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Comparison of Mortality and Therapy in Community Acquired Pneumonia

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Abstract

Background: Community associated pneumonia (CAP) is one the most common causes of hospital admissions, exceeding more than one million per year in the United States, contributing to 3.4% of inpatient mortality. Our objective was to compare 30-day mortality using therapies recommended for treatment of CAP.

Methods: A multicenter retrospective analysis from four different hospitals was assessed from 2008 to 2013. The data was obtained from electronic medical records which included more than 70,000 patients. CAP patients were identified using discharge diagnostic codes during the years 2008-2013, as well as receiving therapy with ceftriaxone and azithromycin or a respiratory fluoroquinolone. Demographic data, antibiotic therapy, and Charlson comorbidity score was obtained to compare the study groups.

Results: A total of 21,800 patients met the inclusion criteria for CAP. 1,740 patients were excluded as they received both beta-lactams and fluoroquinolones. The study included 20,600 patients. 11,201 patients (55.84%) received ceftriaxone with azithromycin, and 8,859 (44.16%) received fluoroquinolone therapy. The mortality rate for patients who received fluoroquinolone therapy was lower compared to the patients who received ceftriaxone plus azithromycin (3.56% vs 6.71%, p-value <0.001).

Conclusions: Our study showed statistically significant lower 30-day mortality using fluoroquinolone therapy compared to ceftriaxone plus azithromycin for treatment of CAP. Prospective blinded randomized control trials would be needed to support this evidence.

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Introduction

Pneumonia is one the most common causes of hospital admissions exceeding more than one-million cases per year, contributing to 3.4% of inpatient mortality [1,2]. There are several studies conducted to compare different antibiotics for the treatment of community acquired pneumonia, however there are limited data from large trials comparing ceftriaxone plus azithromycin to fluoroquinolone therapy for inpatient treatment of CAP. The current IDSA guidelines published in 2007 recommend treatment of CAP in non-ICU patient with fluoroquinolone alone or beta-lactam plus macrolide [3]. Arnold and colleagues [4] compared treatment of pneumonia with current guidelines to non-adherence to guidelines. The study concluded that adhering to the guidelines decreased the mortality rate, length of hospital stay, and time to clinical stability. Wang and colleagues compared fluoroquinolone based therapy to penicillin based therapy in the treatment of community acquired pneumonia in an outpatient setting [5]. The study concluded that the treatment failure rates were less in fluoroquinolone based therapy compared to penicillin based therapy, and no difference in hospitalizations, emergency visits or 30-day mortality. A recent cluster-randomized, crossover trial concluded that beta-lactam monotherapy was non-inferior to the beta-lactam plus macrolide or fluoroquinolone monotherapy [6] .

Better knowledge of optimal treatment is critical to improve outcomes. Our study is unique in comparing 30-day all-cause mortality benefit using ceftriaxone plus azithromycin to fluoroquinolones in a large multicenter cohort for treatment of CAP.

Methods

We conducted a retrospective review from January 2008 to December 2012 including inpatients 18 years of age or older who were hospitalized with the diagnosis of community acquired pneumonia based on ICD-9 discharge diagnosis. Participating centers included four large health care institutions located in Maryland, Michigan, Missouri, and Texas. Information about patients' sex, age, race, discharge diagnosis, cultured organism,

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hospital length of stay, readmission status, and mortality within 30 days was collected from each of the four hospitals' electronic medical records (EMR). Information was obtained from each participating centers' EMR which was then entered into a single database. This database included approximately 70,000 patients. Data was de-identified and coded using explicit data specifications and uploaded into one large database. The study protocol was approved by the institutional review board (IRB) at each participating institution. Teleconferences, enrollments reports, and data audits were conducted between the four study sites to ensure uniform data collection.

All hospitalized patients in these hospitals between January 1, 2008 and December 30, 2012 with a discharge diagnosis of pneumonia were identified. Patients were included in the present study if: 1) They were aged ≥18 years; 2) They had received either ceftriaxone plus azithromycin, levofloxacin, or moxifloxacin for the duration of the hospitalization with no other antibiotics administered. Exclusion criteria included: 1) Patients who received other antimicrobial agents; 2) Patients with diagnosis of pneumonia with no information on therapy; 3) Patients who received both therapies. The primary outcome of the study was 30-day all-cause mortality. In hospital mortality was used as a marker for 30-day mortality, as our database was unable to assess 30-day mortality. The patients' severity of comorbidities was assessed using Charlson comorbidity index.

Statistical Methods

Univariate statistical analysis was used to test the association of demographic and clinical characteristics with all-cause discharge mortality. Categorical variables were analyzed using the Chi-squared test or Fisher's exact test. Continuous variables were analyzed using an unpaired t-test. All variables with a p-value < 0.05 in the univariate analysis were included into the multivariate logistic regression. The stepwise selection method was performed to generate the final model (P≤0.05 required for variable entry, P≤0.10 required for variable removal). All p-values were two-sided. Analyses were performed by using SAS 9.4.

