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Impact of Macrolide Antibiotics on Hospital Readmissions and other Clinically Important Outcomes in Critically Ill Patients with Acute Exacerbations of Chronic Obstructive Pulmonary Disease: A Propensity Score–Matched Cohort Study

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Abstract

Study Objective: To assess whether a macrolide-based antibiotic treatment strategy reduces in-hospital mortality, decreases hospital readmissions, or improves other clinically important outcomes compared with a non-macrolide antibiotic treatment strategy in critically ill patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD).

Design: Propensity score–matched pharmacoepidemiologic cohort study.

Data Source: Premier's Perspective Hospital Database.

Patients: A total of 28,700 adults aged 40 years or older who were admitted to one of 566 United States intensive care units and had the primary diagnosis of AECOPD between January 2010 and December 2014, and received antibiotic treatment within 2 days of hospital admission were included. Patients were divided into macrolide (11,602 patients [40%]) or non-macrolide (17,098 patients [60%]) antibiotic treatment groups. Propensity score analysis successfully matched 8,660 patients in each treatment group.

Measurements and Main Results: In the matched cohort, the macrolide treatment group was not associated with decreased hospital mortality after day 2 (3.0% vs 3.3%, $p=0.28$), intensive care

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unit length of stay (2 days vs 2 days, $p=0.12$), hospital length of stay (6 days vs 6 days, $p=0.86$), or length of assisted ventilation (3 days vs 3 days, $p=0.71$), compared with the non-macrolide treatment group. However, a macrolide-based antibiotic regimen was associated with an overall reduction in 30-day hospital readmissions (7.3% vs 8.8%, $p<0.01$), increased time to next all-cause (159 vs 130 days, $p<0.01$) or AECOPD (200 vs 175 days, $p=0.03$) readmission, and decreased hospital costs (\$32,730 vs \$34,021, $p<0.01$).

Conclusion: The results of this study suggest that inclusion of a macrolide antibiotic in the treatment regimen may have both acute and sustained benefits in critically ill patients admitted to the intensive care unit with an AECOPD, including reductions in hospital readmissions and improvements in time to next readmission.

Keywords

Critical Care; Antibacterial Agents; Intensive Care Unit; Azithromycin; Mortality; Patient Readmission

Chronic obstructive pulmonary disease (COPD) remains the third leading cause of death and disability in the United States, accounting for an estimated \$36 billion in annual medical costs.^{1–3} Up to 60% of these costs are due to acute exacerbations of COPD (AECOPD), which have a profound negative impact on health status, quality of life, rates of hospitalization, readmission, and disease progression.^{2, 4, 5} Patients admitted to the intensive care unit (ICU) for an AECOPD have the highest risk, with long-term mortality ranging from 17.6–50%.^{6–8} Consequently, optimizing therapies for AECOPD is a high priority, especially among those with respiratory failure.

Antibiotics are a mainstay of treatment for AECOPD. They are recommended when increased sputum purulence is accompanied by increased shortness of breath or sputum volume, or for patients with respiratory failure that require invasive or noninvasive mechanical ventilation.² These recommendations are based on studies showing that antibiotics decrease treatment failure for outpatients, inpatients, and inpatients with respiratory failure.^{9, 10} Antibiotics are particularly important for patients with AECOPD who require mechanical ventilation because they decrease mortality, need for additional antibiotics, duration of mechanical ventilation, and hospital length of stay.^{9, 11} The initial, empiric antibiotic choice is not standardized and should be guided by prior antibiotic use, patient risk factors, AECOPD severity, local bacterial resistance, and the likelihood that *Pseudomonas* species are present.^{2, 12} The optimal antibiotic regimen for AECOPD has not been established; however, commonly used antibiotics include β -lactams (e.g. ampicillin with clavulanic acid or a third-generation cephalosporin), fluoroquinolones, tetracyclines, or macrolides.^{2, 12}

Macrolide antibiotics are unique in that they have both antimicrobial activity and broad immunomodulatory effects that may be beneficial for AECOPD.^{13–16} These properties have led to the success of chronic macrolide therapy in the prevention of COPD exacerbations.^{17, 18} In addition, use of macrolides for non-ICU, AECOPD hospitalizations have been associated with a number of clinical benefits compared with fluoroquinolones.^{19, 20}

However, to our knowledge, no studies have compared the efficacy of macrolide antibiotic therapy with other antibiotic classes in the treatment of critically ill patients with AECOPD.

To address this question, we conducted a large, multicenter comparative-effectiveness study to evaluate macrolide versus non-macrolide antibiotic therapy in critically ill patients with AECOPD and hypothesized that macrolide antibiotics may be associated with decreased mortality, hospital readmissions, or other clinically important outcomes, and reduced hospital cost.

Methods

Study Design and Data Source

A pharmacoepidemiologic cohort study was designed to evaluate patient data voluntarily submitted to the Premier Perspective Hospital Database (Premier, Inc., Charlotte, NC). The Premier database currently includes over 970 United States–based hospitals representing approximately 25% of annual U.S. inpatient admissions.²¹ This database contains patient characteristics, therapies, disease state classifications according to the *International Classification of Diseases, Ninth Revision* (ICD-9), and clinical outcomes.²¹ The Colorado Multiple Institutional Review Board provided approval for the conduct of this study.

