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ORIGINAL RESEARCH

Comparative Antibiotic Failure Rates in the Treatment of Community-Acquired Pneumonia: Results from a Claims Analysis

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ABSTRACT

Introduction: Antibiotic treatment failure contributes to the economic and humanistic burdens of community-acquired pneumonia (CAP) by increasing morbidity, mortality, and healthcare costs. This study compared treatment failure rates of levofloxacin with those of other antibiotics in a large US sample. ***Methods:*** Medical and pharmacy claims in the nationally representative SDI database were used to identify adults with a new outpatient diagnosis of CAP receiving a study antibiotic (levofloxacin, amoxicillin/clavulanate, azithromycin, moxifloxacin) between September 1, 2005 and March 31, 2008. Treatment failure was defined as ≥1 of the following events ≤30 days after index date: a refill for the index antibiotic after completed days of therapy, a different antibiotic dispensed >1 day after the index prescription, or hospitalization with a pneumonia diagnosis or emergency department visit >3 days postindex. Cohorts were propensity score matched for demographic and clinical characteristics. Treatment failure rates were compared between pairs of cohorts for the full sample and for high-risk patients (age ≥65 and/or on Medicaid). ***Results:*** Among the 3994 study patients, the numbers of dispensed index prescriptions were 268 for amoxicillin/clavulanate, 1609 for azithromycin, 1460 for levofloxacin, and 657 for moxifloxacin. Unadjusted treatment failure rates for the sample were 20.8% for levofloxacin, 23.9% for amoxicillin/clavulanate, 23.9% for azithromycin, and 19.9% for moxifloxacin. For high-risk patients, unadjusted treatment failure rates were 19.1% for levofloxacin, 26.1% for amoxicillin/clavulanate, 26.3% for azithromycin, and 24.3% for moxifloxacin. Propensity score-matched treatment failure rates were significantly lower with levofloxacin than azithromycin (19.8% vs. 24.5%, odds ratio [OR] comparator vs. levofloxacin 1.38; 95% CI: 1.14, 1.67), a difference amplified in high-risk patients (19.0% vs. 26.4%, OR 1.61; 95% CI: 1.22, 2.13).

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No significant differences were observed for other paired comparisons. ***Conclusion:*** In a large US sample, treatment failure in CAP appeared to be less likely with quinolones (such as levofloxacin) than azithromycin, an effect particularly marked in high-risk patients (age ≥65 and/or on Medicaid).

Keywords: amoxicillin/clavulanate; antibiotic; antimicrobial therapy; azithromycin; community-acquired pneumonia; fluoroquinolone; levofloxacin; macrolide; penicillin

INTRODUCTION

Community-acquired pneumonia (CAP) is a major cause of morbidity, mortality, and healthcare resource expenditure.[1] In the US in 2006, the most recent year for which data are available, pneumonia and influenza were the eighth leading causes of death.[2] Pneumonia accounted for 4.2 million ambulatory care visits, including 1.5 million emergency department visits,[3] and was among the six most common reasons for hospitalization with an average length of stay of 5.1 days.[4] The burden of CAP is particularly significant in the elderly,[5] among whom it is the sixth leading cause of death in the US.[6]

CAP is most often caused by bacterial pathogens including *Streptococcus pneumoniae*, atypical organisms (*Mycoplasma pneumoniae, Chlamydia pneumoniae, Legionella* spp.), *Hemophilus influenzae*, and gram-negative rods;[7] antibiotics are standard treatment for CAP.[5] While the efficacy of antimicrobial therapy in CAP is established, authors of a 2009 Cochrane review concluded that data from well-designed clinical studies are insufficient to make evidence-based recommendations for choosing among antibiotics for the treatment of CAP.[5] The need for a stronger evidential foundation for making treatment decisions has contributed to inconsistencies among CAP treatment recommendations and guidelines and provoked calls for research directed at specific topics to inform clinical practice.[1]

Among the gaps in the evidence base regarding antibiotics for CAP is information on comparative rates of treatment failure, defined as a clinical condition with inadequate response to antimicrobial therapy.[8] Treatment failure, which results in persistence or progression of infection, contributes significantly to the economic and humanistic burdens of CAP by increasing risk of morbidity and mortality as well as healthcare costs.[9-11] In a 2005-2006 study conducted in a US regional managed care organization, the mean direct medical costs per case of CAP management were $493 for successful treatment and $3019 for treatment failure, which was operationalized as a second antibiotic course, follow-up emergency room presentation, or hospitalization for CAP within 28 days of the index visit.[12] The incidence of treatment failure in patients with CAP is not definitively established, but estimates range from approximately one in ten[10,13,14] to one in five patients.[15] Risk factors for treatment failure include older age (>65 years), high-risk pneumonia, liver disease, leukopenia, and discordant antimicrobial therapy.[8,10,11] Data from a prospective study in 1424 patients hospitalized with CAP suggest that initial treatment with fluoroquinolones and influenza vaccination may confer protection against treatment failure.[10]

The study reported herein was conducted to expand the evidence base regarding comparative rates of treatment failure with antibiotics commonly used to treat CAP. Rates of treatment failure with levofloxacin (reference fluoroquinolone) were compared with those of the fluoroquinolone moxifloxacin, the macrolide azithromycin, and the penicillin amoxicillin/clavulanate, based on analysis of claims from large, nationally representative US medical and pharmacy databases.

