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ORIGINAL RESEARCH

Comparative Effectiveness of Macrolides and Quinolones for Patients Hospitalized With Acute Exacerbations of Chronic Obstructive Pulmonary Disease (AECOPD)

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BACKGROUND: Meta-analyses of randomized trials have found that antibiotics are effective in acute exacerbations of chronic obstructive pulmonary disease (AECOPD), but there is insufficient evidence to guide antibiotic selection. Current guidelines offer conflicting recommendations.
OBJECTIVE: To compare the effectiveness of macrolides and quinolones for AECOPD
DESIGN: Retrospective cohort study using logistic regression, propensity score–matching, and grouped treatment models.
SETTING: A total of 375 acute care hospitals throughout the United States.
PATIENTS: Age ≥40 years and hospitalized for AECOPD.
INTERVENTION: Macrolide or quinolone antibiotic begun in the first 2 hospital days.
MEASUREMENTS: Treatment failure (defined as the initiation of mechanical ventilation after hospital day 2, inpatient mortality, or readmission for AECOPD within 30 days), length of stay, and hospital costs.
RESULTS: Of the 19,608 patients who met the inclusion criteria, 6139 (31%) were treated initially with a macrolide and 13,469 (69%) with a quinolone. Compared to patients treated initially with a quinolone, those who received macrolides had a lower risk of treatment failure (6.8% vs. 8.1%; $P < 0.01$), a finding that was attenuated after multivariable adjustment (odds ratio [OR], 0.89; 95% confidence interval [CI], 0.78–1.01), and disappeared in a grouped-treatment analysis (OR, 1.01; 95% CI, 0.75–1.35). There were no differences in adjusted length of stay (ratio, 0.98; 95% CI, 0.97–1.00) or adjusted cost (ratio, 1.00; 95% CI, 0.99–1.02). After propensity score–matching, antibiotic-associated diarrhea was more common with quinolones (1.2% vs. 0.6%; $P < 0.001$).
CONCLUSIONS: Macrolide and quinolone antibiotics are associated with similar rates of treatment failure in AECOPD; however, macrolides are less frequently associated with diarrhea. ***Journal of Hospital Medicine*** **2010;5:261–267.** © *2010 Society of Hospital Medicine.*

KEYWORDS: **antibiotics, chronic obstructive, pulmonary disease, effectiveness, treatment.**

Additional Supporting Information may be found in the online version of this article.

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are responsible for more than 600,000 hospitalizations annually, resulting in direct costs of over $20 billion.[1] Bacterial infections appear responsible for 50% of such exacerbations,[2–5] and current COPD guidelines recommend treatment with antibiotics for patients with severe exacerbations or a change in sputum.[1,6–9] These recommendations are based on a number of small randomized trials, most of which were conducted more than 20 years ago using narrow spectrum antibiotics that are no longer commonly used.[10] Only 4 studies, totaling 321 subjects, included hospitalized patients, and most studies excluded patients who required steroids. Because no

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clinical trials have compared different antibiotic regimens for AECOPD, existing guidelines offer a range of treatment options, including amoxicillin-clavulonate, macrolides, quinolones, cephalosporins, aminopenicillins, and tetracyclines.

Among hospitalized patients, macrolides and quinolones appear to be the most frequently prescribed antibiotics.[11] Both are available in oral formulations, have excellent bioavailability, and are administered once daily. In addition to their antimicrobial activity, macrolides are believed to have antiinflammatory effects, which could be especially advantageous in AECOPD.[12–14] In trials of chronic bronchitis, however, fluoroquinolones have been shown to reduce the risk of recurrent exacerbation when compared to macrolides.[15] The wide variation that has been observed in antibiotic selection for patients hospitalized for AECOPD suggests a high degree of uncertainty among clinicians about the benefits of different treatment options.[11] Given the limited evidence from randomized trials, we sought to evaluate the comparative effectiveness of macrolides and quinolones among a large, representative sample of patients hospitalized with AECOPD.