Patient Population

Patients were included in this study if they were aged 40 years or older; were admitted to an intensive care unit between January 1, 2010, and December 31, 2014, due to a principal admitting diagnosis of AECOPD (ICD-9 code 491.21); and received either macrolide or non-macrolide antibiotic treatment within the first 48 hours of their admission. To narrow the patient population to a primary focus on AECOPD and to evaluate the impact of the first course of inpatient antibiotics on outcomes, patients were excluded if any of the following conditions were present: transfer from outside hospital; hospital stay of 2 days or less; admission diagnosis of pulmonary embolism, pneumothorax, or pneumonia; receipt of intravenous vasopressors on hospital day 1 or 2; solid organ transplantation; receipt of greater than 1 g/day of methylprednisolone or equivalent; or data necessary for analysis were incomplete or missing.

Outcomes

We compared associations between patients treated with macrolide- and non-macrolide-based antibiotic regimens and the primary outcomes of in-hospital mortality, all-cause readmission within 30 days, time to all-cause readmission, and hospital charges. Hospital charges included all billing (e.g., procedures, diagnostic tests, medications, facility fees) during the patient's admission and does not reflect any discounts, insurance payments, billing reductions, or actual patient payments. Secondary outcomes included ICU or hospital length of stay, initiation of noninvasive or invasive ventilation after hospital day 2, tracheostomy, 30-day readmission for a primary diagnosis of AECOPD, and time to next readmission with a primary diagnosis of AECOPD. Outcomes were assessed after hospital day 2 to provide sufficient time to account for treatment effect in each therapeutic group. Occurrence of an outcome was determined via documentation of any hospital admission

after inclusion visit discharge, pharmacy charge codes, current procedural terminology (CPT) codes, or ICD-9 codes as appropriate.

Data Analysis

Statistical analysis was performed by using methodology previously described by our Colorado Pulmonary Outcomes Research Group.^{22–27} Patient and hospital characteristics were compared between groups using the χ^2 test for categorical data and the unpaired *t* test or Kruskal-Wallis test for continuous variables as appropriate. To address the potential for selection bias between patients receiving macrolides over other antibiotics, a propensity score for initial treatment with macrolide antibiotics was developed. The dependent variable of this model was use of a macrolide antibiotic, and the independent covariates were the demographic, patient-specific, and treatment setting factors listed in Tables 1 and 2. Each patient in the macrolide group was matched to a patient in the non-macrolide group to the nearest figro decimal point.

A propensity score–matched analysis was used for evaluation of primary and secondary outcomes and was considered the primary analysis for study outcome interpretation. The matched cohort was evaluated for potential differences in primary and secondary outcomes, and logistic or linear regression was used to evaluate any associations between treatment group and outcome variables, while adjusting for covariate differences ($p < 0.05$) remaining between groups. A secondary analysis was performed to evaluate outcomes on the entire cohort of patients included. A multivariable regression approach was used to evaluate primary and secondary outcomes after adjusting for the propensity to be treated with a macrolide antibiotic (propensity score variable) and inclusion of all patient characteristics, comorbidities, hospital characteristics, admission year, and early therapies and tests (variables in Tables 1 and 2). Additionally, as a sensitivity analysis to assess the effect of modeling structure, final models were repeated in a hierarchical structure including random hospital effect to account for prescribing biases at the hospital level. Use of 1:1 matching and an estimated in-hospital mortality rate of 3.5% provided a greater than 90% power to detect an absolute difference of 1% in mortality.²⁸ All significance tests were two-sided, and a *p* value less than 0.05 was considered to indicate a statistically significant difference. All analyses were conducted by using SAS version 9.3 (SAS institute, Inc., Cary, NC).

Results

A total of 28,700 patients were included from 566 hospitals across the United States, of which 11,602 patients (40%) received macrolide antibiotics and 17,098 patients (60%) received non-macrolide antibiotics. Overall, the majority of patients were aged 60 years or older, and approximately 45% of patients were male in each group (Tables 1 and 2). Nine percent of patients had been admitted to the hospital one or more times for an AECOPD within the previous 12 months. Hypertension, diabetes mellitus, heart failure, cardiac arrhythmias, and fluid and electrolyte disorders were the most common comorbidities present on admission in both groups, and approximately 39% of patients were active tobacco users. A majority of patients were admitted to an urban, nonteaching medical center. Approximately 94% of patients received corticosteroid therapy as an early therapeutic

intervention, and 89% of patients received short-acting bronchodilator therapy. Early (within 48 hours of admission) noninvasive ventilation was used in approximately 43% of patients, and early invasive mechanical ventilation was used in approximately 20% of patients.

Compared to patients in the macrolide group, patients treated with non-macrolide therapy had higher rates of diabetes, heart failure, renal failure, peripheral vascular disease, sleep apnea, and weight loss, but they were less likely to be active tobacco users. Differences in hospital size, location, teaching status, and admission year were observed between treatment groups. Corticosteroid use and sputum testing was higher in the macrolide-treated patients. Loop diuretics were prescribed more commonly in non-macrolide-treated patients. In the macrolide group, 99% of patients received azithromycin, whereas fluoroquinolones were the most commonly prescribed antibiotic class in the non-macrolide group (76.9%). The addition of a β -lactam antibiotic to the antimicrobial regimen was common in both groups, with macrolide-treated patients more commonly receiving concomitant cephalosporin antibiotics. Non-macrolide-treated patients received penicillin or tetracycline antibiotics more frequently than macrolide-treated patients (Table 2). The duration of inpatient antibiotic therapy was similar between treatment groups (median 3 days, interquartile range 2–5 days for both groups; $p=0.07$).