MATERIALS AND METHODS

Data Source

Data for this retrospective, observational, cohort study were extracted from SDI's Health Insurance Portability and Accountability Act (HIPAA)-compliant, nationally representative US databases of deidentified, longitudinal, patient-level medical and pharmacy claims. The pharmacy claims database, established in 2001, includes claims (National Council for Prescription Drug Programs [NCPDP] version 5.2) for more than 1.8 billion prescriptions dispensed annually. The medical claims database, established in 1999, includes more than 600,000 annual claims (CMS-1500 forms) containing diagnosis and visit information and represents activity of more than 450,000 physicians per month. This study was exempt from institutional review board approval as it was retrospective, did not involve an intervention, and utilized anonymized data.

Sample

The study included patients ≥18 years old given a primary or secondary diagnosis of pneumonia (based on CMS-1500 medical claims) (Table 1) in an office outpatient setting between September 1, 2005 and March 31, 2008. Eligible patients received a study antibiotic (levofloxacin, amoxicillin/clavulanate, azithromycin, moxifloxacin) in a dosing regimen consistent with the product label (levofloxacin tablets 250, 500, or 750 mg/day; amoxicillin/clavulanate tablets 750 to 4000 mg/day; azithromycin 250 mg or 500 mg/day for tablets, 2 mg for oral solution; moxifloxacin tablets 400 mg/day) within 3 days of diagnosis, and had a ≥6-month preperiod and a ≥30-day postperiod of stable practitioner observation in the SDI medical dataset and pharmacy observation in the SDI

Table 1. *International Classification of Diseases, 9th Revision (ICD-9)* codes considered to reflect a diagnosis of pneumonia.

Code	Description
115.05	*Histoplasma capsulatum* pneumonia
115.15	*Histoplasma duboisii* pneumonia
115.95	Unspecif ed *Histoplasmosis* pneumonia
480.0	Pneumonia due to adenovirus
480.1	Pneumonia due to respiratory syncytial virus
480.2	Pneumonia due to *parainfluenza* virus
480.3	Pneumonia due to SARS-associated coronavirus
480.8	Pneumonia due to other virus not elsewhere classif ed
480.9	Unspecif ed viral pneumonia
481.0	*Pneumococcal pneumonia (S. pneumoniae* pneumonia)
482.0	Pneumonia due to *Klebsiella pneumoniae*
482.1	Pneumonia due to *Pseudomonas*
482.2	Pneumonia due to *Hemophilus influenzae*
482.30	Pneumonia due to unspecif ed *Streptococcus*
482.31	Pneumonia due to *Streptococcus*, group A
482.32	Pneumonia due to *Streptococcus*, group B
482.39	Pneumonia due to other *Streptococcus*
482.40	Pneumonia due to *Staphylococcus*, unspecif ed
482.41	Methicillin-susceptible pneumonia due to *Staphylococcus aureus*
482.42	Methicillin-resistant pneumonia due to *Staphylococcus aureus*
482.49	Other *Staphylococcus* pneumonia
482.81	Pneumonia due to anaerobes
482.82	Pneumonia due to *Escherichia coli*
482.83	Pneumonia due to other gram-negative bacteria
482.84	Legionnaires' disease
482.89	Pneumonia due to other specif ed bacteria
482.9	Unspecif ed bacterial pneumonia
483.0	Pneumonia due to *Mycoplasma pneumoniae*
483.1	Pneumonia due to *Chlamydia*
483.8	Pneumonia due to other specif ed organism
484.1	Pneumonia in cytomegalic inclusion disease
484.3	Pneumonia in whooping cough
484.5	Pneumonia in anthrax
484.6	Pneumonia in aspergillosis
484.7	Pneumonia in other systemic mycoses
484.8	Pneumonia in other infectious diseases classif ed elsewhere
485.0	Bronchopneumonia, organism unspecif ed
486.0	Pneumonia, organism unspecif ed
487.0	Influenza with pneumonia
507.0	Pneumonitis due to inhalation of food or vomitus
507.1	Pneumonitis due to inhalation of oils and essences
507.8	Pneumonitis due to other solids and liquids
517.1	Rheumatic pneumonia

SARS=severe acute respiratory syndrome.

pharmacy claims dataset. Exclusion criteria included being diagnosed with CAP or dispensed an antibiotic prescription for CAP within 30 days before the index date, being dispensed ≥1 antibiotic on the same incident prescription date, having risk factors for healthcare-associated pneumonia (ie, medical or hospital claim for hospitalization ≥2 days, nursing home or long-term care facility stay, hemodialysis clinic visit, wound care procedure within 90 days before the index date), or any of the following conditions from 6 months preindex to 30 days postindex: malignancy, pregnancy, respiratory tuberculosis, cystic fibrosis, immunodeficiency.