Subjects and Methods

Setting and Subjects

We conducted a retrospective cohort study of all patients hospitalized between January 1 and December 31, 2001 for AECOPD at any 1 of 375 acute care facilities in the United States that participated in Premier's Perspective, a voluntary, fee-supported database developed for measuring quality and healthcare utilization. Participating hospitals represent all geographical regions, and are primarily small-sized to medium-sized nonteaching hospitals located mostly in urban areas. In addition to the information contained in the standard hospital discharge file (Uniform Billing 92) such as patient age, International Classification of Disease, 9th Edition, Clinical Modification (ICD-9-CM) codes, the Perspective database includes a date-stamped log of all billed items, including diagnostic tests, medications, and other treatments, as well as costs, for individual patients. The study was approved by the Institutional Review Board of Baystate Medical Center.

Patients were included if they had a primary diagnosis consistent with AECOPD (ICD-9 codes 491.21 and 493.22) or a primary diagnosis of respiratory failure (ICD-9 codes 518.81 and 518.84) paired with secondary diagnosis of AECOPD; they also had to receive at least 2 consecutive days of either a macrolide or a quinolone, started within 48 hours of hospitalization. Patients receiving both antibiotics were excluded, but patients who received additional antibiotics were included. To enhance the specificity of our diagnosis codes, we limited our study to patients age $\geq$40 years.[16] Because mechanical ventilation initiated after hospital day 2 was an outcome measure, we excluded patients admitted directly to the intensive care unit. We also excluded: those with other bacterial infections, such as pneumonia or cellulitis, who might have another indication for antibiotics; those with a length of stay $<$2 days, because we could not ascertain whether they received a full course of antibiotics; patients with a secondary diagnosis of pulmonary embolism or pneumothorax; and those whose attending physicians were not internists, family practitioners, hospitalists, pulmonologists, or intensivists. For patients with more than 1 admission during the study period, we included only the first admission.

Data Elements

For each patient, we assessed age, gender, race, marital and insurance status, principal diagnosis, comorbidities, and specialty of the attending physician. Comorbidities were identified from ICD-9 secondary diagnosis codes and Diagnosis Related Groups using Healthcare Cost and Utilization Project Comorbidity Software (version 3.1), based on the work of Elixhauser et al.[17] In addition, to assess disease severity we recorded the presence of chronic pulmonary heart disease, the number of admissions for COPD during the 12 months prior to the index admission, and arterial blood gas testing.[18,19] We also identified pharmacy or diagnostic charges for interventions that were recommended in current guidelines (beta-adrenergic and anticholinergic bronchodilators, steroids, and noninvasive positive-pressure ventilation); those that were not recommended or were of uncertain benefit (methylxanthine bronchodilators, spirometry/pulmonary function testing, mucolytic medications, chest physiotherapy, and sputum testing); and drugs that might be associated with severe exacerbations or end-stage COPD (loop diuretics, morphine, and nutritional supplements).[1,6–9] Hospitals were categorized by region (Northeast, South, Midwest, or West), bed size, setting (urban vs. rural), ownership, and teaching status.

Antibiotic Class and Outcome Variables

Our primary predictor variable was the antibiotic initiated during the first 2 hospital days and continued for at least 2 days, regardless of other antibiotics the patient may have received during the course of hospitalization. Because we anticipated low in-hospital mortality, our primary outcome was a composite measure of treatment failure, defined as initiation of mechanical ventilation after hospital day 2, in-hospital mortality, or readmission for COPD within 30 days of discharge.[20] Secondary outcomes included hospital costs and length of stay, as well as allergic reactions identified by ICD-9 code, and antibiotic-associated diarrhea, defined as treatment with either metronidazole or oral vancomycin begun after hospital day 3.

Statistical Analysis

Summary statistics were computed using frequencies and percents for categorical variables; and means, medians, standard deviations, and interquartile ranges for continuous variables. Associations between antibiotic selection and patient and hospital characteristics were assessed using chi-square tests for categorical variables and z-tests for continuous variables.