After propensity score matching, a total of 8,660 patients were included in the macrolide and non-macrolide study groups. There were no significant differences in patient comorbidities, early therapeutic interventions, patient demographics, or treatment setting between groups (Tables 1 and 2).

Propensity Score–Matched Analysis (Primary Analysis)

In the propensity score–matched cohort, in-hospital mortality after day 2 occurred in 3% of the macrolide group and 3.3% of patients in the non-macrolide group ($p=0.28$; Table 3). All cause readmission within 30 days occurred in 7.3% of the macrolide group and 8.8% of the non-macrolide group ($p<0.01$), and time to any readmission occurred at a median of 159 and 130 days, respectively ($p<0.01$). There were no significant differences in the 30-day readmission rates for a primary diagnosis of AECOPD, but macrolide use was significantly associated with an increased time to readmission for an AECOPD (200 days vs 175 days, $p=0.03$). There were no significant differences in ICU length of stay, hospital length of stay, or duration of assisted (noninvasive or invasive) ventilation (Table 3). The need for late (after 48 hours) initiation of noninvasive or mechanical ventilation was similar between the macrolide and non-macrolide treatment groups (11.2% vs 11.6%, respectively, $p=0.33$). Tracheostomy was performed in 1.3% of macrolide-treated patients and 1.7% of non-macrolide-treated patients ($p=0.06$). Hospital charges were significantly lower in patients receiving macrolides: \$32,730 in patients receiving macrolides compared with \$34,021 in patients receiving non-macrolide antibiotics ($p=0.03$).

Adverse Effects

After propensity matching, there were minimal differences in the occurrence of potential antibiotic-related adverse effects between macrolide and non-macrolide treatment groups (Table 4). Treatment with a macrolide-based antibiotic regimen was not associated with

significant differences in the rates of *Clostridium Difficile* infection, antibiotic-associated diarrhea, cardiac dysrhythmias, or allergic reactions. Documentation of an acquired ventilator-associated pneumonia was low in both groups (5 macrolide-treated vs 9 non-macrolide-treated patients, $p=0.29$). Use of insulin therapy occurred in 45.2% of macrolide-treated patients and 43.9% of non-macrolide-treated patients ($p = 0.11$). Patients receiving only non-macrolide antibiotics were more likely to develop acute kidney injury (3.0% vs 2.1%, $p<0.01$). No significant differences in critical illness-related myopathy or polyneuropathy, delirium, hyperglycemia, catheter-associated bloodstream infections, catheter-associated urinary tract infections, hospital-acquired pneumonia, cellulitis, fungal infections, or cellulitis were observed between groups ($p>0.05$ for all comparisons).

Multivariable Analysis of the Entire Cohort

The total cohort (28,700 patients) was analyzed after adjusting for the propensity to be treated with a macrolide antibiotic and differences in patient characteristics, comorbidities, hospital characteristics, admission year, and early therapies, and tests. In this analysis, treatment with a macrolide antibiotic was associated with reduced in-hospital mortality (odds ratio [OR] 0.81, 95% confidence interval [CI] 0.71–0.94). Treatment with macrolide antibiotic was also associated with reduced 30-day hospital readmissions, increased time to next hospital admission, and reduced cost (Table 3).

Subgroup Analysis of Common Monotherapy and Combination Antibiotic Regimens

Antibiotic prescribing during the first 24 hours of hospitalization was highly variable and included frequent adjustments to therapy prior to determining a definitive treatment regimen. In the entire cohort, the most commonly prescribed antibiotics during hospital day 1 in the macrolide group were macrolide + cephalosporin ($n=4665$), macrolide monotherapy ($n=1769$), macrolide + cephalosporin + fluoroquinolone ($n=880$), macrolide + fluoroquinolone ($n=525$), or macrolide + cephalosporin + vancomycin ($n=165$). The most commonly prescribed antibiotic regimens during hospital day 1 in the non-macrolide group were fluoroquinolone monotherapy ($n=6945$), fluoroquinolone + cephalosporin ($n=1279$), fluoroquinolone + penicillin ($n=827$), or fluoroquinolone + penicillin + vancomycin ($n=759$).

As a majority of patients received multiple antibiotics, subgroup analyses were conducted to evaluate the effects of macrolide monotherapy or the most common combination therapy (e.g., macrolide + cephalosporin) compared with fluoroquinolone monotherapy or a fluoroquinolone combined with a cephalosporin on the primary and secondary outcomes. In the propensity score-matched cohort, azithromycin ($n= 1,101$) and levofloxacin ($n=2504$) were the most commonly used monotherapy options. In-hospital mortality (1.3% vs 1.5%, $p=0.65$) and 30-day hospital readmissions (9.9% vs 8.8%, $p=0.33$) were similar between the azithromycin and levofloxacin monotherapy treatment options, respectively.