Endpoints and Data Analyses

The primary outcome of interest was the treatment failure rate. Treatment failure was defined, in a manner consistent with the medical literature,[6,10-12,15] as ≥1 of the following events ≤30 days after the index date: a refill of the index antibiotic dispensed after the completed days of therapy, a different antibiotic dispensed >1 day after the index antibiotic prescription, or hospitalization for pneumonia or emergency department visit for any diagnosis >3 days after the index diagnosis.

Three methods were used to compare the treatment failure rate of levofloxacin with the failure rate for each of the other study antibiotics. The first method compared unadjusted treatment failure rates using the chi-square test. The second method, propensity score matching, was applied to test the robustness of the results of the unadjusted analyses described above. Propensity score matching reduces the likelihood of intercohort imbalance among pretreatment characteristics in an observational study by matching patients by their likelihood (ie, propensity score) of receiving a particular treatment based on observable pretreatment characteristics. To select matched samples for the three pairwise comparisons of levofloxacin with a comparator antibiotic, three logistic regression models were estimated to compute the probabilities of receiving: 1) levofloxacin versus amoxicillin/clavulanate; 2) levofloxacin versus azithromycin; and 3) levofloxacin versus moxifloxacin. The independent variables in the models were age, gender, payer type, physician specialty, census region, preindex influenza, preindex upper respiratory tract infections, preindex outpatient visits, and comorbidities. For each patient, comorbidities were obtained and Charlson Comorbidity Index (CCI) was calculated using the diagnosis codes on all medical claims (both office and hospital data) during the 6 months prior to the index date. Comorbidities were clinically grouped into respiratory, cardiovascular, and other comorbidities (diabetes, liver, and renal disease). Propensity scores (predicted probabilities) were estimated from each of the three logistic regression models, and levofloxacin patients were then matched 1:1 by propensity score to patients with the comparator antibiotic using nearest-neighbor matching within a predefined caliper. Treatment failure rates were compared using Bowker's test for paired observations. The third method compared treatment failure rates in the propensity score-matched treatment cohorts using logistic regression analyses. Odds ratios (OR) for the likelihood of treatment failure with each comparator antibiotic versus levofloxacin and 95% CIs were calculated.

The analyses described above, which were done in the full patient sample, were also conducted for a subset of patients considered to be at high risk for treatment failure. The high-risk subset was defined as being ≥65 years old and/or on Medicaid.[16]

In both the sample as a whole and the high-risk subset, levofloxacin was compared with

each of the other antibiotics for demographics and baseline clinical characteristics in both the unadjusted dataset and propensity score-matched samples. For the unadjusted data, paired *t*-tests were used to test for statistically significant differences between cohorts for continuous variables, and the chi-square test was used for categorical variables. In the propensity score-matched samples, paired *t*-tests were used to test for statistically significant differences between cohorts for continuous variables, and Bowker's test was used for categorical variables.

RESULTS

Sample Characteristics

Of 1,634,383 patients ≥18 years old given a primary or secondary diagnosis of pneumonia in an outpatient setting between September 1, 2005 and March 31, 2008 in the database, 3994 patients met the inclusion and exclusion criteria and comprised the study sample (Figure 1). Of the 3994 patients in the sample, 1460 were initially prescribed levofloxacin, 268 amoxicillin/clavulanate, 1609 azithromycin, and 657 moxifloxacin. The number of patients propensity score matched to levofloxacin-treated patients was 266 with amoxicillin/clavulanate, 1295 with azithromycin, and 655 with moxifloxacin. The proportion of azithromycin patients propensity score matched to levofloxacin patients was lower than the proportions of amoxicillin/clavulanate- and moxifloxacin-prescribed patients because of the more marked differences in baseline characteristics between the azithromycin and levofloxacin patient cohorts compared with other cohort pairs.

The number of patients in the high-risk subset was 1869, of whom 765 were initially prescribed levofloxacin, 111 amoxicillin/clavulanate, 668 azithromycin, and 325 moxifloxacin. In the high-risk subset, the number of patients propensity score matched to levofloxacin-treated patients was 107 with amoxicillin/clavulanate, 617 with azithromycin, and 321 with moxifloxacin.

Demographics and baseline clinical characteristics (unadjusted data) of the full sample and the high-risk subset are shown in Table 2. Before propensity score matching, the

Figure 1. Patient disposition.

