CHEST

Original Research

COPD

Association Between Antibiotic Treatment and Outcomes in Patients Hospitalized With Acute Exacerbation of COPD Treated With Systemic Steroids

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Background: **Antibiotics are widely used in acute exacerbations of COPD (AE-COPD), but their additional benefit to a therapeutic regimen that already includes steroids is uncertain. We evaluated the association between antibiotic therapy and outcomes among a large cohort of patients treated with steroids who were hospitalized with AE-COPD and compared the effectiveness of three commonly used antibiotic regimens.**

Methods: **We conducted a retrospective cohort study of patients aged ≥ 40 years hospitalized for AE-COPD from January 1, 2006, through December 1, 2007, at 410 acute care hospitals throughout the United States.**

Results: **Of the 53,900 patients who met the inclusion criteria, 85% were treated with antibiotics in the first 2 hospital days; 50% were treated with a quinolone, 22% with macrolides plus cephalosporin, and 9% with macrolide monotherapy. Compared with patients not treated with antibiotics, those who received antibiotics had lower mortality (1% vs 1.8%, $P < .0001$). In multivariable analysis, receipt of antibiotics was associated with a 40% reduction in the risk of in-hospital mortality (RR, 0.60; 95% CI, 0.50-0.73) and a 13% reduction in the risk of 30-day readmission for COPD (RR, 0.87; 95% CI, 0.79-0.96). The risk of late ventilation and readmission for *Clostridium difficile* colitis was not significantly different between the two groups. We found little difference in the outcomes associated with three common antibiotic treatment choices.**

Conclusions: **Our results suggest that the addition of antibiotics to a regimen that includes steroids may have a beneficial effect on short-term outcomes for patients hospitalized with AE-COPD.**

CHEST 2013; 143(1):82–90

Abbreviations: AE-COPD = acute exacerbations of COPD; RCT = randomized placebo-controlled trial

COPD is the fourth leading cause of death worldwide,[1] and severe acute exacerbations of COPD (AE-COPD) are life-threatening events[2] that result in > 700,000 hospitalizations each year in United States.[3,4] Identifying optimal treatment strategies for patients with severe AE-COPD remains a high priority.

Guidelines for management of patients hospitalized with AE-COPD recommend increasing the dose and frequency of bronchodilators and adding systemic corticosteroids for all patients, whereas antibiotics are recommended for those with signs of infection or who require mechanical ventilation.[5,6] Despite their widespread use, it is unclear whether antibiotics provide additional benefit when added to a regimen that already includes steroids. The number of randomized placebo-controlled trials (RCTs) that have assessed the role of antibiotics in AE-COPD is small, and most were performed before systemic corticosteroids were recommended as standard treatment.[7,8] Additionally, there is little evidence concerning the relative value of different antibiotic classes when used in the hospital setting.[9]

We examined the association between antibiotic therapy and outcomes among a large cohort of patients treated with steroids who were hospitalized with AE-COPD and compared the outcomes associated with three commonly used antibiotic regimens. This analysis extends the findings of a previous study published by our group that assessed the role of antibiotics in patients hospitalized with COPD irrespective of systemic steroid use.[10]

Materials and Methods

We conducted a retrospective cohort study using data from 410 hospitals that participate in Perspective, an inpatient administrative database. The information available includes patient demographics, principal and secondary diagnoses, discharge status, source of admission, date of service, medications dispensed, diagnostic tests, and physician and hospital characteristics.

Patients were included if they were aged ≥ 40 years and were discharged between January 1, 2006, and December 1, 2007, with a principal diagnosis of AE-COPD (*International Classification of Diseases, Ninth Revision, Clinical Modification* diagnostic codes 491.21, 491.22) or emphysema (492.8) or a principal diagnosis of respiratory failure (518.81, 518.82, 518.84) and a secondary diagnosis of AE-COPD or emphysema.[11] We restricted our analysis to patients who received treatment with systemic corticosteroids on the first 2 days of the hospitalization. We excluded patients on mechanical ventilation on the first 2 hospital days and those admitted directly to the ICU, because evidence for prescribing antibiotics for these patients is clear[12,13]; patients with a diagnosis of other bacterial infections that would warrant antibiotic treatment (eg, pneumonia); patients hospitalized or survived < 2 days; and patients transferred from or to another facility. For patients with more than one eligible admission during the study period, we randomly selected one.