After excluding patients receiving any other antibiotics, macrolide plus cephalosporin therapy ($n=3,205$) was associated with similar hospital mortality (2.4% vs 1.8%, $p=0.36$) and a trend toward reduced 30-day readmission rates (6.9% vs 9.2%, $p=0.05$) compared with fluoroquinolone plus cephalosporin therapy ($n=813$). Median time to next readmission was

186 days in the macrolide plus cephalosporin group compared to 144 days in the fluoroquinolone plus cephalosporin group ($p < 0.01$). The combination of a macrolide and cephalosporin was associated with reduced 30-day readmissions compared to fluoroquinolone monotherapy (6.9% vs 8.8%, $p=0.02$) and increased the time until the next hospital readmission (median 186 days vs 156 days, $p < 0.01$).

Sensitivity Analysis

We conducted analyses to determine whether antibiotic prescribing differences at the hospital level contributed to differences in patient outcomes (e.g., hospital treatment effect). When individual patients were assigned a probability of initial treatment with macrolide therapy equal to the hospital rate where they were admitted, each 10% increase in the hospital rate of macrolide use was associated with no change in the odds of mortality (OR 1.03, 95% CI 0.97–1.10, $p=0.31$), suggesting that the effects of macrolide therapy were not related to different treatment patterns in hospitals that were more likely to treat patients with macrolide therapy. Results for other outcomes in the hierarchical analysis were not significantly different from the propensity score matched model.

Discussion

The primary finding of this study is that inclusion of a macrolide antibiotic in the treatment regimen may be beneficial for critically ill patients admitted to the ICU with an AECOPD. This conclusion is based on the fact that macrolide antibiotics were associated with a significant reduction in all-cause 30-day readmissions and hospital charges, and a significant increase in time to next all-cause and AECOPD readmissions. It is notable that these benefits were observed when used in addition to the usual standard of care including bronchodilators, corticosteroids, and assisted ventilation. In contrast, use of macrolide antibiotics was not associated with an improvement in mortality.

In addition to providing adequate coverage for the most frequently identified pathogens in AECOPD, therapeutic concentrations of macrolides convey a broad range of antiinflammatory activities, including suppression of nuclear factor- κ B and modulation of activator protein-1 signaling, increased phagocytosis of apoptotic cells, mitigation of oxidant burst, decrease of mucous viscosity, suppression of angiogenesis, and modulation of virulence factors.^{13, 15, 16, 29, 30} Additionally, macrolides may modulate the response to corticosteroids by improving the recruitment of histone deacetylase 2, a major contributor to the inflammatory gene repression produced by corticosteroids in patients with COPD.¹⁴ The unique antiinflammatory properties of macrolide antibiotics may account for the reductions in readmissions observed in this study and similar cohort studies in non-critically ill patients with AECOPD.^{19, 20}

The reduction in hospital readmission rates and improvements in time to readmission mirrors the results generated with the use of chronic daily azithromycin for the prevention of COPD exacerbations. With chronic use, azithromycin significantly reduced the incidence and time to first COPD exacerbation compared with placebo.¹⁷ However, chronic daily use did not demonstrate significant differences in the rates of hospitalization related to COPD.¹⁷ Our study reinforces the findings that azithromycin increases the time to next COPD

exacerbation by demonstrating that macrolide use for ICU patients with AECOPD exhibits similar increases in the time to next exacerbation. With chronic use of azithromycin, median time to first exacerbation was increased from 174 days with placebo to 266 days with azithromycin.¹⁷ Our study substantiates these results, with a median time to exacerbation of 200 days with macrolides and 175 days with non-macrolide antibiotics. These results are also similar to prior comparisons between macrolides and fluoroquinolones in non-critically ill, hospitalized patients with AECOPD.²⁰ As airway inflammation is increased for up to 90 days after AECOPD,¹⁰ macrolide antibiotics may modulate the risk of acute worsening over a prolonged period. Despite the observed benefits in reduction in future hospitalizations, improvements in time to readmission, and reduced hospital charges associated with macrolide therapy in this study, only 40% of patients admitted to the ICU for AECOPD were prescribed macrolide therapy as component of their treatment regimen. These results suggest the need for providers to increase the advocacy for macrolide-containing regimens in the treatment AECOPD due to the benefits conveyed by their use.

Our study further highlights the significant morbidity and costs associated with ICU admissions for AECOPD. Patients spent a median of 2 days in the ICU and 6 days in the hospital, accumulating hospital charges of approximately \$30,000. The majority of patients required some form of assisted ventilation (invasive or noninvasive) for a median of 3 days during hospitalization. Macrolide use was not associated with improvements in ICU length of stay, hospital length of stay, or the length of time undergoing assisted ventilation compared to non-macrolide antibiotic therapy. These findings are consistent with previous data in non-ICU patients, where choice of antibiotic was not associated with significant differences in hospital length of stay or need for initiation of late ventilation.²⁰ Our data suggest that macrolide therapy may not provide significant additional synergistic effects with standard therapy initially but may have some sustained effects that confer morbidity benefits after hospital discharge. Use of a macrolide-based antibiotic regimen was associated with modest reductions in hospital charges of approximately \$2,000 per admission, but the source of this reduction is unclear, as ICU and hospital lengths of stay were similar between groups, and cost disparities in macrolide- versus fluoroquinolone-based antibiotic regimens are unlikely to explain the difference.