Results

A total of 21,800 patients met our inclusion criteria for CAP, however 1,740 patients were excluded as they received both beta-lactams and fluoroquinolones. The study included 20,600 patients. 11,201 patients (55.84%) received ceftriaxone with azithromycin, and 8,859 (44.16%) received fluoroquinolone therapy. Demographic and clinical characteristics of patients are shown in **Table 1**. The mortality rate for patients who received fluoroquinolone therapy was lower compared to the patients who received ceftriaxone plus azithromycin (3.56% vs 6.71%, p-value <0.001).

Discussion

Our study demonstrated that the use of fluoroquinolone therapy for treatment of CAP decreased 30-day all-cause mortality compared to ceftriaxone plus azithromycin. Despite high comorbidity index in the cohort treated with fluoroquinolones, those treated with fluoroquinolones had better outcomes than those treated with ceftriaxone plus azithromycin. Our study is unique in several ways. First, the large sample size of this study strengthens the analysis as well as significantly different variables. Second, there have been limited studies conducted to compare ceftriaxone plus azithromycin to fluoroquinolone therapy with respect to mortality. The present study only included patients treated with these agents. Third, the data is collected from four different hospitals which are located in various locations throughout United States. Despite various geographic locations of the hospitals with different antibiograms, fluoroquinolones had mortality benefit over ceftriaxone plus azithromycin. Our study results are dis-concordant with the meta-analysis of randomized controlled trials by Vardakas et al [7]. Their interpretation did reveal that fluoroquinolone therapy has a higher success rate in treatment of pneumonia compared to beta-lactam therapy with and without macrolides, however the data showed that there was no mortality benefit with fluoroquinolones. One of the possibilities several studies favor fluoroquinolone therapy is that there is different spectrum of coverage of fluoroquinolones including MSSA, gram-negative coverage including anti-pseudomonal activity for some agents such as levofloxacin, as well as atypical coverage [8]. Another factor may be the emergence of Streptococcus pneumonia which are resistant to macrolides. Multiple studies favor monotherapy with a fluoroquinolone over combination therapy. Querol-Ribelles et al. in a prospective observational cohort study showed improved mortality in patients treated with levofloxacin compared to those treated with combination therapy of ceftriaxone plus clarithromycin [9]. Another meta-analysis of randomized controlled trials by Raz-Pasteur et al. did not reveal a mortality benefit between monotherapy and combination therapy with a beta-lactam; however, the study was significant for decreased failure rates of therapy and treatment discontinuation in those receiving monotherapy with a fluoroquinolone [10]. Limitations of the present study include that it was a retrospective observational study with information gathered using only electronic medical records. The immune status of patients were unable to be obtained. Pneumonia severity index and CURB-65 scores, which are markers of disease severity, were unable to be obtained. Without calculating these scores, we cannot rule out the possibility of confounding by indication of the use of therapy based on disease severity. Many patients with CAP have no organism identified further limiting comparison of outcomes between the groups. Another limitation is that it is possible that activity against organisms isolated were different in one group versus another, which was not evaluated in this study. Finally, mortality during hospitalization was obtained, we did not have information on 30-day mortality, thus in hospital mortality was used as a marker for 30-day mortality.

Conclusions

Our study showed statistically significant lower 30-day mortality using fluoroquinolone therapy compared to ceftriaxone plus azithromycin for treatment of community acquired pneumonia. Further randomized controlled trials would be needed to support this evidence.

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

Table 1 Demographics and clinical characteristics and outcomes of patients admitted to the hospital with CAP

Patient characteristics	Fluoroquinolone therapy n (%)	Ceftriaxone plus azithromycin n (%)	p-value
Total patients	8859 (44.16)	11201(55.84)	
Age			
Mean Age	64.2764 ± 17.1823	59.5046 ± 18.3095	<0.001
>65 years	4266 (48.15)	6660 (59.46)	<0.001
<65 years	4593 (51.85)	4541 (40.84)	<0.001
Gender			
Male	4172 (47.09)	5469 (48.83)	0.0147
Female	4687 (52.91)	5732 (51.17)	
Race			
White	5369 (60.61)	5263 (46.99)	
Black	2476 (27.95)	4615 (41.20)	
Hispanic	738 (8.33)	655 (5.85)	
Asian	137 (1.55)	141 (1.26)	
Other	97 (1.09)	161 (1.44)	
Unknown	42 (0.47)	366 (3.27)	
Comorbidities			
HIV	264 (2.98)	857 (7.65)	<0.0001
DM	3104 (35.04)	3542 (31.62)	<0.0001
Transplant	315 (3.56)	450 (4.02)	0.0899
Asthma	1443 (16.29)	1974 (17.62)	0.0125
COPD	2701 (30.49)	2868 (25.60)	<0.0001
Sickle Cell	95 (1.07)	140 (1.25)	0.2459
CAD	2885 (32.57)	3056 (27.28)	<0.0001
Asplenia	1061 (11.98)	982 (8.77)	<0.0001
CKD	1076 (12.15)	1239 (11.06)	0.017
Heart Failure	2693 (30.40)	3052 (27.25)	<0.0001
Cancer	1633 (18.43)	1785 (15.94)	<0.0001
Hypertension	6514 (73.53)	7518 (67.12)	<0.0001
Charlson score	4.0227 ± 2.2527	3.5011 ± 2.2537	<0.0001
Mortality	315 (3.56%)	752 (6.71%)	<0.0001

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