Treatment with antibiotics was defined as a charge for macrolide, quinolone, cephalosporin, tetracycline, trimethoprim-sulfamethoxazole, or amoxicillin with or without clavulanic acid during the first 2 days of hospitalization and continued for at least 2 consecutive days. Patients who received antibiotics not recommended by GOLD (Global Initiative for Chronic Obstructive Lung Disease) guidelines for AE-COPD (ie, β-lactams with *Pseudomonas* activity and vancomycin) were excluded from the analysis.[6] Patients started on antibiotics after hospital day 3 were grouped with those who were not treated, because late treatment is likely to be initiated in the face of clinical deterioration.

In addition to demographics, primary payer, and principal diagnosis, we classified comorbidities using the Healthcare Cost and Utilization Project Comorbidity Software, version 3.1 and 3.2 (Agency for Healthcare Research and Quality),[14] and we calculated the number of admissions for COPD during the prior 12 months. We also assessed for receipt of a broad range of pharmacologic therapies and diagnostic tests on the first 2 days of hospitalization, including bronchodilators, diuretics, morphine, arterial blood gas levels, and sputum culture. We recorded the hospital's bed size, teaching status, geographic region, and whether the institution served an urban or rural population.

The primary outcome was in-hospital mortality. Secondary outcomes included late mechanical ventilation (defined as invasive mechanical ventilation started on day 3 or later), hospital cost, length of stay, and 30-day all-cause and COPD readmission. We assessed allergic reactions, antibiotic-associated diarrhea, and readmission within 30 days with diagnosis of *Clostridium difficile* colitis.

Statistical Analysis

In the first analysis we examined the outcomes associated with antibiotic exposure in patients already receiving steroids. In the second set of analyses we compared the outcomes associated with the choice of antibiotics among patients who were treated with both antibiotics and steroids.

Associations of early antibiotic treatment with patient and hospital characteristics were assessed using χ^2 tests, *t* tests, and nonparametric analogs. We developed a series of multivariable models as a function of patient, treatment, and hospital characteristics. Generalized estimating equation models were used to account for clustering of patients and physicians within hospitals. A propensity model was developed with early antibiotic treatment as the outcome, and all patient and hospital characteristics, early treatments and diagnostic tests, comorbidities, and selected interaction terms as independent variables. Unadjusted, covariate-adjusted, and propensity score-adjusted models were evaluated. In addition, we matched patients who did not receive treatment with antibiotics with those with similar propensity who received early antibiotics and carried out conditional logistic regression analysis.

In a sensitivity analysis, we used instrumental variable analysis as a method of adjusting for the impact of unmeasured confounders at the hospital level. Recognizing that antibiotic prescribing practice varies among hospitals, we used the proportion of all patients treated with antibiotics at a given hospital in place of actual treatment.[15] Second, we explored how the presence of a hypothetical

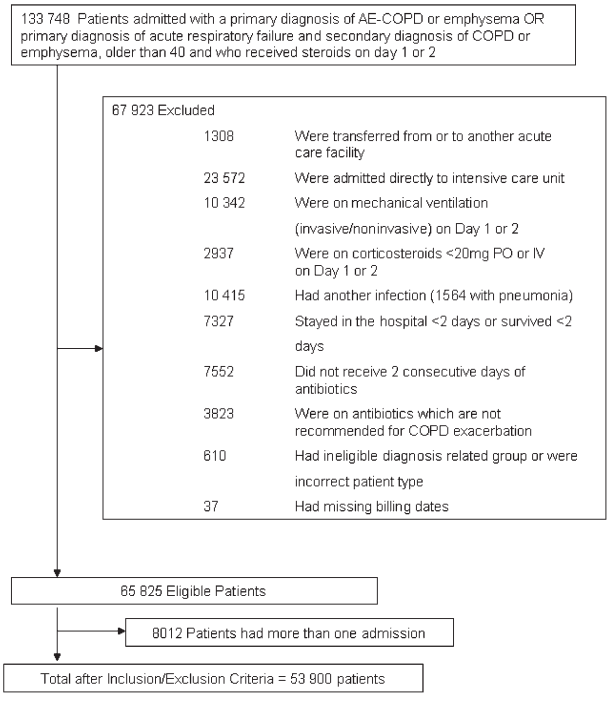

Figure 1. Patient selection flow diagram. AE-COPD = acute exacerbation of COPD.