Major adverse reactions associated with antibiotic therapy occurred infrequently in our study. No significant differences in antibiotic-associated diarrhea, *Clostridium difficile* colitis, cardiac dysrhythmias, or allergic reactions were observed between treatment groups. In a previous study of antibiotic use in patients with AECOPD, the use of macrolide monotherapy was associated with reduced risk of *Clostridium difficile* readmissions when compared to quinolone monotherapy.²⁰ However, when a cephalosporin antibiotic was combined with macrolide therapy, this reduction was lost.²⁰ Therefore, our inability to find an association may be attributable to the frequent use of combination therapy with β -lactams in patients who received macrolide therapy or differences in patient populations between studies. Compared with amoxicillin, the risk of cardiac dysrhythmias and associated mortality with azithromycin therapy has been a concern in previous epidemiologic studies; however, the risk did not differ significantly when compared to levofloxacin therapy.³¹ Our results corroborate these findings and suggest that the risk of cardiac dysthymias is similar between azithromycin and levofloxacin. The incidence of acute kidney injury was higher in

the non-macrolide-treated patients in our study. The importance of this finding is unknown, as antibiotics with known nephrotoxicity (e.g., aminoglycosides) were infrequently used. It is likely that the incidence of acute kidney injury reflects the use of other medications or therapies rather than a protective effect of macrolide therapy.

Several limitations need to be considered when interpreting our study results. Due to the retrospective nature of this study, it was not feasible to capture data on COPD exacerbations that were managed in an outpatient setting and patients with AECOPD who did not seek medical care, and it is unknown whether patients were discharged with chronic daily azithromycin therapy. We are unable to discern from the database whether outpatient COPD clinic pathways or transitions-of-care programs had any impact on the evaluated outcomes. As mentioned, the observed reductions in the rate of 30-day hospital readmissions may reflect a capturing of some chronic macrolide-treated patients. On the last day of hospitalization, 29% of patients were still taking macrolide therapy, and a formal discontinuation of macrolide therapy was found in 82.5% of patients during their hospital admission. We did not have access to outpatient pharmacy records to determine antibiotic therapy or other medication use before or after hospital admission.

There are a variety of factors that may account for the lack of association between macrolide use and hospital mortality. The absence of an acute effect of macrolide antibiotics on outcomes may be due to the use of other antiinflammatory or immunomodulatory pharmacologic treatments in the hospital setting. For example, more than 90% of patients in our study received corticosteroid therapy. In the non-macrolide group, fluoroquinolone antibiotics were the most commonly prescribed antibiotics. These agents are known to confer antiinflammatory properties that may have confounded our attempts to isolate the antiinflammatory effects of the macrolides over other antimicrobial agents.³² The in-hospital mortality rate in this study was much lower than that reported previously for patients with both hospital and ICU admissions for AECOPD and partially reflects our exclusion of over 1000 patients who died in the first 2 hospital days.^{33, 34} In turn, this may have impaired our ability to detect significant differences between treatment groups. However, long-term outcomes in patients hospitalized in the ICU for AECOPD are poor, with relatively high mortality rates.³³ The retrospective nature of this study may have prevented the detection of differences in long-term mortality due to macrolide therapies during the hospitalized treatment period or may have impaired our ability to examine the delayed antiinflammatory effects of the macrolides. Ongoing research using macrolides in the acute exacerbation period, followed by chronic therapy during the known high-risk postexacerbation period, may answer this important question.³⁵

Database limitations are also a consideration when interpreting results. Data were only included through 2014, so the impact of contemporary best practices related to evidence that has emerged since our study period cannot be evaluated. As laboratory parameters (e.g., culture data) and pulmonary function test results were unavailable in the database, we were unable to adjust for confounding factors such as degree of chronic airflow limitation, assessment of the appropriateness of antimicrobial therapy, or preexisting pharmacotherapy prior to hospital admission. Patients who stayed in the hospital for 2 days or less were not included in the analysis, so patients with early mortality or less severe illness with early

discharge were not evaluated. We were only able to determine associations between antimicrobial treatment and patient outcomes and cannot determine causality. Specific antibiotic therapies could not be directly linked to the evaluated adverse events. Our comparison of antibiotic monotherapy and the most common antibiotic combinations and outcomes within treatment groups was not conducted using an evaluation of the propensity to receive monotherapy versus combination antibiotic therapy and should only be considered exploratory in nature. Despite our rigorous statistical approach, the retrospective nature of this study limited our ability to completely mitigate potential prescriber biases and confounding by indication.

Conclusion

The antiinflammatory effects of macrolides provide a biologically plausible explanation for the observed benefits of macrolide therapy conveyed in this study. Use of macrolide therapy in patients admitted for AECOPD was associated with reductions in hospital readmissions and improvements in time to readmission. Our results suggest that macrolides may confer a unique set of benefits for patients admitted to the ICU with AECOPD. Further research is needed regarding antimicrobial selection in this treatment setting, including determining the effects of macrolide therapy on long-term outcomes in patients admitted for AECOPD.

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Table 1.

