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ORIGINAL RESEARCH

Beta-lactam plus a Macrolide versus a Fluoroquinolone for Empiric Therapy of Hospitalized Patients with Community-Acquired Pneumonia: Result from the University of Louisville Pneumonia Study

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Abstract

Background: Current guidelines recommend a β-lactam plus a macrolide or fluoroquinolone monotherapy as the initial empiric antibiotic therapy for treatment of patients hospitalized with community-acquired pneumonia (CAP). Multiple studies have shown different results comparing the two regimens for the treatment of CAP. Our objective, in a city-wide prospective study, was to compare outcomes among hospitalized patients with CAP who received empiric treatment either with a β-lactam plus a macrolide or fluoroquinolone monotherapy.
Methods: This was a propensity score matched case-control study. It was a prospective population-based cohort study of all hospitalized adults with CAP. Patients were divided into two groups and propensity score matched based on empiric therapy; a β-lactam plus a macrolide compared to fluoroquinolone monotherapy. Study outcomes included time to clinical stability, length of stay, and in-hospital, 30-day and 1-year mortality. Stratified Cox proportional hazards regression was performed to analyze continuous variable differences between groups, and conditional logistic regression was performed to analyze dichotomous variable differences in mortality.
Results: An association was not found between the two groups for time to clinical stability (aHR: 1.06; 95% CI: 0.93-1.22), length of stay (aHR: 1.14; 95% CI: 0.99-1.32) or mortality.
Conclusions: The present study failed to demonstrate differences in short or long-term outcomes for hospitalized CAP patients treated with either a β-lactam plus a macrolide or fluoroquinolone monotherapy. Therefore, our study does not support the superiority of one treatment over another.

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Introduction

Community-acquired pneumonia (CAP) is the leading cause of death among those with an infectious disease [1]. It accounts for hospitalization, high mortality and increased health care cost [2]. Mortality due to CAP ranges from 3% for outpatients up to 50% for patients admitted in the ICU [1].

Of the majority of patients with CAP treated in an outpatient setting, only a small proportion require hospitalization [3]. Following hospitalization, the optimal empiric antimicrobial treatment needs to be selected based on cost-effectiveness, spectrum of activity, local resistance patterns, and possible toxicities. The empiric regimen should have activity against *Streptococcus pneumoniae* and atypical pathogens like *Chlamydia pneumoniae, Legionella pneumophila* and *Mycoplasma pneumoniae* [4].

Choosing an appropriate empiric antibiotic regimen plays a crucial role in determining the clinical success of hospitalized patients with CAP. The 2007 Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) guidelines for CAP recommend either a respiratory fluoroquinolone or a β-lactam plus a macrolide for hospitalized patients [5]. Retrospective studies have documented decreased mortality, length of stay and less re-admission rate when patients are treated with guideline-concordant antimicrobial therapy [6, 7].

Studies leading up to and after the 2007 IDSA/ATS guidelines, have reached varying conclusions regarding superiority of one regimen over another. Some studies favored a β-lactam plus a macrolide over fluoroquinolone monotherapy, whereas other studies favored fluoroquinolone monotherapy [2, 8-12]. While other studies documented similar outcomes in patients receiving either regimen [13-16].

A study is needed that includes guideline-concordant antimicrobial regimens, identification of CAP with clinical, rather than with billing criteria, and includes a "real-world" population. It should also be large and enroll consecutive patients in an entire city over a long period. The present study sought to have these characteristics.

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Objective

This study sought to define whether clinical outcomes were similar or different for hospitalized patients with CAP based on the use of a β-lactam plus a macrolide versus fluoroquinolone monotherapy.