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We developed a series of multivariable models to evaluate the impact of initial antibiotic selection on the risk of treatment failure, length of stay, and total cost. In order to account for the effects of within-hospital correlation, generalized estimating equation (GEE) models with a logit link were used to assess the effect of antibiotic selection on the risk of treatment failure, and identity link models were used for analyses of length of stay and cost. Unadjusted and covariate-adjusted models for treatment failure were evaluated with and without adjustments for propensity score. A propensity score is the probability that a given patient would receive treatment with a macrolide, derived from a nonparsimonious model in which treatment with a macrolide was considered the outcome. The propensity model included all patient characteristics, other early treatments and tests, comorbidities, hospital and physician characteristics, and selected interaction terms.[21] Length of stay and cost were trimmed at 3 standard deviations above the mean, and natural log-transformed values were modeled due to extreme positive skew. In addition, we carried out matched analyses in which we compared the outcomes of patients who were treated with a macrolide to those with similar propensity scores (ie, with similar likelihood of receiving a macrolide) who received a quinolone.[22]

Finally, to reduce the threat of residual confounding by indication, which can occur if sicker patients are more likely to receive a particular antibiotic, we developed a grouped treatment model, in which all patients treated at the same hospital were assigned a probability of treatment with a macrolide equal to the overall treatment rate at that hospital.[23] This is an adaptation of instrumental variable analysis, a well-accepted technique in econometrics with growing use in health care.[24,25] It attempts to assess whether patients treated at a hospital at which quinolones are used more frequently have better outcomes than patients treated at hospitals at which macrolides are used more frequently, while adjusting for other patient, physician, and hospital variables. It ignores the actual treatment the patient received, and instead substitutes the hospital's rate of macrolide use. By grouping treatment at the hospital level, this method greatly reduces the possibility of residual selection bias, unless hospitals that use a lot of macrolides have patients who differ in a consistent way from hospitals which use mostly quinolones.

All analyses were performed using SAS version 9.1 (SAS Institute, Inc., Cary, NC).

Results

Of 26,248 AECOPD patients treated with antibiotics, 19,608 patients met the inclusion criteria; of these, 6139 (31%) were treated initially with a macrolide; the median age was 70 years; 60% were female; and 78% were white. A total of 86% of patients had a primary diagnosis of obstructive chronic bronchitis with acute exacerbation, and 6% had respiratory failure. The most common comorbidities were hypertension, diabetes, and congestive heart failure. Twenty-two percent had been admitted at least once in the preceding 12 months. Treatment failure occurred in 7.7% of patients, and 1.3% died in the hospital. Mean length of stay was 4.8 days. Hospital prescribing rates for macrolides varied from 0% to 100%, with a mean of 33% and an interquartile range of 14% to 46% (Supporting Appendix Figure 1).

Compared to patients receiving macrolides, those receiving quinolones were older, more likely to have respiratory failure, to be cared for by a pulmonologist, and to have an admission in the previous year (Table 1). They were also more likely to be treated with bronchodilators, methylxanthines, steroids, diuretics, and noninvasive positive pressure ventilation, and to have an arterial blood gas, but less likely to receive concomitant treatment with a cephalosporin (11% vs. 57%). With the exception of cephalosporin treatment, these differences were small, but due to the large sample were statistically significant. Comorbidities were similar in both groups. Patients in the quinolone group were also more likely to experience treatment failure (8.1% vs. 6.8%), death (1.5% vs. 1.0%), and antibiotic-associated diarrhea (1.1% vs. 0.5%).

In the unadjusted analysis, compared to patients receiving quinolones, those treated with macrolides were less likely to experience treatment failure (OR, 0.83; 95% CI, 0.74–0.94) (Table 2). Adjusting for all patient, hospital, and physician covariates, including the propensity for treatment with macrolides, increased the OR to 0.89 and the results were no longer significant (95% CI, 0.78–1.01). Propensity matching successfully balanced all measured covariates except for the use of short-acting bronchodilators and additional antibiotics (Table 1). In the propensity-matched sample (Figure 1), quinolone-treated patients were more likely to experience antibiotic-associated diarrhea (1.2% vs. 0.6%; $P = 0.0003$) and late mechanical ventilation (1.3% vs. 0.8%; $P = 0.02$). There were no differences in adjusted cost or length of stay between the 2 groups. The results of the grouped treatment analysis, substituting the hospital's specific rate of macrolide use in place of the actual treatment that each patient received suggested that the 2 antibiotics were associated with similar rates of treatment failure. The OR for a 100% hospital rate of macrolide treatment vs. a 0% rate was 1.01 (95% CI, 0.75–1.35).