Patient Demographics and Comorbidities Before and After Propensity Score Matching

Characteristic	Unmatched Groups		p value	Matched Groups		p value
	Macrolide (n=11,602)	Non-Macrolide (n=17,098)		Macrolide (n=8,660)	Non-Macrolide (n=8,660)	
Age (yrs)						
40–49	567 (4.9)	864 (5.1)	0.94	422 (4.9)	429 (5)	0.95
50–59	2,292 (19.8)	3,356 (19.6)		1,693 (19.5)	1,712 (19.8)	
60–69	3,464 (29.9)	5,053 (29.6)		2,559 (29.5)	2,538 (29.3)	
70–79	3,210 (27.7)	4,758 (27.8)		2,409 (27.7)	2,376 (27.4)	
80–89	2,069 (17.8)	3,067 (17.9)		1,577 (18.2)	1,605 (18.5)	
Sex						
Male	5,399 (46.5)	7,828 (45.8)	0.21	3,977 (45.9)	3,935 (45.4)	0.52
Female	6,203 (53.5)	9,270 (54.2)		4,683 (54.1)	4,725 (54.6)	
Race-ethnicity						
White	9,033 (77.9)	13,185 (77.1)	0.061	6,717 (77.6)	6,700 (77.4)	0.81
Black	1,031 (8.9)	1,679 (9.8)		791 (9.1)	826 (9.5)	
Hispanic	67 (0.6)	89 (0.5)		49 (0.6)	46 (0.5)	
Other	1,471 (12.7)	2,145 (12.5)		1,103 (12.7)	1,088 (12.6)	
Comorbidities ^a						
Hypertension	7,870 (67.8)	11,697 (68.4)	0.30	5,916 (68.3)	5,940 (68.6)	0.70
Diabetes mellitus	3,715 (32)	5,872 (34.3)	<0.01	2,871 (33.2)	2,881 (33.3)	0.87
Heart failure	3,628 (31.3)	5,853 (34.2)	<0.01	2,855 (33)	2,816 (32.5)	0.53
Depression	1,970 (17)	3,010 (17.6)	0.17	1,507 (17.4)	1,495 (17.3)	0.81
Deficiency anemias	1,732 (14.9)	2,665 (15.6)	0.13	1,322 (15.3)	1,328 (15.3)	0.90
Hypothyroidism	1,533 (13.2)	2,361 (13.8)	0.15	1,169 (13.5)	1,176 (13.6)	0.88
Obesity	2,213 (19.1)	3,350 (19.6)	0.28	1,671 (19.3)	1,636 (18.9)	0.50
Chronic pulmonary heart disease	1,394 (12)	2,158 (12.6)	0.13	1,049 (12.1)	1,080 (12.5)	0.47
Renal failure	1,796 (15.5)	2,920 (17.6)	<0.01	1,415 (16.3)	1,415 (16.3)	0.99
Peripheral vascular disease	898 (7.7)	1,462 (8.6)	0.014	723 (8.3)	708 (8.2)	0.68
Neurologic disorders	751 (6.5)	1,195 (7)	0.09	601 (6.9)	595 (6.2)	0.86
Valvular disease	777 (6.7)	1,172 (6.9)	0.60	580 (6.7)	582 (6.7)	0.95
Psychoses	787 (6.8)	1,226 (7.2)	0.21	617 (7.1)	578 (6.7)	0.24
Alcohol abuse	698 (6)	951 (5.6)	0.11	505 (5.8)	488 (5.6)	0.56
Sleep apnea	1,719 (14.8)	2,793 (16.3)	<0.01	1,316 (15.2)	1,265 (14.6)	0.28
Weight loss	744 (6.4)	1,237 (7.2)	<0.01	587 (6.8)	584 (6.7)	0.93
Tobacco use disorder	4,603 (39.7)	6,395 (37.4)	<0.01	3,353 (38.7)	3,369 (38.9)	0.80
Pulmonary circulation disease	1,398 (12)	2,161 (12.6)	0.14	1,053 (12.2)	1,081 (12.5)	0.52
Acute renal failure	1,141 (9.8)	1,695 (9.9)	0.83	864 (10)	864 (10)	0.99
Cardiac arrhythmias	3,258 (28.1)	4,868 (28.5)	0.50	2,435 (28.1)	2,437 (28.1)	0.97
Fluid and electrolyte disorders	3,737 (32.2)	5,589 (32.7)	0.4	2,824 (32.6)	2,794 (32.3)	0.63

Data are no. (%) of patients.

^aThe following comorbidities were present in < 5% of patients, and the percentages of patients with each of these comorbidities were not statistically significantly different between groups: rheumatoid arthritis or collagen vascular disease, drug abuse, solid tumor without metastasis, metastatic cancer, drug abuse, hepatic disease, hepatic failure, paralysis, human immunodeficiency virus/acquired immunodeficiency syndrome, tachycardia, altered mental status, disseminated intravascular coagulopathy syndrome, coagulopathy, and encephalopathy.

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Table 2.

Treatment Setting Characteristics and Early Therapeutic Interventions on ICU Day 1 or 2, Before and After Propensity Score Matching