Methods

Study design and study population

This was a propensity score matched case-control study; a prospective population-based cohort study of hospitalized adult residents of a metropolitan city in the midwest region of the United States with CAP from all 9 hospitals in the city [21]. Patients were analyzed from June 1, 2014, to May 31, 2016. Patients meeting inclusion criteria were split into two antibiotic treatment arms: either a β-lactam plus a macrolide or fluoroquinolone monotherapy. Demographic and clinical data were collected for each patient. The source reviewed for laboratory test results were blood, sputum, tracheal aspirate, bronchoalveolar lavage, urine, nasopharynx and oropharynx.

Inclusion Criteria

A diagnosis of CAP required radiographic criteria, clinical criteria and the initiation of antimicrobials within 24 hours of admission. A new pulmonary infiltrate on imaging (computed tomography or chest radiograph) was required at time of admission to the hospital. Each patient had to have at least one of the following signs or symptoms of CAP: new or increased cough, fever >37.8°C (100.0°F) or hypothermia <35.6°C (96.0°F) or a change in serum white blood cells (leukocytosis with >11,000 cells/mm3, left shift with >10% band forms/μL, or leukopenia with <4,000 cells/mm^3). Patients were eligible for inclusion if they had empiric therapies with either 1) a β-lactam plus a macrolide, or 2) fluoroquinolone monotherapy. An organism identified in the laboratory was not a criterion for inclusion.

Propensity score matching

Patient groups were matched using propensity scores with a nearest neighbor algorithm, with a caliper of 0.20 standard deviations to prevent poor matches. Variables included in the creation of the propensity score were age, sex, race, hospital attended, ICU admission, nursing home residency, altered mental status on admission, serum sodium on admission and a history of the following: neoplastic disease, congestive heart failure, stroke, renal disease, diabetes or, chronic obstructive pulmonary disease.

Group 1 included patients who received a β-lactam and a macrolide given as combination therapy during the first 24 hours of hospitalization. Group 2 included patients who received a fluoroquinolone given as monotherapy during the first 24 hours of hospitalization. Macrolides included azithromycin, clarithromycin or erythromycin. β-lactams included amoxicillin, amoxicillin-clavulanate, ampicillin, ampicillin-sulbactam, cefaclor, cefazolin, cefepime, cefixime, cefoperazone, cefotaxime, cefotetan, cefpodoxime, ceftazidime, ceftriaxone, cefuroxime, cephalexin, imipenem-cilastin, meropenem, nafcillin, penicillin G, piperacillin and piperacillin-tazobactam. Fluoroquinolones included ciprofloxacin, levofloxacin and moxifloxacin.

Study Outcomes

Study outcomes included time to clinical stability, length of stay and mortality. Time to clinical stability was defined as the day when the patient met the following four criteria: improvement in cough and shortness of breath, lack of fever for at least 8 hours, improved leukocytosis (normal or decreased at least 10% from the previous day) and toleration of oral intake with adequate gastrointestinal absorption. Patients were prospectively evaluated daily for the first seven days of hospitalization to determine when time to clinical stability was reached. Length of stay was defined in days from admission to discharge. Patients hospitalized for more than 14 days were censored at 14 days in an effort to record length of stay related to CAP. Mortality was defined as death by any cause during hospitalization at 30 days and 1 year.

Statistical Analysis

Descriptive statistics were performed, with comparisons between groups analyzed by using a χ^2 test or Fisher's exact test for categorical data (e.g., male versus female) and the Wilcoxon-Mann-Whitney U test for continuous data (e.g., temperature). Cox proportional hazards regression and the log-rank test were performed to analyze differences between groups with and without accounting for potentially confounding variables, respectively. Logistic regression was performed to analyze differences in mortality. Variables were selected for multivariate analysis if they contained a *P*-value of less than 0.20 in a univariate Cox proportional hazards or logistic regression. A *P*-value of less than 0.05 was considered statistically significant. Differences in outcomes adjusting for propensity score matching were analyzed using stratified Cox proportional hazards regression for time to clinical stability and length of stay. Conditional logistic regression was used for mortality.