Discussion

In this large observational study conducted at 375 hospitals, we took advantage of a natural experiment in which antibiotic prescribing patterns varied widely across hospitals to compare the effectiveness of 2 common antibiotic regimens for AECOPD. Treatment with macrolides and quinolones were associated with a similar risk of treatment failure, costs, and length of stay; however, patients treated with macrolides were less likely to experience late mechanical ventilation or treatment for antibiotic-associated diarrhea.

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TABLE 1. Selected Characteristics of Patients with AECOPD Who Were Treated Initially With a Quinolone or a Macrolide

Characteristic	Complete Cohort			Propensity-matched Subsample		
	Quinolone (n = 13469)	Macrolide (n = 6139)	*P* Value	Quinolone (n = 5610)	Macrolide (n = 5610)	*P* Value
Antibiotics received during hospitalization* [n (%)]						
Macrolide	264 (2)	6139 (100)		119 (2)	5610 (100)	
Quinolone	13469 (100)	459 (8)		5610 (100)	424 (8)	
Cephalosporin	1696 (13)	3579 (59)	<0.001	726 (13)	3305 (59)	<0.001
Tetracycline	231 (2)	75 (2)	0.01	101 (2)	73 (2)	0.06
Other antibiotics	397 (3)	220 (4)	0.02	166 (3)	193 (3)	0.03
Age (years) (mean [SD])	69.1 (11.4)	68.2 (11.8)	<0.001	68.6 (11.7)	68.5 (11.7)	0.58
Male sex (n [%])	5447 (40)	2440 (40)	0.36	2207 (39)	2196 (39)	0.85
Race/ethnic group (n [%])			<0.001			0.44
White	10454 (78)	4758 (78)		4359 (78)	4368 (78)	
Black	1060 (8)	540 (9)		470 (8)	455 (8)	
Hispanic	463 (3)	144 (2)		157 (3)	134 (2)	
Other	1492 (11)	697 (11)		624 (11)	653 (12)	
Primary diagnosis (n [%])			<0.001			0.78
Obstructive chronic bronchitis with acute exacerbation	11650 (87)	5298 (86)		4884 (87)	4860 (87)	
Chronic obstructive asthma/asthma with COPD	908 (7)	569 (9)		466 (8)	486 (9)	
Respiratory failure	911 (7)	272 (4)		260 (5)	264 (5)	
Admissions in the prior year (n [%])			<0.001			0.84
0	9846 (73)	4654 (76)		4249 (76)	4231 (75)	
1	1918 (14)	816 (13)		747 (13)	750 (13)	
2+	1085 (8)	445 (7)		397 (7)	420 (8)	
Missing	620 (5)	224 (4)		217 (4)	209 (4)	
Physician specialty (n [%])			<0.001			0.84
Internal medicine/hospitalist	7069 (53)	3321 (54)		3032 (54)	3072 (55)	
Family/general medicine	3569 (27)	2074 (34)		1824 (33)	1812 (32)	
Pulmonologist	2776 (21)	727 (12)		738 (13)	711 (13)	
Critical care/intensivist	55 (0)	17 (0)		16 (0)	15 (0)	
Tests on hospital day 1 or 2 (n [%])						
Arterial blood gas	8084 (60)	3377 (55)	<0.001	3195 (57)	3129 (56)	0.22
Sputum test	1741 (13)	766 (13)	0.39	20 (0)	16 (0)	0.62
Medications/therapies on hospital day 1 or 2 (n [%])						
Short-acting bronchodilators	7555 (56)	3242 (53)	<0.001	2969 (53)	2820 (50)	0.005
Long-acting beta-2 agonists	2068 (15)	748 (12)	<0.001	704 (13)	719 (13)	0.69
Methylxanthine bronchodilators	3051 (23)	1149 (19)	<0.001	1102 (20)	1093 (20)	0.85
Steroids			0.04			0.68
Intravenous	11148 (83)	4989 (81)		4547 (81)	4581 (82)	
Oral	772 (6)	376 (6)		334 (6)	330 (6)	
Severity indicators (n [%])						
Chronic pulmonary heart disease	890 (7)	401 (7)	0.85	337 (6)	368 (7)	0.24
Sleep apnea	586 (4)	234 (4)	0.08	211 (4)	218 (4)	0.77
Noninvasive positive pressure ventilation	391 (3)	128 (2)	<0.001	128 (2)	114 (2)	0.40
Loop diuretics	4838 (36)	1971 (32)	<0.001	1884 (34)	1862 (33)	0.67
Hospital characteristics (n [%])						
Staffed beds			<0.001			0.71
6–200	3483 (26)	1688 (28)		1610 (29)	1586 (28)	
201–300	3132 (23)	1198 (20)		1174 (21)	1154 (21)	
301–500	4265 (32)	2047 (33)		1809 (32)	1867 (33)	
500+	2589 (19)	1206 (20)		1017 (18)	1003 (18)	
Hospital region (n [%])			<0.001			0.65
South	8562 (64)	3270 (53)		3212 (57)	3160 (56)	
Midwest	2602 (19)	1444 (24)		1170 (21)	1216 (22)	
Northeast	1163 (9)	871 (14)		687 (12)	704 (13)	
West	1142 (9)	554 (9)		541 (10)	530 (9)	
Teaching hospital			<0.001			0.63
No	12090 (90)	5037 (82)		4896 (87)	4878 (87)	
Yes	1379 (10)	1102 (18)		714 (13)	732 (13)	
Comorbidities (n [%])						
Congestive heart failure	2673 (20)	1147 (19)	0.06	1081 (19)	1060 (19)	0.63