Manuscript received March 9, 2012; revision accepted June 1, 2012.
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Funding/Support: Dr Stefan is supported by the National Cancer Institute [Grant KM1 CA156726] and by the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health [Grant UL1 RR025752].
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DOI: 10.1378/chest.12-0649

Table 1—*Selected Characteristics of Patients Hospitalized With AE-COPD*

Characteristics	All Patients (N = 53,900)	All Cohort		Matched Cohort	
		Early AB (n = 45,806)	Late/None (n = 8,094)	Early AB (n = 8,037)	Late/None (n = 8,037)
Patient characteristics					
Age, median (IQR), y	70 (61-78)	70 (61-78)	71 (62-79)	71 (62-79)	71 (62-79)
Sex					
Female	58.0	58.0	58.0	57.0	58.0
Race[a,b]					
White	75.5	76.2	71.9	73.5	71.9
Black	9.0	8.5	12.4	10.8	12.4
Hispanic	2.3	2.4	2.2	2.2	2.2
Other	13.0	13.0	13.5	13.5	13.6
Principal diagnosis[a]					
AE-COPD	90.0	90.0	92.1	92.0	92.0
Respiratory failure	10.0	10.0	7.9	8.0	8.0
Admissions for COPD or respiratory failure in year prior[a]					
0	80.1	81.0	75.7	76.6	75.8
1	13.5	13.0	16.0	15.7	15.9
2+	6.4	6.0	8.4	7.7	8.3
Attending specialty[a]					
Internal medicine	53.5	54.1	50.5	49.5	50.5
Family/general medicine	19.4	19.4	19.3	19.8	19.3
Pulmonology	11.7	11.4	13.3	13.6	13.3
Hospitalist	6.9	7.1	6.0	6.4	5.9
Other	8.4	8.0	11.0	10.7	10.9
Hospital characteristics					
No. of beds[a]					
≤ 200	19.4	20.0	15.9	16.5	15.9
201-300	17.4	17.2	18.6	18.5	18.5
301-500	36.4	36.5	36.1	35.6	36.1
> 500	26.8	26.3	29.3	29.5	29.5
Population served[a,b]					
Urban	83.0	82.0	87.0	86.0	87.0
Rural	17.0	18.0	13.0	14.0	13.0
Region[a]					
South	51.9	53.0	45.5	44.7	45.4
Midwest	19.3	19.5	18.5	18.8	18.6
Northeast	15.5	14.3	22.5	22.8	22.4
West	13.3	13.2	13.6	13.7	13.6
Teaching status[a]					
Nonteaching	66.0	68.0	58.0	58.0	58.0
Teaching	34.0	32.0	42.0	42.0	42.0
Comorbidities[c]					
Diabetes[a]	26.0	26.0	28.0	28.0	27.0
Heart failure[a]	23.0	22.0	29.0	29.0	29.0
Chronic pulmonary disease[a]	9.7	10.0	7.9	8.3	7.8
Obesity[a]	9.1	8.9	9.9	9.9	9.9
Renal failure[a]	7.9	7.6	9.8	10.0	9.7
Chronic pulmonary heart disease[a]	7.2	6.8	9.5	9.8	9.3
Alcohol abuse	3.7	3.6	4.0	4.3	4.0
Sleep apnea	2.4	2.4	2.9	2.4	2.8
Pulmonary circulation disease	1.4	1.4	1.7	1.9	1.6
Early therapies and tests					
Anticholinergic bronchodilator[a]	60.0	60.0	56.0	56.0	56.0
Short-acting β_2-agonist[a]	78.0	79.0	76.0	77.0	76.0
Long-acting β_2-agonist	38.0	38.0	38.0	39.0	38.0
Methylxanthine bronchodilators	9.1	9.0	9.4	10.2	9.4
High-dose glucocorticoids[a]	89.0	90.0	83.0	83.0	83.0
Morphine	7.4	7.2	8.2	9.0	8.2
Loop diuretics[a]	34.0	33.0	40.0	41.0	40.0
Smoking cessation medications[a]	11.0	12.0	8.7	9.1	8.7