Results

Patients receiving a β-lactam plus a macrolide were matched to patients receiving fluoroquinolone monotherapy with 706 in each group (**Figure 1**). The mean age of patients was 67 years. Characteristics of hospitalized patients in each group are in **Table 1**. After propensity score matching, the hematocrit was the only variable significantly differing between groups. The number of organisms that were identified in patients with a positive test for a pathogen is in **Table 2**.

The percentage of patients who reached clinical stability in the first seven days for each group were similar (**Figure 2**). The median time to clinical stability was two days for each group, which was not significantly different; (adjusted hazard ratio (aHR) 1.06; 95% confidence interval (CI) 0.93-1.22). The percentage of patients discharged in the first two weeks for each group were also similar (**Figure 3**). The median length of stay was 4 days in each group, which was not significantly different; (aHR1.14; 95% CI 0.99-1.32).

In-hospital mortality, 30-day mortality and 1-year mortality were also not significantly different in the β-lactam plus macrolide group and the fluoroquinolone group (**Figure 4**). In-hospital mortality was in 15 patients versus 16, respectively; (adjusted Odds Ratio (aOR) 1.64; 95% CI; 0.54-4.91). The 30-day mortality was in 38 patients versus 33 patients, respectively; (aOR 0.97; 95% CI 0.48, 1.94). One-year mortality was in 129 patients versus 126 patients, respectively; (aOR 1.02; 95% CI 0.72-1.44).

Table 1 Demographics and characteristics of the study population for each group

	β-lactam+ Macrolide	Quinolone Alone	P-value
Patients No.	706	706	
Demographics			
Male sex, No. (%)	318 (45.0)	309 (43.8)	0.668
Black race, No. (%)	151 (21.4)	149 (21.1)	0.948
Age, Median years [IQR]	67 [54, 79]	67 [56, 78]	0.745
Comorbidities	**Frequency (%)**		**P-value**
COPD, No. (%)	358 (50.7)	368 (52.1)	0.632
Current smoker, No. (%)	247 (35.0)	247 (35.0)	>0.999
Diabetes mellitus, No. (%)	208 (29.5)	196 (27.8)	0.517
Congestive heart failure, No. (%)	179 (25.4)	200 (28.3)	0.230
Renal disease, No. (%)	154 (21.8)	151 (21.4)	0.897
Neoplastic disease, No. (%)	71 (10.1)	71 (10.1)	>0.999
Stroke, No. (%)	60 (8.5)	71 (10.1)	0.359
HIV disease, No. (%)	15 (2.1)	12 (1.7)	0.698
Physical Exam Findings	**Median [IQR]**		**P-value**
Heart rate, Beats/Minute [IQR]	104 [92, 117]	104 [91, 116]	0.446
Respiratory rate, Breaths/Minute [IQR]	22 [20, 26]	22 [20, 25]	0.231
Systolic blood pressure, mmHg [IQR]	119 [104, 136.8]	121 [104, 139]	0.176
Diastolic blood pressure, mmHg [IQR]	59 [51, 69]	60 [52, 71]	0.224
Temperature °Celsius, [IQR]	37.2 [36.8, 37.8]	37.1 [36.8, 37.7]	0.089
Laboratory Findings	**Median [IQR]**		**P-value**
Hematocrit, median % [IQR]	36.5 [32.4, 40.5]	37.4 [33, 41.1]	0.017
Serum bicarbonate, median mEq/L [IQR]	26 [24, 29]	26 [24, 29]	0.357
Blood urea nitrogen, mg/dL [IQR]	17 [12, 25]	18 [12, 25]	0.428
Serum glucose, mg/dL [IQR]	139 [113, 197]	139 [113, 179]	0.450
Serum sodium, mEq/L [IQR]	137 [134, 139]	137 [134, 140]	0.297
Severity of Disease on Admission	**Frequency (%)**		**P-value**
Need for intensive care, No. (%)	50 (7.1)	53 (7.5)	0.838
Altered mental status, No. (%)	58 (8.2)	72 (10.2)	0.231
Need for vasopressors, No. (%)	1 (0.1)	4 (0.6)	0.370
Need for ventilatory support, No. (%)	51 (7.2)	51 (7.2)	>0.999
PSI risk class IV or V, No. (%)	328 (46.5)	337 (47.7)	0.670

Abbreviations: COPD, Chronic obstructive pulmonary diseases;

HIV, Human immunodeficiency virus infection;

IQR, Interquartile range;

PSI, Pneumonia severity index

Table 2 Micro-organisms identified for patients* in each group.