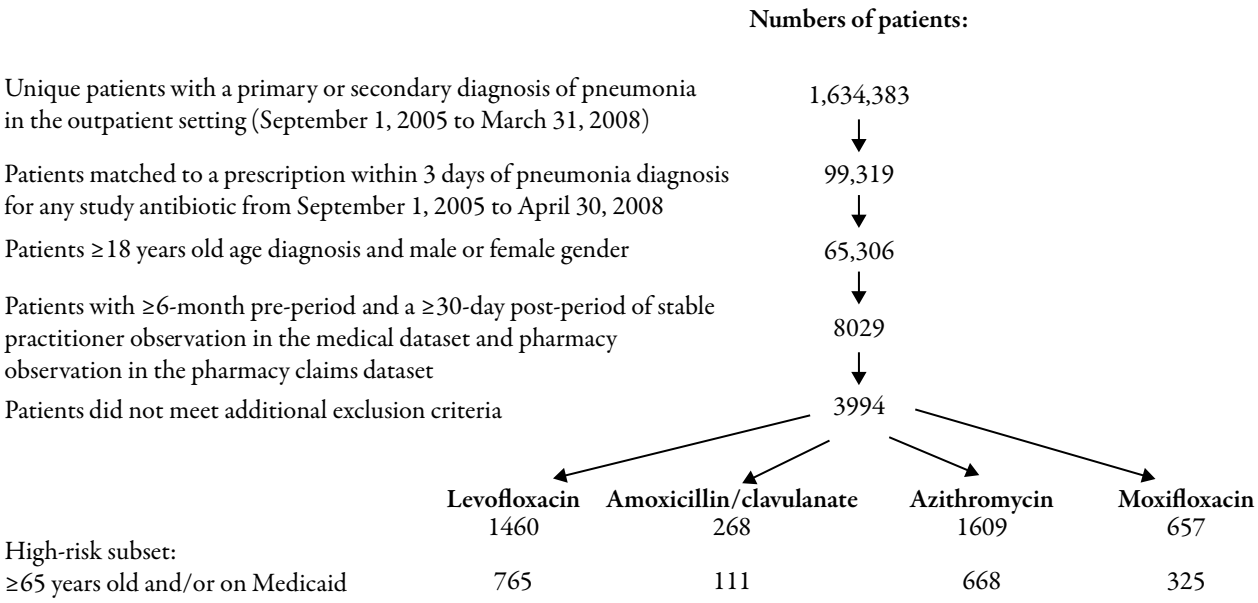


Table 2. Demographics and baseline clinical characteristics (unadjusted data).

	Levofloxacin		Amoxicillin/clavulanate		Azithromycin		Moxifloxacin	
	Full sample	High-risk subset	Full sample	High-risk subset	Full sample	High-risk subset	Full sample	High-risk subset
n	1460	765	268	111	1609	668	657	325
Mean age, years (SD)	63.8 (15.4)	75.7 (7.6)	59.1 (16.2)*	73.0 (9.4)*	58.2 (17.9)*†	74.1 (11.3)*	62.4 (15.5)	74.9 (8.3)
Female, %	55.2	53.9	53.4	63.1	61.0*	59.9*	57.1	59.1
Health insurance by payer, %			*	*	*	*		
Commercial	50.9	19.1	57.8	18.9	64.8	27.5	56.5	24.0
Medicare	45.0	76.9	35.8	70.3	30.1	65.0	40.6	73.2
Medicaid	1.2	2.2	3.7	9.0	2.5	6.0	1.1	2.2
All others	2.9	1.8	2.6	1.8	2.5	1.5	1.8	0.6
Census region, %			*	*	*†	*	*	*
Northeast	15.6	14.8	19.4	18.9	18.1	19.3	32.0	31.7
Midwest	23.2	22.4	29.1	30.6	20.3	17.5	15.1	15.4
South	28.3	29.4	17.9	18.9	16.4	19.5	28.3	28.9
West	32.9	33.5	33.6	31.5	45.2	43.7	24.7	24.0
Patients with influenza diagnosis ≤30 days before index date, %	0.8	0.4	1.1	0.0	0.5	0.1	0.3	0.6
Patients with upper respiratory infection ≤30 days before index date, %	6.8	4.8	12.3*	9.9*	0.8	6.9	8.8	7.7
Mean (SD) outpatient visits ≤6 months before index date	5.0 (4.4)	5.4 (4.3)	5.8 (4.8)*	6.8 (4.9)*	4.7 (4.3)	5.5 (4.9)*	5.3 (4.9)	5.9 (4.9)
Mean (SD) Charlson Comorbidity Score ≤6 months before index date	0.8 (1.2)	1.1 (1.5)	0.9 (1.2)	1.2 (1.3)	0.6 (1.0)*†	0.9 (1.1)*†	0.8 (1.1)	1.0 (1.1)
Patients with respiratory comorbidities‡ ≤6 months before index date, %	46.0	45.0	53.7	54.1	40.0	40.3	48.4	46.8
Patients with cardiovascular comorbidities§ ≤6 months before index date, %	45.2	58.0	43.7	60.4	35.5	55.2	42.8	57.5

*$P<0.05$ vs. levofloxacin, unadjusted data.