(Continued)

Table 1—*Continued*

Characteristics	All Patients (N = 53,900)	All Cohort		Matched Cohort	
		Early AB (n = 45,806)	Late/None (n = 8,094)	Early AB (n = 8,037)	Late/None (n = 8,037)
Sputum testing[a]	9.0	9.9	4.0	4.3	4.0
Arterial blood gas[a]	43.0	44.0	40.0	40.0	40.0
Brain natriuretic peptide[a,b]	56.0	56.0	59.0	61.0	59.0

Data presented as % unless otherwise noted. AB = antibiotic; AE-COPD = acute exacerbations of COPD; IQR = interquartile range.
[a]*P* value for the cohort < .01.
[b]*P* value for the matched cohort < .05.
[c]Additional comorbidities evaluated in models but not reported in tables include valvular disease, peripheral vascular disease, paralysis, other neurologic disorders, hypothyroidism, liver disease, peptic ulcer disease excluding bleeding, AIDS, lymphoma, metastatic cancer, solid tumor without metastasis, rheumatoid arthritis/collagen vascular disease, coagulopathy, weight loss, chronic blood loss anemia, deficiency anemias, drug abuse, psychoses, depression, and hypertension.

unmeasured confounder associated with both antibiotic use and mortality might influence the effect estimates for antibiotic treatment. We hypothesized a range of ORs for mortality associated with the unmeasured confounder from 1.5 to 3 and varied its prevalence among the two groups. Using the method by Lin et al,[16] we explored the combination of prevalence and effect sizes that would result in nonsignificant ORs. In another sensitivity analysis designed to eliminate the possibility of immortal time bias, we first performed an analysis excluding deaths occurring prior to the fourth hospital day, because in a small percentage of cases exposure to antibiotic therapy required survival through hospital day 3; second, we carried out the analysis including only patients started on antibiotics on day 1 of admission.

To compare the effectiveness of different antibiotics, we developed a set of models as described previously, including both propensity score adjustment and matching. We compared the outcomes between the following groups of treated patients: (1) quinolones vs macrolides, (2) quinolones vs macrolides plus cephalosporins, (3) macrolides vs macrolides plus cephalosporins.

All analyses were performed using SAS version 9.2 (SAS Institute, Inc). The institutional review board at Baystate Medical Center reviewed and approved our study protocol (approval number 132220-12).

Results

A total of 53,900 patients were included in the analysis (Fig 1). The median age was 70 years, 58% were women, and 76% were white. Eighty-five percent of the patients received antibiotics within the first 2 hospital days; 50% received a quinolone, 22% a macrolide combined with a cephalosporin, and 9% macrolide monotherapy. An additional 1,662 patients (3.1%) received an antibiotic starting after day 3 and were analyzed in the group of patients who did not receive early antibiotics. The median hospital antibiotic rate of use was 86.1% (interquartile range, 80%-91.5%). The mean length of stay was 4.6 days, the in-hospital mortality rate was 1.1%, and 6% were readmitted within 30 days of discharge for another COPD exacerbation.

Compared with patients who were treated with steroids and antibiotics, those treated with steroids alone were older and more likely to be black, to be cared for by a pulmonologist, to have two or more admissions for COPD in the prior year, to receive diuretics or morphine, and to have brain natriuretic peptide testing, but less likely to have an arterial blood gas or sputum test (Table 1). The observed in-hospital mortality was 1.02% among those treated with antibiotics and steroids compared with 1.78% among those receiving steroids alone (Table 2).

Multivariable Analysis

In multivariable models that adjusted for patient and hospital characteristics, treatments and diagnostic

Table 2—*Outcomes of Patients Hospitalized With AE-COPD*

Outcomes	All Patients (N = 53,900)	All Cohort		Matched Cohort	
		Early AB (n = 45,806)	Late/None (n = 8,094)	Early AB (n = 8,037)	Late/None (n = 8,037)
In-hospital mortality[a,b]	1.13	1.02	1.78	0.96	1.78
Late ventilation (after day 2)	0.84	0.86	0.73	0.86	0.72
Readmission for COPD within 30 d[a,b]	5.62	5.42	6.75	5.91	6.76
Clostridium difficile readmission	0.22	0.23	0.15	0.22	0.15
Length of stay, median (IQR),[a,b] d	4 (3-6)	4 (3-6)	4 (3-6)	4 (3-6)	4 (3-6)
Total cost, median (IQR),[a,b] US$	4,801 (3,426-7,002)	4,819 (3,444-7,019)	4,690 (3,310-6,916)	5,036 (3,566-7,431)	4,690 (3,313-6,916)