Organism	β-lactam+ Macrolide	Fluoroquinolone Alone
Typical Pathogens		
Streptococcus pneumoniae	26	16
Pseudomonas aeruginosa	9	3
MRSA	6	5
MSSA	5	4
Staphylococcus – coagulase-negative	6	4
Klebsiella pneumoniae	2	2
Streptococcus pyogenes	2	1
Other Streptococci	5	2
Moraxella catarrhalis	0	3
Atypical Pathogens		
Mycoplasma pneumoniae	2	2
Legionella spp.	1	0
Viruses		
Influenza A 2009 H1N1, A H3, Untyped, B	8	15
Haemophilus influenzae, parainfluenzae	7	8
Human metapneumovirus	7	8
Rhinovirus/Enterovirus	7	16
Parainfluenza virus 1,3,4	6	4
Corona virus HKU1, NL63, OC43	6	3
Respiratory syncytial virus A, Unknown type	3	4
Mycobacteria		
Nontuberculous mycobacteria	0	1
Fungi		
Aspergillus spp.	0	2
Candida tropicalis	0	1
Saprophytic fungus	1	0
Other		
Enterobacter spp.	4	0
Escherichia coli	2	4
Corynebacterium species	1	2
Propionibacterium acne	1	0
Enterococcus faecalis	1	0
Micrococcus luteus	0	1
Acinetobacter spp.	1	0
Achromobacter xylosoxidans	1	0
Serratia spp.	1	0
Citrobacter spp.	0	1

MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-resistant *Staphylococcus aureus*

* Some patients had more than one organism identified.