†$P<0.05$ vs. levofloxacin after propensity score matching.

‡Respiratory comorbidities: acute respiratory infections, chronic sinusitis, chronic obstructive pulmonary disease, asthma, other respiratory diseases.

§Cardiovascular comorbidities: hypertension, congestive heart failure, ischemic heart disease, cerebrovascular disease, peripheral arterial disease.

levofloxacin cohort statistically significantly differed from the other cohorts on several demographic and baseline characteristics (Table 2). After propensity score matching, demographics and baseline clinical characteristics were similar between the levofloxacin cohort and the other cohorts with the exception of significant differences between levofloxacin and azithromycin in mean age in the full sample (higher with levofloxacin), census region in the full sample, and mean CCI in the full sample and the high-risk subset (higher with levofloxacin) (Table 2).

Unadjusted Treatment Failure Rates

In the full sample, unadjusted treatment failure rates were 20.8% for levofloxacin, 23.9% for amoxicillin/clavulanate, 23.9% for azithromycin, and 19.9% for moxifloxacin (Figure 2). The unadjusted treatment failure rate was significantly lower with levofloxacin than azithromycin (P=0.035) in the full sample; results of the other pairwise comparisons were not statistically significant. In the high-risk subset, unadjusted treatment failure rates were 19.1% for levofloxacin, 26.1% for amoxicillin/clavulanate, 26.3% for azithromycin, and 24.3% for moxifloxacin (Figure 2). The unadjusted treatment failure rate was significantly lower with levofloxacin than azithromycin (P<0.005) in the high-risk subset; results of the other pairwise comparisons were not statistically significant. In both the full sample and the high-risk subset, the most common reason for being classified as a treatment failure was filling a CAP antibiotic prescription that differed from the index antibiotic. Table 3 summarizes reasons for treatment failures for each antibiotic.

Propensity Score-Matched Treatment Failure Rates

Propensity score-matched treatment failure rates were significantly lower with levofloxacin compared with azithromycin in the full sample of matched patients (19.8% vs. 24.5%, P<0.005) and in the high-risk subset (19.0% vs. 26.4%, P<0.05) (Figure 3). No other significant differences were found in propensity score-matched treatment failure rates in either the full sample or the high-risk subset (Figure 3).

Adjusted ORs for Treatment Failure, Propensity Score-Matched Samples

Patients treated with azithromycin were 38% more likely to experience treatment failure

Figure 2. Unadjusted treatment failure rates in the full sample and the high-risk subset. *P<0.05 vs. levofloxacin.