Data presented as % unless otherwise noted. See Table 1 legend for expansion of abbreviations.
[a]*P* value for the cohort < .01.
[b]*P* value for the matched cohort < .05.

tests, and the propensity score, receipt of antibiotics was associated with a 40% reduction in the odds of in-hospital mortality (OR, 0.60; 95% CI, 0.50-0.74). Patients treated with antibiotics were also less likely to be readmitted for COPD within 30 days (OR, 0.87; 95% CI, 0.79-0.97) (Fig 2).

Some 99.3% of the patients who were treated with steroids were successfully matched to a patient with a similar propensity score who received early antibiotics in addition to steroids. Propensity score matching successfully balanced most of the covariates among the two groups of patients (Table 1). In the matched cohort, the hospital mortality rate was 1% in the antibiotic-treated group and 1.8% in the untreated group (OR, 0.53; 95% CI, 0.40-0.71). Patients treated with antibiotics had slightly longer hospital stay (OR, 1.07; 95% CI, 1.06-1.09) and higher cost (OR, 1.07; 95% CI, 1.05-1.09). The risk of late ventilation and readmission for *C difficile* colitis was not different between the two groups (Fig 2).

Sensitivity Analyses

In the instrumental variable analysis, the OR for a 100% hospital rate of antibiotic treatment vs a 0% rate was 0.5 (95% CI, 0.18-1.36) for mortality and 0.67 (95% CI, 0.47-0.97) for 30-day readmission for COPD. We also explored how our estimates of antibiotic effectiveness might have been influenced by residual unmeasured confounder (Fig 3). If the OR for mortality associated with the unmeasured confounder was 2, a difference in prevalence between the treated and untreated patients of $>40\%$ would result in a nonsignificant effect for antibiotics; if OR was 1.5, a difference in prevalence of 80% would be required to render the effect nonsignificant.

When we excluded deaths occurring prior to hospital day 4 to reduce the threat of immortal time bias, the mortality rate was 0.77% in the antibiotic-treated

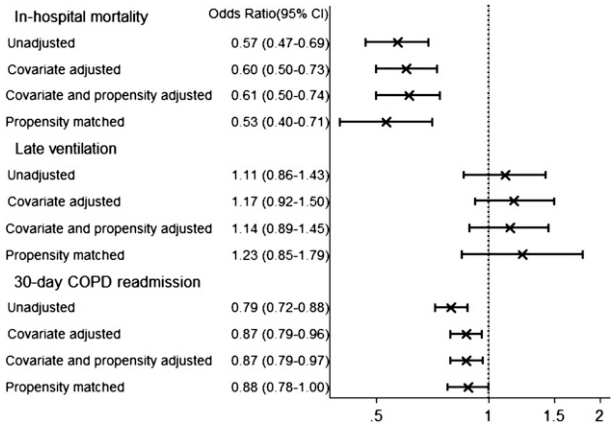

FIGURE 2. Outcomes of early antibiotic treatment vs late or not-treated in patients hospitalized for acute exacerbation of COPD.

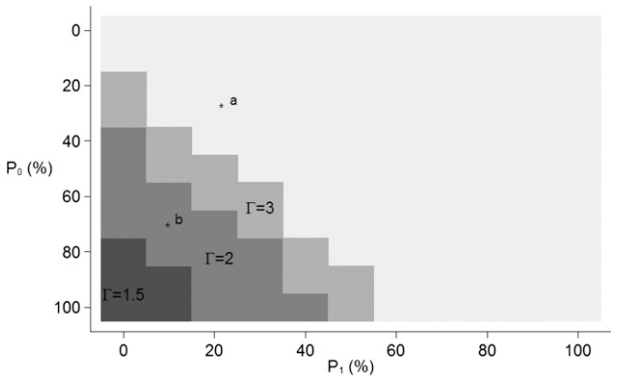

FIGURE 3. Sensitivity analysis to estimate the potential impact of unmeasured confounding.

group compared with 1.14% in the nontreated group (OR, 0.68; 95% CI, 0.54-0.85). In the analysis that included only patients started on antibiotics on day 1, the mortality OR was 0.62 (0.51-0.78). Finally, in an additional analysis restricted only to patients with a principal diagnosis of acute COPD exacerbation, the results did not change meaningfully (data not shown).