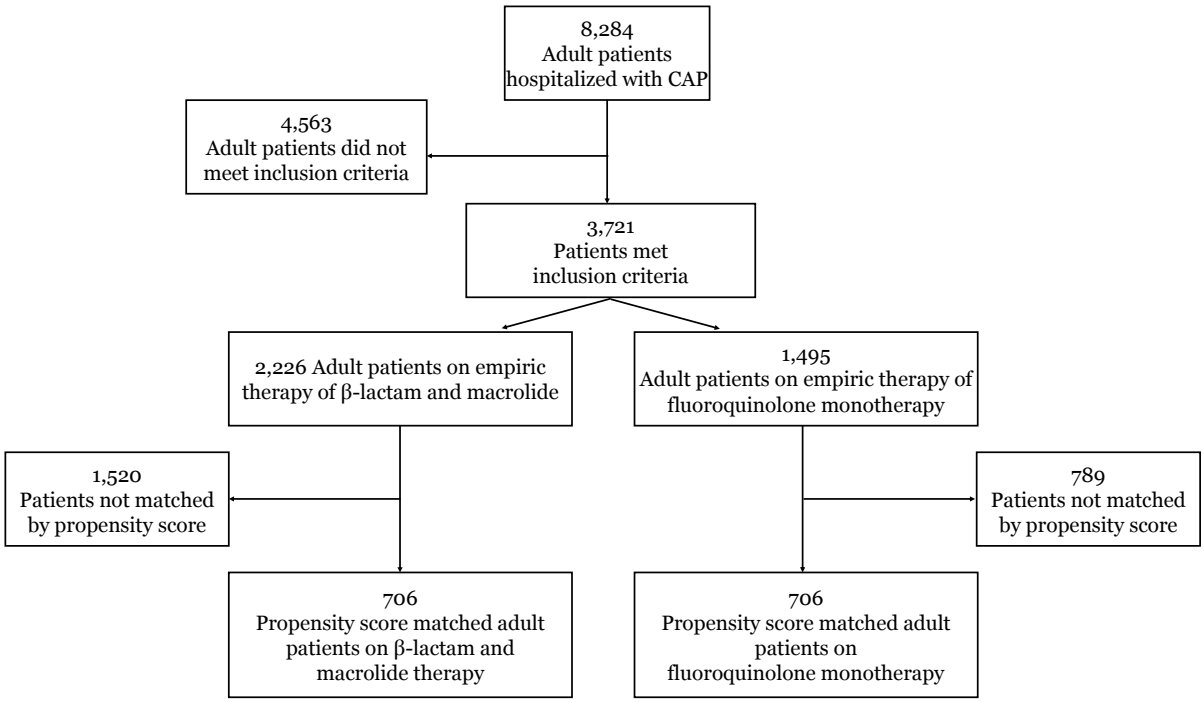

Figure 1 Eligibility and inclusion of study population

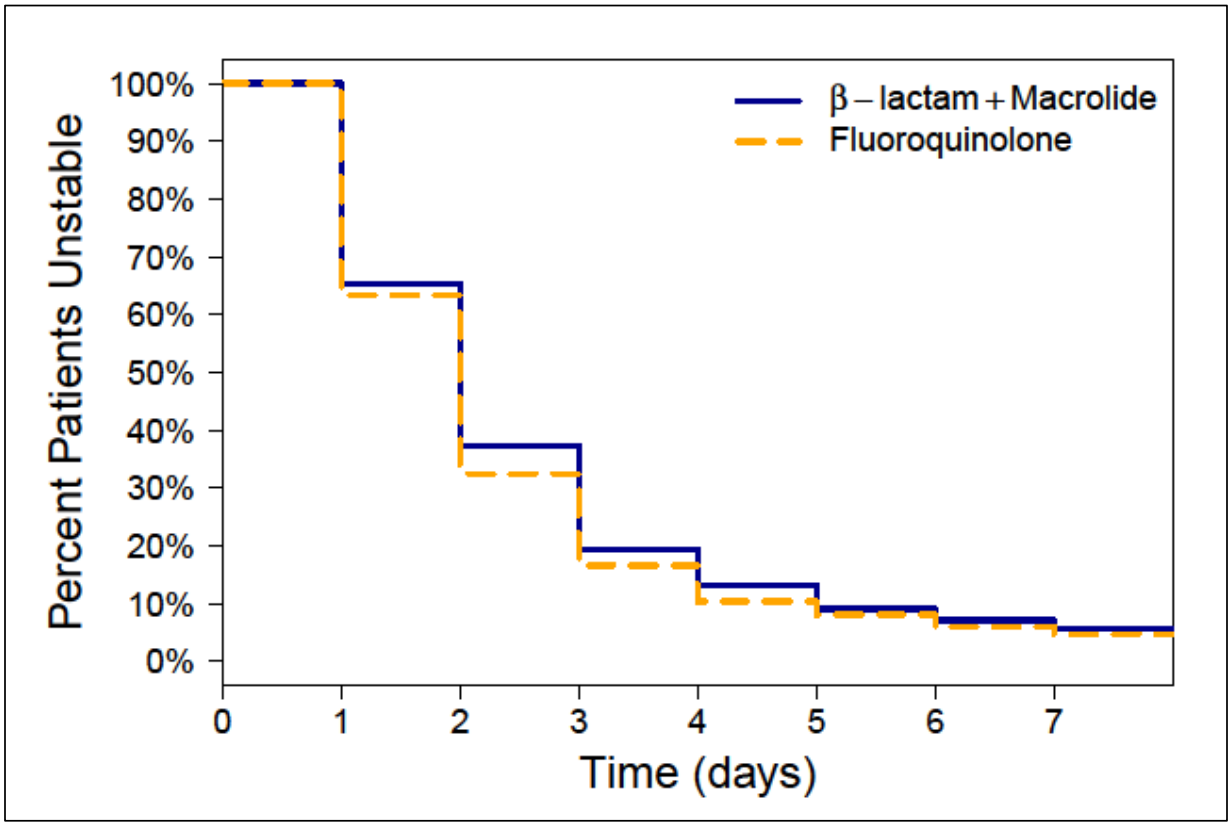

Figure 2 Kaplan – Meier estimates for time to clinical stability for each antibiotic group hospitalized for CAP.