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TABLE 1. (*Continued*)

Characteristic	Complete Cohort			Propensity-matched Subsample		
	Quinolone (n = 13469)	Macrolide (n = 6139)	*P* Value	Quinolone (n = 5610)	Macrolide (n = 5610)	*P* Value
Metastatic cancer	134 (1)	27 (0)	<0.001	34 (1)	38 (1)	0.72
Depression	1419 (11)	669 (11)	0.45	598 (11)	603 (11)	0.90
Deficiency anemias	1155 (9)	476 (8)	0.05	426 (8)	432 (8)	0.86
Solid tumor without metastasis	1487 (11)	586 (10)	0.002	550 (10)	552 (10)	0.97
Hypothyroidism	1267 (9)	527 (9)	0.07	481 (9)	482 (9)	1.00
Peripheral vascular disease	821 (6)	312 (5)	0.005	287 (5)	288 (5)	1.00
Paralysis	165 (1)	46 (1)	0.003	49 (1)	51 (1)	0.92
Obesity	957 (7)	435 (7)	0.98	386 (7)	398 (7)	0.68
Hypertension	5793 (43)	2688 (44)	0.31	2474 (44)	2468 (44)	0.92
Diabetes			0.04			0.45
Without chronic complications	2630 (20)	1127 (18)		1057 (19)	1066 (19)	
With chronic complications	298 (2)	116 (2)		115 (2)	97 (2)	

NOTE: A complete list of patient characteristics and outcomes can be found in Supporting Appendix Tables 1 and 2.

Abbreviations: AECOPD, acute exacerbations of chronic obstructive pulmonary disease; SD, standard deviation.

*Refers to all antibiotics received during the hospitalization, not limited to the first 2 days. Patients may receive more than 1 antibiotic, so percentages do not sum to 100.

TABLE 2. Outcomes of Patients Treated With Macrolides Compared to Those Treated With Quinolones for Acute Exacerbation of COPD

Models	Treatment Failure		Cost		LOS	
	OR	95% CI	Ratio	95% CI	Ratio	95% CI
Unadjusted	0.83	0.73–0.93	0.98	0.97–1.00	0.96	0.95–0.98
Adjusted for propensity score only*	0.89	0.79–1.01	1.00	0.98–1.01	0.98	0.97–1.00
Adjusted for covariates†	0.87	0.77–0.99	1.00	0.99–1.02	0.99	0.97–1.00
Adjusted for covariates and propensity score	0.89	0.78–1.01	1.00	0.99–1.02	0.98	0.97–1.00
Matched sample, unadjusted‡	0.87	0.75–1.00	0.99	0.98–1.01	0.99	0.97–1.01
Matched sample, adjusted for unbalanced variables‡	0.87	0.75–1.01	1.00	0.98–1.02	0.99	0.97–1.01
Grouped treatment model, unadjusted§	0.90	0.68–1.19	0.97	0.89–1.06	0.92	0.87–0.96
Group treatment model, adjusted for covariates‖	1.01	0.75–1.35	0.96	0.88–1.05	0.96	0.91–1.00

Abbreviations: AIDS, acquired immune deficiency syndrome; CI, confidence interval; COPD, chronic obstructive pulmonary disease; LOS, length of stay; OR, odds ratio.