Characteristic	Unmatched Groups		p value	Matched Groups		p value
	Macrolide (n=11,602)	Non-Macrolide (n=17,098)		Macrolide (n=8,660)	Non-Macrolide (n=8,660)	
No. of Hospital Beds						
<200	3,510 (30.3)	4,595 (26.9)		2,520 (29.1)	2,541 (29.3)	
200–300	2,209 (19)	3,201 (18.7)		1,672 (19.3)	1,628 (18.8)	
301–400	2,298 (19.8)	3,639 (21.3)	<0.01	1,772 (20.5)	1,740 (20.1)	0.81
401–500	1,771 (15.3)	2,442 (14.3)		1,268 (14.6)	1,283 (14.8)	
>500	1,814 (15.6)	3,221 (18.8)		1,428 (16.5)	1,468 (17)	
Patient Population						
Urban	9,372 (80.8)	14,230 (83.2)	<0.01	7,089 (81.9)	7,064 (81.6)	0.63
Rural	2,230 (19.2)	2,868 (16.8)		1,571 (18.1)	1,596 (18.4)	
Region						
South	4,921 (42.4)	8,126 (47.5)		3,891 (44.9)	3,854 (44.5)	
Midwest	3,039 (26.2)	4,999 (29.2)	<0.01	2,369 (27.4)	2,457 (28.4)	0.42
Northeast	1,637 (14.1)	1,649 (9.6)		1,035 (12)	990 (11.4)	
West	2,005 (17.3)	2,324 (13.6)		1,365 (15.8)	1,359 (15.7)	
Teaching Status						
Nonteaching	7,394 (63.7)	10,528 (61.6)	<0.01	5,461 (63.1)	5,439 (62.8)	0.73
Teaching	4,208 (36.3)	6,570 (38.4)		3,199 (36.9)	3,221 (37.2)	
Primary Insurance Status						
Medicare	8,153 (70.3)	12,120 (70.9)		6,097 (70.4)	6,123 (70.7)	
Medicaid	1,335 (11.5)	1,909 (11.2)	0.34	991 (11.4)	976 (11.3)	0.93
Private	1,401 (12.1)	1,976 (11.6)		1,040 (12)	1,020 (11.8)	
Self-pay/other	713 (6.1)	1,093 (6.4)		532 (6.1)	541 (6.2)	
Admission Year						
2010	1,984 (17.1)	3,361 (19.7)		1,558 (18)	1,607 (18.6)	
2011	2,320 (20)	3,354 (19.6)		1,702 (19.7)	1,709 (19.7)	
2012	2,569 (22.1)	3,515 (20.6)	<0.01	1,855 (21.4)	1,867 (21.6)	0.44
2013	2,510 (21.6)	3,672 (21.5)		1,916 (22.1)	1,817 (21.0)	
2014	2,219 (19.1)	3,196 (18.7)		1,629 (18.8)	1,660 (19.2)	
Early Therapeutic Interventions ^a						
Corticosteroid therapy	10,956 (94.4)	15,869 (92.8)	<.0001	8,130 (93.9)	8,126 (93.8)	0.90
Anticholinergic bronchodilator and/or short-acting β ₂ -agonist	10,302 (88.8)	15,205 (88.9)	0.7241	7,720 (89.1)	7,672 (88.6)	0.25
Long-acting bronchodilator	3,253 (28)	4,894 (28.6)	0.2808	2,456 (28.4)	2,420 (27.9)	0.54
Mechanical ventilation	2,363 (20.4)	3,540 (20.7)	0.4882	1,767 (20.4)	1,746 (20.2)	0.69
Noninvasive ventilation	4,979 (42.9)	7,225 (42.3)	0.2681	3,720 (43)	3,653 (42.2)	0.30
Methylxanthine bronchodilator	875 (7.5)	1,198 (7)	0.0857	641 (7.4)	627 (7.2)	0.68
Mucolytic medication	280 (2.4)	391 (2.3)	0.4863	196 (2.3)	210 (2.4)	0.48

Characteristic	Unmatched Groups		p value	Matched Groups		p value
	Macrolide (n=11,602)	Non-Macrolide (n=17,098)		Macrolide (n=8,660)	Non-Macrolide (n=8,660)	
Chest physiotherapy	444 (3.8)	589 (3.4)	0.0883	316 (3.6)	318 (3.7)	0.93
Sputum testing	1,780 (15.3)	2,396 (14)	0.0017	1,280 (14.8)	1,274 (14.7)	0.90
Spirometry	1,016 (8.8)	1,408 (8.2)	0.1185	745 (8.6)	769 (8.9)	0.52
Arterial blood gas	1,766 (15.2)	2,659 (15.6)	0.4474	1,361 (15.7)	1,296 (15)	0.17
Brain natriuretic peptide	8,237 (71)	12,148 (71)	0.9228	6,148 (71)	6,154 (71.1)	0.92
Loop diuretics	4,510 (38.9)	7,139 (41.8)	<.0001	3,489 (40.3)	3,480 (40.2)	0.89
Bronchoscopy	76 (0.7)	138 (0.8)	0.1424	55 (0.6)	63 (0.7)	0.46
Antibiotic use on ICU days 1 and 2^b						
Macrolides	11,602 (100)	0 (0.0)	NA	8,660 (100)	0 (0.0)	NA
Fluoroquinolones	2,876 (24.8)	13,096 (76.9)	<0.0001	2,170 (25.1)	6,658 (77.2)	<0.01
Cephalosporins	8,075 (69.6)	4,275 (25.1)	<0.0001	6,002 (69.3)	2,183 (25.3)	<0.01
Penicillins	1,473 (12.7)	3,817 (22.4)	<0.0001	1,103 (12.7)	1,851 (21.5)	<0.01
Tetracyclines	356 (3.1)	1,397 (8.2)	<0.0001	285 (3.3)	686 (8.0)	<0.01
Other antibiotics	1,600 (13.8)	3,780 (22.2)	<0.0001	1,213 (14.0)	1,817 (21.1)	<0.01

Data are no. (%) of patients.

ICU = intensive care unit; NA = not applicable.