Outcomes Associated With Choice of Antibiotic: There were a number of differences in the characteristics of patients who received each of the different antibiotic regimens (Table 3). Propensity matching between paired categories of antibiotics was achieved for $>95\%$ of patients in each of the three treatment groups. The results of the covariate and propensity-adjusted models and of the propensity-matched cohort suggested that the three antibiotics were associated with similar rates of mortality and late ventilation (Table 4). Patients treated with quinolones had increased odds for 30-day readmission compared with patients treated with other antibiotics. Patients treated with macrolides had the lowest risk for developing diarrhea during hospitalization or for readmission for *C difficile* colitis, and they had slightly shorter hospital stays and lower costs compared with the other two groups.

DISCUSSION

In this study of $>50{,}000$ patients hospitalized with AE-COPD, we observed that the addition of antibiotic therapy to a treatment regimen that included systemic corticosteroids was associated with a substantial reduction in the risk of hospital death and readmission. These findings were robust to a variety of analytic approaches and in sensitivity analyses. At the same time, antibiotic choice was not associated with in-hospital mortality.

Acute exacerbations are a major contributor to the morbidity, costs, and mortality in COPD and are the

Table 3—*Selected Characteristics of Patients Hospitalized With AE-COPD Treated Initially With an Antibiotic*

Characteristic	Quinolone, n = 20,441 (49.7%)	Macrolide, n = 3,704 (9%)	Macrolide + CS, n = 8,915 (21.7%)
Patient characteristics			
Age, median (IQR),[a,b,c] y	70 (61-78)	70 (60-78)	71 (62-79)
Sex[a,c]			
Female	57.0	61.0	56.0
Race[a,b,c]			
White	76.2	74.6	77.2
Black	8.6	10.6	6.4
Hispanic	2.2	2.4	2.7
Other	13.0	12.4	13.7
Principal diagnosis[a,c]			
AE-COPD	90.0	93.1	89.4
Respiratory failure	10.0	6.9	10.6
Admissions for COPD or respiratory failure in year prior[a,b,c]			
0	80.7	79.4	82.6
1	13.3	13.8	12.3
2+	6.0	6.8	5.1
Attending specialty[a,b,c]			
Internal medicine	54.1	56.2	55.3
Family/general medicine	18.9	19.1	22.1
Pulmonology	12.4	8.8	9.1
Hospitalist	6.8	6.8	6.2
Hospital characteristics			
Number of beds[a,b,c]			
≤ 200	18.8	16.7	24.0
201-300	17.2	17.1	17.6
301-500	37.5	38.3	34.3
> 500	26.5	27.9	24.1
Population served[a,c]			
Urban	81.6	88.5	82.0
Rural	18.4	11.5	18.0
Region[a,b,c]			
South	56.1	44.2	47.8
Midwest	19.3	19.6	19.0
Northeast	12.1	20.3	20.9
West	12.5	15.9	12.4
Teaching status[a,c]			
Nonteaching	68.9	58.8	68.2
Teaching	31.1	41.2	31.8
Comorbidities			
Diabetes	26.0	25.0	26.0
Heart failure	22.0	23.0	21.0
Chronic pulmonary disease[a,c]	10.0	6.9	10.6
Obesity[c]	9.0	10.0	8.5
Renal failure	7.1	7.6	7.5
Chronic pulmonary heart disease	6.8	6.9	6.4
Alcohol abuse[a,c]	3.3	4.5	3.3
Sleep apnea	2.4	2.1	2.2
Pulmonary circulation disease	1.3	1.0	1.4
Early therapies and tests			
Anticholinergic bronchodilator[a,b]	62.0	58.0	58.0
Short-acting β_2-agonist[b,c]	80.0	79.0	76.0
Long acting β_2-agonist[b,c]	38.0	39.0	36.0
Methylxanthine bronchodilators	9.4	8.8	8.7
High-dose glucocorticoids[a,c]	91.1	87.6	90.7
Morphine[b]	7.4	7.0	6.4
Loop diuretics[b,c]	33.0	34.0	32.0
Smoking cessation medications	12.0	12.0	11.0
Sputum testing[a,b,c]	9.8	7.9	11.7
Arterial blood gas[a,c]	44.0	38.0	43.0
Brain natriuretic peptide	55.0	55.0	54.0