*Logistic regression model incorporating nonparsimonious propensity score only.

†Covariates in all models included: age; gender; primary diagnosis; region; teaching status; sleep apnea; hypertension; depression, paralysis; other neurological disorders; weight loss; heart failure; pulmonary circulation disease; valve disease; metastatic cancer; and initiation of oral or intravenous steroids, short-acting bronchodilators, arterial blood gas, loop diuretics, methylxanthine bronchodilators, and morphine in the first 2 hospitals days. In addition, LOS and cost models included: insurance; attending physician specialty; hospital bed size; admission source; prior year admissions for COPD; chronic pulmonary heart disease; diabetes; hypothyroid; deficiency anemia; obesity; peripheral vascular disease; blood loss; alcohol abuse; drug abuse; AIDS; and initiation of long acting beta-2 agonists, noninvasive ventilation, mucolytic medications, chest physiotherapy, and sputum testing in the first 2 hospital days. The LOS model also included pulmonary function tests. The cost model also included rural population, renal failure, psychoses, and solid tumor without metastasis. Interactions in the treatment failure model were the following: age with arterial blood gas, and loop diuretics with heart failure and with paralysis. Interactions in the LOS model were the following: loop diuretics with heart failure; and long-acting beta-2 agonists with gender and metastatic cancer. Interactions in the cost model were loop diuretics with heart failure, sleep apnea and chronic pulmonary heart disease, long-acting beta-2 agonists with metastatic cancer, and obesity with hypothyroid.

‡Each macrolide-treated patient was matched on propensity with 1 quinolone-treated patient. Of 6139 macrolide-treated patients, 5610 (91.4%) were matched.

§In place of actual treatment received, the subjects are assigned a probability of treatment corresponding to the hospital's overall macrolide rate.

‖In addition to covariates in the treatment failure model, the group treatment model also included race/ethnicity and attending physician specialty.

Despite broad consensus in COPD guidelines that patients with severe acute exacerbations should receive antibiotics, there is little agreement about the preferred empiric agent. Controversy exists regarding antibiotics' comparative effectiveness, and even over which pathogens cause COPD exacerbations. Given the frequency of hospitalization for AECOPD, understanding the comparative effectiveness of treatments in this setting could have important implications for health outcomes and costs. Unfortunately, most antibiotic studies in AECOPD were conducted >20 years ago, using antibiotics that rarely appeared in our sample.[26] Consequently, clinical practice guidelines offer conflicting recommendations. For example, the National Institute for Clinical Excellence recommends empirical treatment with an

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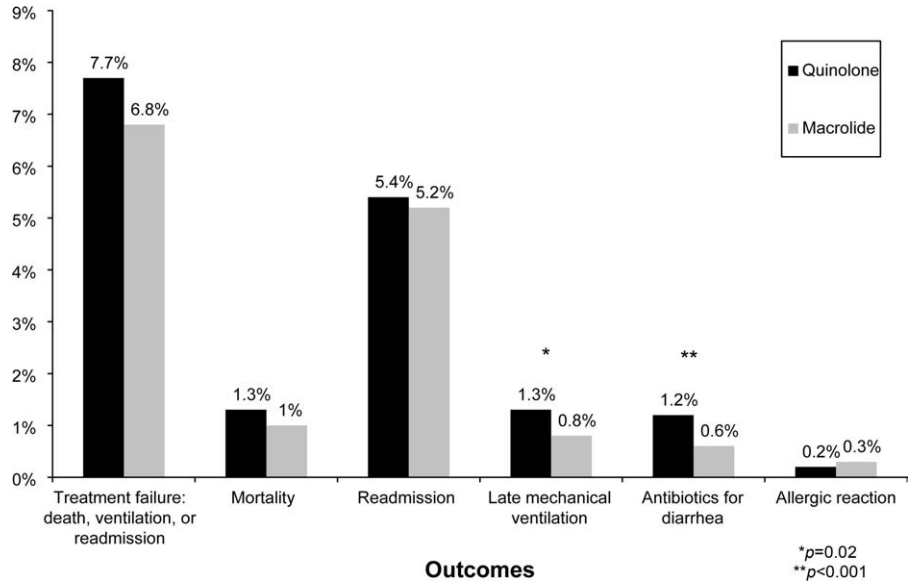

