14)	64 (13)	0.843
Physical Exam			
Altered mental status on admission, n (%)	8 (13)	70 (14)	0.849
Respiratory Rate, Median (IQR)	22 (10)	22 (8.8)	0.933
Systolic blood pressure, Median (IQR)	126 (32)	130 (30)	0.666
Temperature (degrees Celsius), Median (IQR)	37.2 (1.8)	37.4 (1.8)	0.696
Heart rate, Median (IQR)	95.5 (21)	100 (25.5)	0.403
Lab/Radiography			
pH, Median (IQR)	7.5 (0.1)	7.5 (0.1)	0.775
PaO2, Median (IQR)	66 (25)	59.3 (18.9)	0.038
Blood Urea Nitrogen, Median (IQR)	24 (21)	39 (35)	0.002
Serum sodium, Median (IQR)	136 (6)	137 (6)	0.977
Serum glucose, Median (IQR)	133 (61.5)	119 (45.8)	0.916
Hematocrit, Median (IQR)	40 (6)	38 (8)	0.117
Pleural effusion, n (%)	12 (19)	131 (27)	0.223
Severity of Disease			
ICU admission, n (%)	7 (11)	40 (8)	0.468
Pneumonia Severity Index, Median (IQR)	103 (46)	121 (48)	0.001

RESULTS

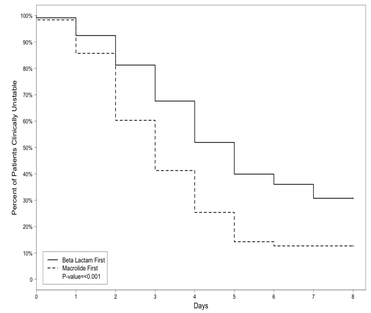

Figure 2. Time to Clinical Stability

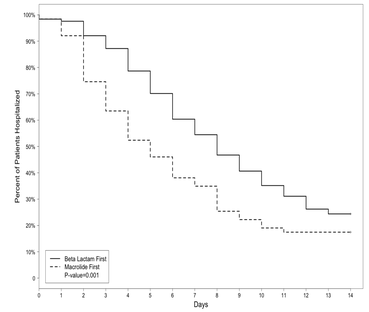

Figure 3. Length of Stay

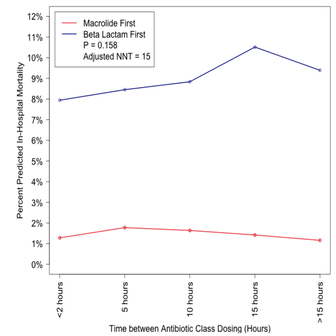

Figure 4. Mortality

CONCLUSIONS

- These data suggest that, although not statistically significant, there is a clinically relevant decrease in in-hospital mortality if a macrolide is given before a beta-lactam.
- The likely explanation for the decreased mortality when macrolides are given prior to beta-lactam antibiotics is due to their anti-inflammatory effects as opposed to their coverage of atypical pathogens. If the decreased mortality associated with macrolide use were to be due to their coverage of atypical pathogens, the use before or after a beta-lactam antibiotic will not influence mortality.
- On the other hand, the increased mortality seen when beta-lactams are given first may be related to the bacteriolysis, release of a large number of antigens and the raised levels of blood cytokines. This will generate an exaggerated inflammatory response that may damage the lung and produce poor outcomes.
- New recommendations may be needed for the empiric treatment of patients with CAP if further studies prove that the initial administration of a macrolide before the beta-lactam decreases mortality. For example, the first antibiotic in the emergency room should be a macrolide with a beta-lactam as a second antibiotic given at least one hour apart.

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