(Continued)

Table 3—*Continued*

Characteristic	Quinolone, n = 20,441 (49.7%)	Macrolide, n = 3,704 (9%)	Macrolide + CS, n = 8,915 (21.7%)
Patient outcomes			
In-hospital mortality[a]	1.07	0.70	0.92
Late ventilation (after day 2)	0.80	1.05	0.77
Readmission for COPD within 30 d[a, b]	5.85	4.72	4.46
Clostridium difficile readmission[a,c]	0.24	0.05	0.28
Length of stay, median (IQR),[a,b,c] d	4 (3-6)	4 (3-5)	4 (3-6)
Total cost, median (IQR),[b,c] US$	4,705 (3,367-6,900)	4,733 (3,339-6,689)	5,057 (3,634-7,338)

CS = cephalosporin. See Table 1 legend for expansion of other abbreviations.

[a]*P* value for quinolone vs macrolides < .05.

[b]*P* value for quinolone vs macrolides plus cephalosporins < .05.

[c]*P* value for macrolides vs macrolides plus cephalosporins < .05.

most frequent cause of death.[17] Antibiotics are widely used for AE-COPD, although recommendations from published guidelines are often inconsistent and vague.[12,18] Clinical studies of adequate design and quality that assessed the optimal approach of antibiotic use in AE-COPD are relatively few, and this has undoubtedly contributed to the lack of consensus. Data from RCTs and meta-analyses provide some evidence that antibiotics are clinically beneficial and reduce in-hospital mortality in moderate and severe episodes of exacerbation.[19-21] However, most of these RCTs were performed prior to the routine use of corticosteroids, the majority enrolled a small number of patients, and few were conducted in hospitalized patients. More importantly, in most of these studies patients on steroids were excluded.[13]

Because bacterial pathogens are implicated in up to 60% of acute exacerbations,[22,23] one would think that in moderate to severe AE-COPD there would be additive benefits when both steroids and antibiotics are used. The only recent RCT that studied the effectiveness of an antibiotic (doxycycline) added to bronchodilators and systemic steroids concluded that the antibiotic treatment achieved clinical and microbiologic success at 10 days but did not improve clinical outcomes at 30 days.[24] However, the study was underpowered to detect a mortality difference, and increasing resistance of bacteria to doxycycline might have been one reason for the lack of difference in outcomes. In this context, our study answered an important question regarding the benefit of early antibiotics treatment in patients hospitalized with AE-COPD when systemic corticosteroids are coadministered. We observed a larger mortality benefit than in a prior study done by our group, which used the same database but assessed the role of antibiotics in patients hospitalized with COPD irrespective of systemic steroid use.[25] By restricting our analysis to patients who

Table 4—*Compared Outcomes of Patients Treated With the Three Antibiotic Regimens for AE-COPD*