FIGURE 1. Outcomes of quinolone-treated and macrolide-treated patients in the sample matched by propensity score.

aminopenicillin, a macrolide, or a tetracycline,[8] while the American Thoracic Society recommends amoxicillin-clavulonate or a fluoroquinolone.[9]

As might be expected in light of so much uncertainty, we found wide variation in prescribing patterns across hospitals. Overall, approximately one-third of patients received a macrolide and two-thirds a quinolone. Both regimens provide adequate coverage of *H. influenza*, *S. pneumoniae*, and *M. catarrhalis*, and conform to at least 1 COPD guideline. Nevertheless, patients receiving macrolides often received a cephalosporin as well; this pattern of treatment suggests that antibiotic selection is likely to have been influenced more by guidelines for the treatment of community-acquired pneumonia than COPD.

Previous studies comparing antibiotic effectiveness suffer from shortcomings that limit their application to patients hospitalized with AECOPD. First, they enrolled patients with "chronic bronchitis," and included patients without obstructive lung disease, and most studies included patients as young as 18 years old. Second, many either did not include treatment with steroids or excluded patients receiving more than 10 mg of prednisone daily. Third, almost all enrolled only ambulatory patients.

While there are no studies comparing quinolones and macrolides in patients hospitalized for AECOPD, a meta-analysis comparing quinolones, macrolides, and amoxicillin-clavulonate identified 19 trials of ambulatory patients with chronic bronchitis. That study found that all 3 drugs had similar efficacy initially, but that quinolones resulted in the fewest relapses over a 26-week period.[27] Macrolides and quinolones had similar rates of adverse effects. In contrast, we did not find a difference in treatment failure, cost, or length of stay, but did find a higher rate of diarrhea associated with quinolones. Others have also documented an association between fluoroquinolones and *C. difficile* diarrhea.[28–30] This trend, first noted in 2001, is of particular concern because the fluoroquinolone-resistant strains appear to be hypervirulent and have been associated with nosocomial epidemics.[31–34]

Our study has several limitations. First, its observational design leaves open the possibility of selection bias. For this reason we analyzed our data in several ways, including using a grouped treatment approach, an adaptation of the instrumental variable technique, and accepted only those differences which were consistent across all models. Second, our study used claims data, and therefore we could not directly adjust for physiological measures of severity. However, the highly detailed nature of the data allowed us to adjust for numerous tests and treatments that reflected the clinician's assessment of the patient's severity, as well as the number of prior COPD admissions. Third, we cannot exclude the possibility that some patients may have had concurrent pneumonia without an ICD-9 code. We think that the number would be small because reimbursement for pneumonia is generally higher than for COPD, so hospitals have an incentive to code pneumonia as the principal diagnosis when present. Finally, we compared initial antibiotics only. More than one-quarter of our patients received an additional antibiotic before discharge. In particular, patients receiving macrolides were often prescribed a concomitant cephalosporin. We do not know to what extent these additional antibiotics may have affected the outcomes.

Despite the large number of patients hospitalized annually for AECOPD, there are no randomized trials comparing different antibiotics in this population. Studies comparing antibiotics in chronic bronchitis can offer little guidance, since they have primarily focused on proving equivalence between existing antibiotics and newer, more expensive formulations.[35] Because many of the patients enrolled in such trials do not benefit from antibiotics at all, either because

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they do not have COPD or because their exacerbation is not caused by bacteria, it is relatively easy to prove equivalence. Given that AECOPD is one of the leading causes of hospitalization in the United States, large, randomized trials comparing the effectiveness of different antibiotics should be a high priority. In the meantime, macrolides (often given together with cephalosporins) and quinolones appear to be equally effective initial antibiotic choices; considering antibiotic-associated diarrhea, macrolides appear to be the safer of the 2.

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