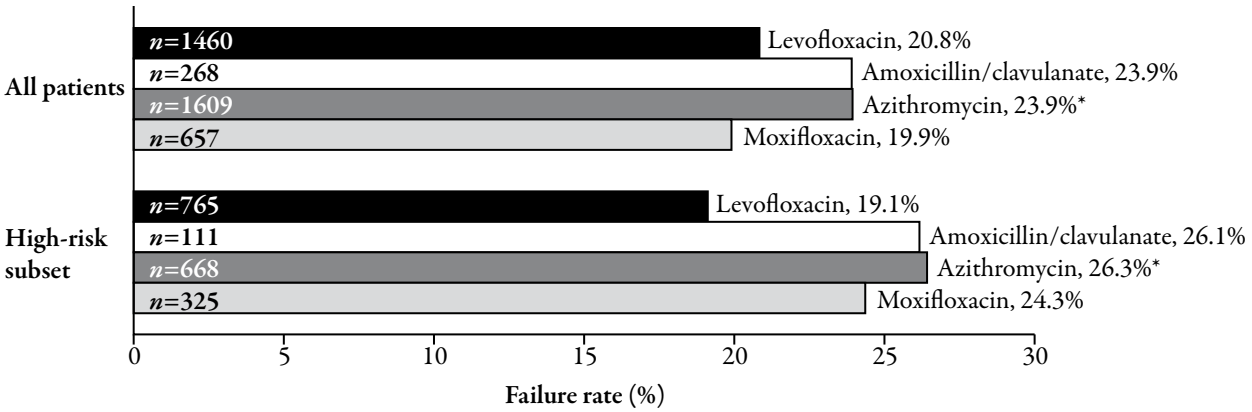
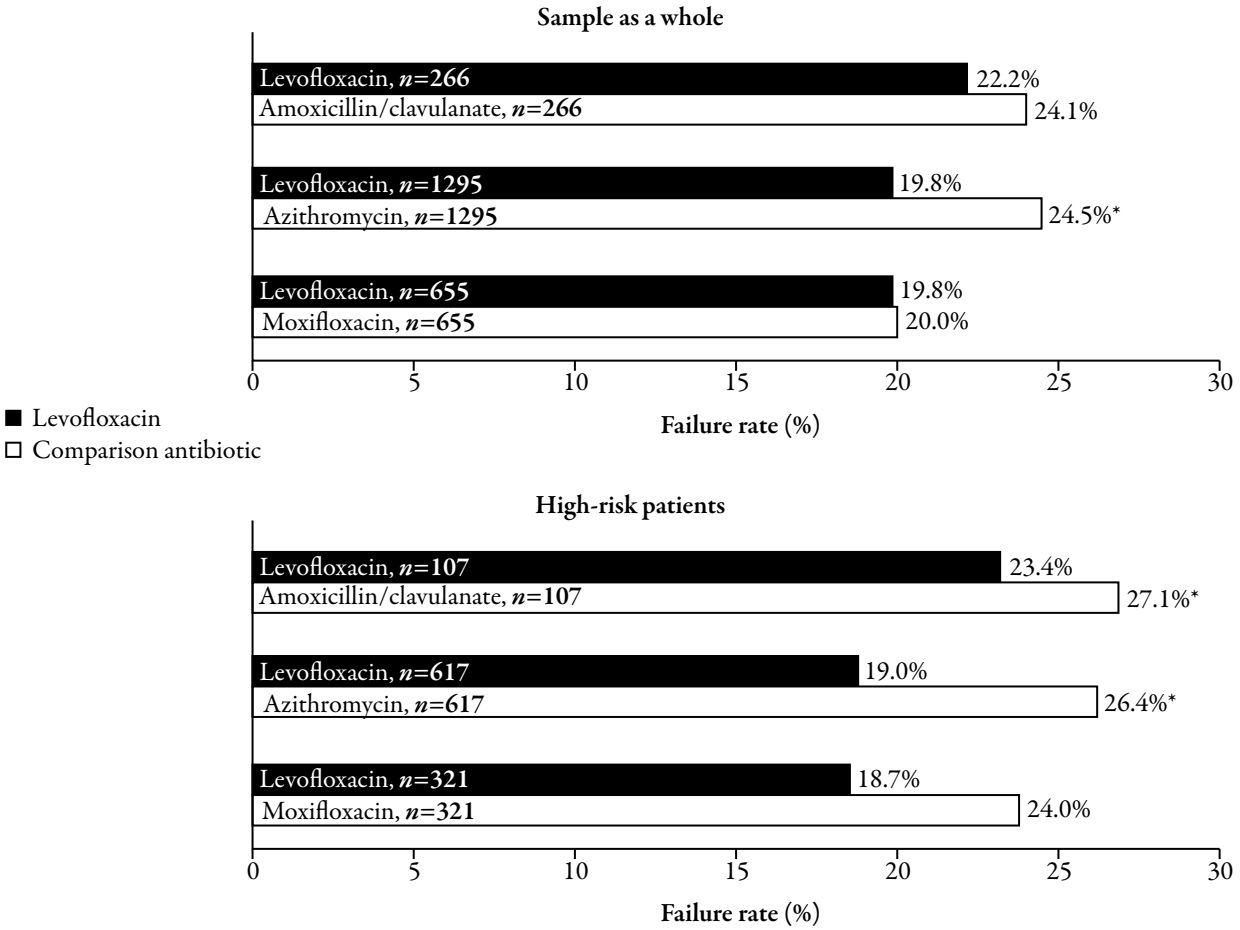


Table 3. Reasons for treatment failure.

	Azithromycin		Levofloxacin		Moxifloxacin		Amoxicillin/clavulanate	
	Full sample	High-risk subset	Full sample	High-risk subset	Full sample	High-risk subset	Full sample	High-risk subset
Unadjusted, prepropensity matching (percentage of patients)								
Patient count, *n*	1609	668	1460	765	657	325	268	111
Antibiotic Rx, inpatient pneumonia and/or emergency department visit	23.9	26.3	20.8	19.1	19.9	24.3	23.9	26.1
a) Antibiotic Rx (w/ ref ll and/or dispensed)	21.2	21.4	17.6	15.4	16.3	18.2	20.1	19.8
i) Ref ll Rx for same antibiotic	4.8	4.5	6.0	5.8	3.5	4.3	2.2	4.5
ii) Dispensed new Rx for dif erent antibiotic	17.8	17.8	12.2	10.3	13.2	14.5	17.9	15.3
b) Hospitalization (inpatient diagnosis of pneumonia)	4.5	7.5	5.1	6.3	5.9	8.9	5.2	9.9
c) Emergency department visit (any diagnosis)	1.2	1.6	0.8	0.8	0.8	1.2	0.4	0.9
Unadjusted, postpropensity matching (percentage of patients)								
Patient count, *n*	1295	617	266	107	655	321	266	107
Antibiotic Rx, inpatient pneumonia and/or emergency department visit	24.5	26.4	22.2	23.4	20.0	24.0	24.1	27.1
a) Antibiotic Rx (w/ ref ll and/or dispensed)	21.6	21.2	19.9	17.8	16.3	18.1	20.3	20.6
i) Ref ll Rx for same antibiotic	4.9	4.5	8.3	11.2	3.5	4.0	2.3	4.7
ii) Dispensed new Rx for dif erent antibiotic	18.0	17.7	12.8	7.5	13.3	14.6	18.0	15.9
b) Hospitalization (inpatient diagnosis of pneumonia)	4.5	7.8	3.4	7.5	6.0	8.7	5.3	10.3
c) Emergency department visit (any diagnosis)	1.0	1.6	0.8	0.0	0.8	1.2	0.4	0.9

Rx=medical prescription.