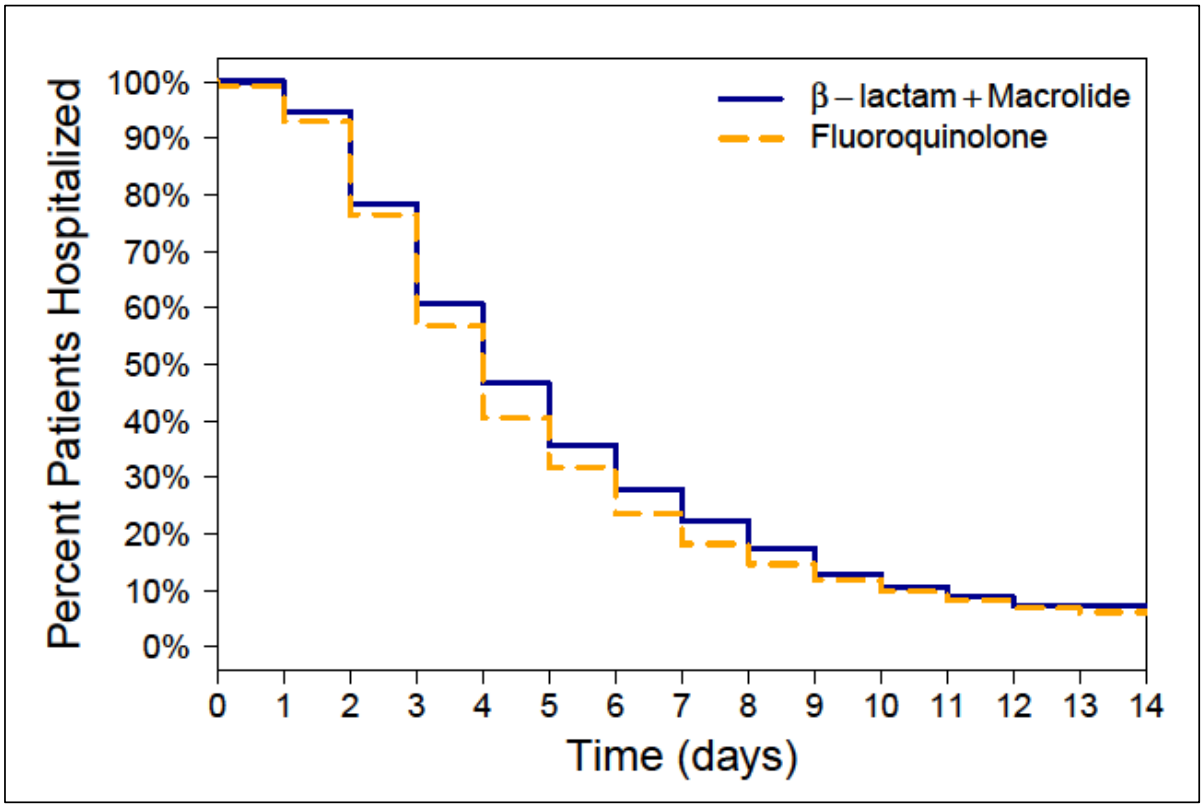

Figure 3 Kaplan – Meier estimates for length of stay for each antibiotic group hospitalized for CAP.