^a Anticholinergic bronchodilator (e.g., ipratropium); short acting β_2 -agonist (e.g., albuterol); long-acting bronchodilator (long-acting muscarinic antagonists [e.g., tiotropium]) or long-acting β -agonist (e.g., salmeterol); methylxanthine bronchodilator (theophylline, aminophylline); mucolytic medication (e.g., acetylcysteine); and loop diuretics (furosemide, bumetanide, or torsemide).

^b Macrolides (e.g., azithromycin), fluoroquinolones (e.g., levofloxacin), cephalosporins (e.g., ceftriaxone), penicillins (e.g., ampicillin-sulbactam), tetracyclines (e.g., doxycycline), and other antibiotics (e.g., vancomycin).

Table 3.

Primary and Secondary Outcomes Before and After Propensity Score Matching

Outcome	Unmatched Entire Cohort		Odds Ratio (95% CI), propensity score and covariate adjusted (n=28,700)	p value	Propensity Score-Matched Cohort		Odds Ratio (95% CI), matched sample (n=17,320)	p value
	Macrolide (n=11,602)	Non-Macrolide (n=17,098)			Macrolide (n=8,660)	Non-Macrolide (n=8,660)		
Hospital mortality, no. (%)	335 (2.9)	604 (3.5)	0.81 (0.71–0.94)	<0.01	261 (3)	286 (3.3)	0.91 (0.77–1.07)	0.28
30-day hospital readmission, no. (%)	828 (7.1)	1558 (9.1)	0.80 (0.74–0.87)	<0.01	631 (7.3)	765 (8.8)	0.81 (0.72–0.91)	<0.01
Outcome	Unmatched Entire Cohort		Linear Regression Coefficient (95% CI), Propensity score and covariate adjusted (n=28,700)	P value	Propensity Matched Cohort		Linear Regression Coefficient, matched sample (n=17,320)	p value
	Macrolide (n=11,602)	Non-Macrolide (n=17,098)			Macrolide (n=8,660)	Non-Macrolide (n=8,660)		
Time to next readmission (days), median (IQR)	159 (48–419)	131 (35–382)	28 (18–37)	<0.01	159 (47–417)	130 (36–377)	26 (11–41)	<0.01
Time to next AECOPD readmission (days), median (IQR)	212 (68–468)	171 (55–426)	28 (14–43)	<0.01	200 (64–464)	175 (55–425)	24 (2–47)	0.03
Hospital length of stay (days), median (IQR)	6 (4–8)	6 (4–8)	–0.09 (–0.19–0.00)	0.058	6 (4–8)	6 (4–8)	–0.08 (–0.23–0.07)	0.29
ICU length of stay (days), median (IQR)	2 (1–4)	2 (1–4)	0.03 (–0.06–0.11)	0.53	2 (1–4)	2 (1–4)	–0.01 (–0.12–0.10)	0.81
Length of assisted ventilation ^a (days), median (IQR)	3 (2–6)	3 (2–6)	0.07 (–0.06–0.19)	0.28	3 (2–6)	3 (2–6)	0.03 (–0.14–0.20)	0.71
Total hospital charges/patient (\$)	33,175 (20,625–55,587)	33,763 (20,834–56,964)	–2,218 (–3,585 to –851)	<0.01	32,730 (20,421–54,776)	34,021 (20,846–57,587)	–2183 (–4107 to –259)	0.03

CI = confidence interval; IQR = interquartile range; AECOPD = acute exacerbations of chronic obstructive pulmonary disease; ICU = intensive care unit.

^a Only includes patients receiving assisted ventilation (includes both noninvasive and invasive ventilation): 6,211 (macrolide group) vs 9,301 (non-macrolide group) patients in the unmatched entire cohort and 4,633 (macrolide group) vs 4,686 (non-macrolide group) patients in the matched cohort.

Odds ratio < 1 demonstrates benefit toward treatment with macrolide antibiotic.

For time to next readmission variables, linear regression coefficient > 0 demonstrates benefit toward treatment with macrolide therapy.

For length of stay, length of assisted ventilation, and hospital cost variables, linear regression coefficient < 0 demonstrates benefit toward treatment with macrolide therapy.

Table 4.
Potential Treatment-Related Adverse Effects in the Unmatched Entire Cohort and after Propensity Score Matching

Adverse Effect ^a	Unmatched Group		p value	Matched Group		p value
	Macrolide (n=11,602)	Non-Macrolide (n=17,098)		Macrolide (n=8,660)	Non-Macrolide (n=8,660)	
Acute Kidney Injury	241 (2.1)	516 (3.0)	< 0.01	182 (2.1)	264 (3.0)	<0.01
<i>Clostridium difficile</i> infection	36 (0.3)	65 (0.4)	0.33	26 (0.3)	35 (0.4)	0.25
Antibiotic-associated diarrhea	212 (1.8)	327 (1.9)	0.60	162 (1.9)	169 (2)	0.70
Cardiac Dysrhythmias	526 (4.5)	870 (5.1)	0.03	402 (4.6)	429 (5)	0.33
Allergic Reaction	5 (<0.01)	6 (<0.01)	0.73	4 (<0.01)	3 (<0.01)	0.71

Data are no. (%) of patients.

^a Adverse effects listed in this table were determined by *International Classification of Diseases, Ninth Revision* code documentation in the patient's medical record.s