Figure 3. Propensity score-matched treatment failure rates in the full samples (top) and the high-risk subsets (bottom). *$P<0.05$ vs. levofloxacin.

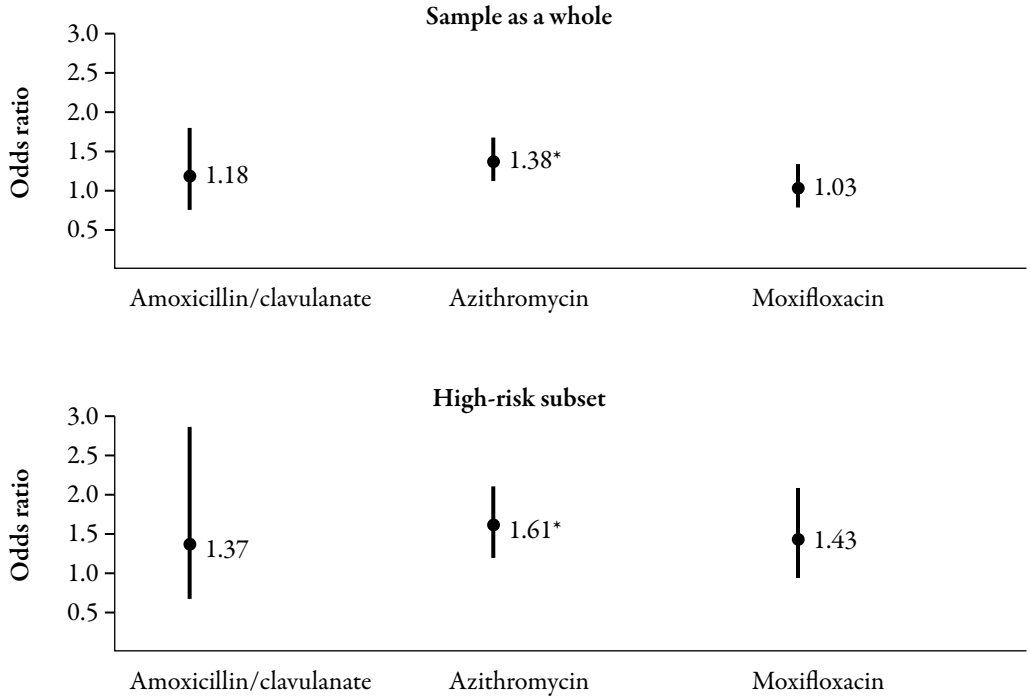


than patients treated with levofloxacin in the estimates from the logistic regressions on the full propensity score-matched sample (adjusted OR 1.38; 95% CI: 1.14, 1.67). In the high-risk subset, patients treated with azithromycin were 61% more likely to experience treatment failure than patients treated with levofloxacin (adjusted OR 1.61; 95% CI: 1.22, 2.13). No other significant differences were found in treatment failure rates from the logistic regressions on the propensity score-matched sample (Figure 4).

DISCUSSION

Treatment failure in CAP is associated with heightened risk of morbidity and mortality and increased healthcare costs.[9-11] While previous research suggests that initial treatment with fluoroquinolones protects against treatment failure,[10,11] little is known about how antibiotics compare with respect to treatment failure rates. In this claims analysis involving nearly 4000 patients with newly diagnosed CAP, treatment failure was significantly less likely when levofloxacin was given as an initial antibiotic than when azithromycin was given. In analyses involving propensity score-matched data, the odds of treatment failure were 38% greater with azithromycin than levofloxacin. The benefit of levofloxacin over azithromycin with respect to treatment failure was particularly marked in high-risk patients (ie, those ≥65 years old

Figure 4. Propensity score-matched treatment failure rates. Adjusted odds ratio for treatment failure with comparator antibiotics versus levofloxacin in the full samples (top) and the high-risk subsets (bottom). *P<0.05 versus levofloxacin.



and/or on Medicaid), among whom the odds of treatment failure were 61% greater with azithromycin than levofloxacin. Treatment failure rates were lower with levofloxacin than azithromycin in the sample as a whole and in high-risk patients despite the older age, on average, of the levofloxacin cohort and the tendency of the levofloxacin cohort to have a greater comorbidity burden.