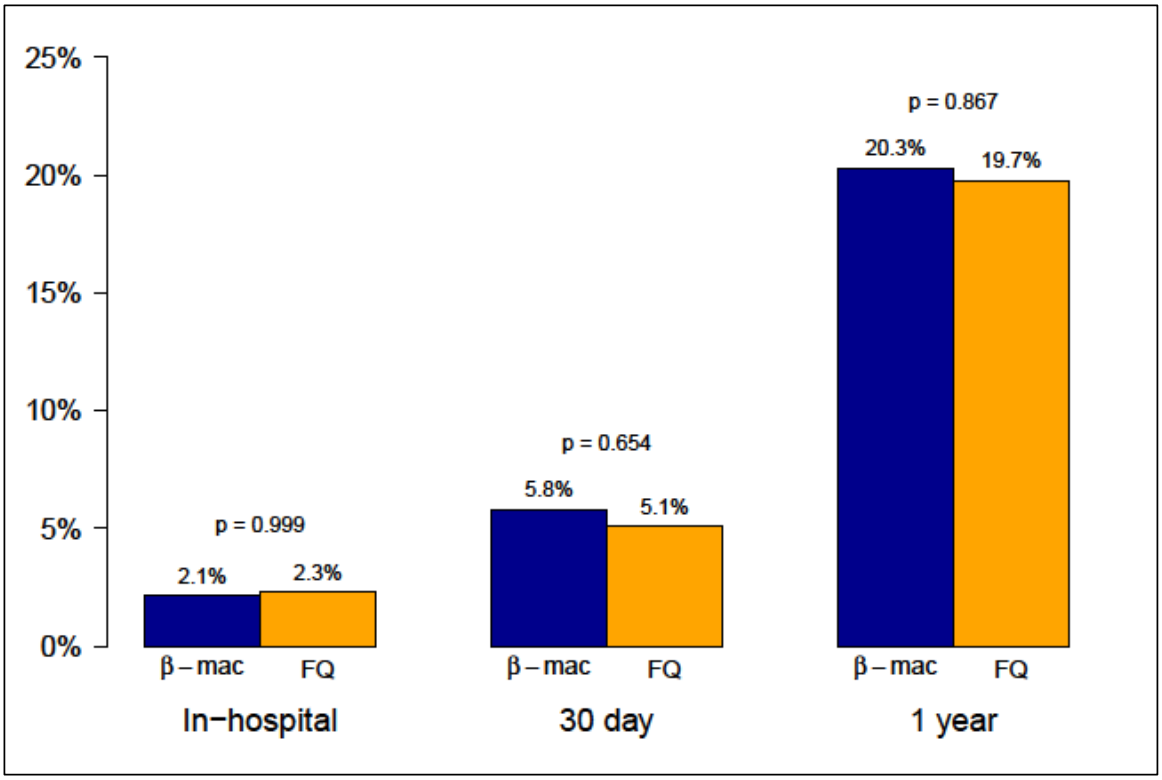

Figure 4 Mortality for each antibiotic group hospitalized for CAP.

Discussion

The present study showed equivalent outcomes in hospitalized patients with CAP who were treated with a β-lactam plus a macrolide compared to fluoroquinolone monotherapy. The findings do not favor one treatment regimen over another.

Multiple studies have been published showing either improved outcomes with one regimen over another or equivalence. The following studies found similar outcomes with either a β-lactam plus a macrolide or a fluoroquinolone alone. Several randomized clinical trials reported equal clinical efficacy among both treatment groups in non-ICU CAP patients [13, 14, 20, 22, 23]. In one of these randomized studies, 236 patients were randomized into one of two treatment groups. The clinical success rate was defined as a resolution of signs and symptoms of CAP, which was 94.1% in the levofloxacin group and 92.3% in the ceftriaxone plus azithromycin group (95% CI, -10.20 to 6.58)[14]. A meta-analysis of patients treated with guideline-concordant antibiotics reported no difference in mortality when patients were treated with a β-lactam plus a macrolide (5.3% patients) compared to a respiratory fluoroquinolone (5.8% patients); (RR 1.17; 95% CI, 91–1.50; P = 0.22) [24]. A retrospective study of a large data set from Medicare and Medicaid services compared mortality data of 27,330 CAP patients. In patients stratified by ICU admission and initial antimicrobial treatment, 30-day mortality among non-ICU patients treated with a cephalosporin plus a macrolide compared to those who received fluoroquinolone monotherapy had similar mortality (RR 0.9; 95% CI 0.78-1.04; P=0.161) [25]. These studies were in concordance with the present study.