These findings are consistent with the previous observation that initial treatment of CAP with fluoroquinolones, compared with other guidelines-concordant antibiotics, is linked to a reduced risk of treatment failure.[10,11] The results of this study are also consistent with data from a retrospective, claims-based analysis of patients with CAP treated in an outpatient setting in a large US health plan.[15] In a propensity score-adjusted analysis, patients with CAP treated with levofloxacin (n=2520) were significantly less likely than those treated with a macrolide (n=2520) to experience treatment failure, defined as a second antibiotic claim after the index prescription date or hospital admission with a primary or secondary diagnosis of CAP. Moreover, the incidence of CAP-related emergency department visits was 22% lower among levofloxacin-treated patients than macrolide-treated patients although significant differences were not observed for CAP-related hospitalizations or total CAP-related healthcare costs. In that study,[15] as in the current study, benefits of levofloxacin were particularly marked in patients aged ≥65 years. Whereas levofloxacin was associated with a 16% lower risk of treatment failure than macrolides in the sample as a whole, levofloxacin was associated with a 35% lower risk of treatment failure in patients aged ≥65 years. Considered in aggregate, the results of the current study and previous research support the use of fluoroquinolones as an important antimicrobial treatment for reducing the risk

of treatment failure and attendant morbidity and mortality in CAP, especially among elderly patients.

The reason for the lower treatment failure rates with levofloxacin compared with azithromycin (and with macrolides generally in the study reported above)[15] have not been elucidated. Bacterial resistance probably plays a role.[17] Fluoroquinolones are associated with relatively low rates of bacterial resistance and remain active against *S. pneumoniae* and the majority of other common causative pathogens, including atypical pathogens, in CAP.[18] In contrast, pneumococcal resistance to macrolides has risen steadily in the US and worldwide in recent decades.[19-22] In the Prospective Resistance Organism Tracking and Epidemiology for the Ketolide Telithromycin Surveillance Study, which tested 6747 *S. pneumoniae* isolates from 119 US centers in 2005-2006, macrolide resistance increased to 35.3% from a rate of approximately 30.0% for the previous 3 years.[20] Levofloxacin susceptibility rates were >98% irrespective of genotype. Consistent with the possibility that macrolide resistance contributes significantly to treatment failure, nonsusceptible isolates were recovered from 71% of patients in a study of 122 cases of CAP that had failed to respond to >2 days of macrolide therapy.[23]

In the current study, the benefit of levofloxacin over azithromycin with respect to treatment failure was manifested both in the unadjusted data and in the propensity score-matched data. Propensity score matching is a well-documented, quasi-empirical method of correcting for selection biases in making estimates. Propensity score matching reduces the likelihood of imbalances among cohorts in pretreatment characteristics in an observational study. Balancing of cohorts using the propensity score-matching technique is achieved by matching patients by their likelihood of receiving a particular treatment based on their observable pretreatment characteristics. In interpreting the results of this study, it should be borne in mind that propensity score matching can help to reduce main sources of bias in observational datasets but does not eliminate potential sources of bias.

Neither propensity score-adjusted nor unadjusted treatment failure rates significantly differed between levofloxacin and the fluoroquinolone moxifloxacin, or between levofloxacin and the penicillin amoxicillin/clavulanate. However, numerical trends toward lower treatment failure rates with levofloxacin were observed versus amoxicillin/clavulanate in the full sample, and versus both amoxicillin/clavulanate and moxifloxacin among high-risk patients. The small size of the amoxicillin/clavulanate cohort, in particular, might have allowed for the operation of type II error that obscured treatment-related differences. Additional research with larger samples is warranted to further compare treatment failure rates among these antibiotics.

The results of the study should be interpreted in the context of its limitations. First, the definition of treatment failure might have led to inflation of the treatment failure rate. Treatment failure could entail a refill of the index antibiotic dispensed after the completed days of therapy or a different antibiotic dispensed >1 day after the index antibiotic prescription. The diagnosis for which the second prescription was made was not obtained from pharmacy claims, and the second prescription could have been for the treatment of a condition other than CAP. However, any inflation of treatment failure rates because of the misattribution of diagnoses for the second prescription would be expected to affect the treatment cohorts similarly and therefore should not have affected the pattern of results. Other limitations of the study include

the possibility of data entry errors in claims originating at the site of care and the inability to account for out-of-network care. Finally, the retrospective, observational nature of the study makes the results subject to selection bias. Attempts to minimize the potential impact of selection bias included the application of restrictive inclusion and exclusion criteria, and the use of multivariate analyses with the propensity score-matched data.

CONCLUSION

Its limitations notwithstanding, the study provides new information about treatment failure rates associated with antibiotics commonly prescribed for CAP. The results show that levofloxacin was associated with a significantly lower rate of treatment failure than azithromycin in both the sample as a whole and a high-risk subset of patients who were ≥65 years old and/or on Medicaid. The results of this study show that the treatment failure rate tended to be lower in the levofloxacin group compared with the amoxicillin/clauvulanate group or the moxifloxacin group although the differences were not statistically significant.

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