In contrast, several studies are discordant to the present study and favor one regimen over another. First, there have been studies favoring fluoroquinolone use. One randomized study documented earlier resolution or improvement in signs and symptoms among patients who received a fluoroquinolone [9]. In another randomized study, 628 CAP patients with varying severity reported statistically significant higher clinical success rates in a moxifloxacin treatment group, bacteriologic success and one day shorter time to resolution of fever and duration of hospitalization [9]. There were also fewer deaths (nine (3%) versus 17 (5%)), and less serious adverse events (38 (12%) versus 53 (16%)) in the moxifloxacin group than in the comparator group. Other studies have shown less serious side effects among patients who received a fluoroquinolone for CAP [9, 12]. Finally, a meta-analysis of 23 randomized trials reported that a fluoroquinolone was more effective in resolving CAP signs and symptoms than treatment with a combination of a β-lactam and a macrolide among CAP patients with mild to moderate severity (OR 1.39; 95% CI 1.02–1.90) [27].

Second, there have also been studies favoring a β-lactam plus a macrolide over fluoroquinolone monotherapy. A retrospective study of 515 hospitalized patients with CAP documented significantly lower mortality at 14 days and 30 days among patients with a pneumonia severity index (PSI) risk class V treated with a β-lactam plus a macrolide as compared to fluoroquinolone monotherapy [2]. In an observational study of 270 CAP patients hospitalized in the ICU with shock, a cephalosporin plus a macrolide was associated with significantly higher 28-day survival compared to fluoroquinolone monotherapy (aHR, 1.69; 95% CI, 1.09-2.60; *P* = .01) [28].

A variety of factors may explain the superiority of one therapy over another. Some of these factors are not necessarily related to antimicrobial activity. Three reasons other than antimicrobial activity that may encourage or preclude one from prescribing an antimicrobial other than the outcomes we measured include oral bioavailability and the implication of earlier discharge [8], the risk for isolating a multidrug-resistant organism [29-31], and a drug's immunomodulatory properties [32-33]. Immunomodulation may benefit patients with CAP by suppressing pro-inflammatory cytokines, interfering attachment of pathogens to respiratory epithelial cells and by favoring apoptosis over necrosis in the presence of neutrophils [32].

One of the strengths of the present study is that it was a population-based study with a large sample size including multiple patient populations with CAP. The definition for CAP in this study was based on clinical criteria rather than billing information. Compared to similar studies, the present study stands out because it analyzed comprehensive outcomes for early- and late-term outcomes. Time to clinical stability, length of stay and three periods of mortality were evaluated. The present study also has limitations: only penicillin sensitivity information for *S. pneumoniae* and vancomycin sensitivity information for *Staphylococcus aureus* was collected. No specific antibiotic resistance data for other isolated pathogens were included in this study. During the enrollment period, a few patients were not enrolled due to refusal by the patient, the family or the admitting physician.

In conclusion, the present study did not show a significant difference in time to clinical stability, length of stay or mortality when comparing a β-lactam plus a macrolide to fluoroquinolone monotherapy. Hence, our study supports the recommended IDSA/ATS guidelines for the treatment of patients with CAP recommending either regimen for hospitalized patients: either a β-lactam plus a macrolide or fluoroquinolone monotherapy.

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Conflict of Interest: All authors declared no conflict of interest in relation to the main objective of this work.

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