Outcome	Quinolones vs Macrolides	Quinolones vs Macrolides + CS	Macrolides vs Macrolides + CS
Mortality			
Unadjusted	1.51 (1.01-2.27)	1.15 (0.88-1.51)	0.76 (0.50-1.17)
Adjusted for covariates	1.28 (0.85-1.92)	1.22 (0.93-1.6)	0.97 (0.63-1.49)
Adjusted for covariates and propensity score	1.29 (0.86-1.95)	1.21 (0.92-1.6)	0.90 (0.58-1.41)
Matched cohort, adjusted for unbalanced variables	1.40 (0.81-2.43)	1.35 (0.93-1.95)	1.04 (0.59-1.86)
Instrumental variable analysis	2.14 (0.9-5.07)	1.62 (0.82-3.21)	0.80 (0.23-2.79)
Late ventilation			
Unadjusted	0.86 (0.59-1.25)	1.11 (0.82-1.5)	1.27 (0.85-1.9)
Adjusted for covariates	0.86 (0.60-1.23)	1.06 (0.78-1.44)	1.45 (0.96-2.18)
Adjusted for covariates and propensity score	0.86 (0.59-1.24)	1.06 (0.78-1.46)	1.43 (0.95-2.16)
Matched cohort, adjusted for unbalanced variables	0.64 (0.37-1.10)	1.26 (0.85-1.86)	1.51 (0.91-2.51)
Instrumental variable analysis	0.66 (0.18-2.46)	0.86 (0.56-1.31)	0.46 (0.16-1.28)
COPD readmissions			
Unadjusted	1.26 (1.07-1.47)	1.34 (1.18-1.52)	1.06 (0.88-1.28)
Adjusted for covariates	1.29 (1.09-1.51)	1.31 (1.15-1.49)	1.03 (0.85-1.24)
Adjusted for covariates and propensity score	1.30 (1.10-1.53)	1.31 (1.15-1.48)	1.01 (0.83-1.23)
Matched cohort, adjusted for unbalanced variables	1.25 (1.02-1.54)	1.19 (1.04-1.38)	0.99 (0.79-1.24)
Instrumental variable analysis	1.18 (0.84-1.66)	1.37 (1-1.87)	0.89 (0.54-1.47)

Data presented as OR (95% CI).

were treated with steroids, it is likely that we selected for a higher-risk group of patients. One possible explanation for the larger effect estimate we observed in this study is that there is heterogeneity of treatment effectiveness according to initial severity of illness, with benefit higher among those with more severe disease. Additionally, it is possible that when steroids are administered without antibiotics, their immunosuppressive proprieties may increase mortality risk. Our results are similar to those reported by Roede el al[26] in a study among 18,928 outpatients, which found that treatment with corticosteroids and antibiotics compared with oral corticosteroids alone was associated with a decrease in mortality and the risk of a new exacerbation.

An interesting finding of this study is that relative to white patients, black patients were less likely to be treated with antibiotics. Although data are limited, published studies showed that black patients are less likely to receive influenza vaccination and smoking cessation counseling.[27-30] In contrast to a large body of literature highlighting racial and ethnic differences in management and outcomes for other respiratory diseases, such as asthma and lung cancer, there is a notable lack of data regarding racial disparities in COPD, and further research in this area is needed.[31,32]

Most exacerbations of COPD are treated without obtaining sputum bacteriology, and the choice of antibiotic is generally made empirically. At the same time, there is limited evidence supporting the optimal empirical regimen for exacerbations of COPD.[33-35] Whether the antibiotic choice is important in AE-COPD is still debatable; the results of our analysis do not strongly support one antibiotic over the other. As has been demonstrated in other studies, patients treated with macrolides were less likely than those treated with fluoroquinolone to be readmitted with *C difficile* colitis[36,37] and had lower cost and length of stay, but the differences were small. Well-designed RCTs would help resolve this question; however, our results suggest the trials would need to be extremely large.

Our study has a number of limitations. First, although we controlled for a large number of potential confounders, including treatments and diagnostic tests that might serve as proxies for disease severity, and although we used several analytic strategies, we cannot exclude the possibility that our results reflect residual confounding by indication. Nevertheless, one might have expected that any selection bias would have favored those patients who did not receive antibiotic therapy. Second, we did not have access to physiologic measures, such as oxygen saturation or pulmonary function tests. Although it is impossible to eliminate the threat of residual selection bias, our sensitivity analyses demonstrated that our results were robust in the face of even a strong unmeasured confounder. Third, our study was not designed to develop a risk stratification approach in deciding the optimal antibiotic treatment or to identify a group of patients who might not benefit from treatment. Fourth, we were not able to assess the impact of antibiotic use on selection of resistant bacterial strains. Finally, our study is limited to inpatient events and readmission to the index hospital and for patients hospitalized in the United States.

Most important, our study should not be interpreted as evidence for indiscriminate prescribing of antibiotics to any hospitalized patient with AE-COPD. We did not have clinical data and could not assess when antibiotics were used inappropriately. The benefit of antibiotics should not be generalized to all subgroups of patients, and treating only certain patients is still preferable.

In conclusion, when added to a treatment regimen that includes systemic corticosteroids, the addition of antibiotics is associated with reduced inpatient mortality and lower risk of readmission within 30 days. We found little difference in the outcomes associated with three common antibiotic treatment choices. Our results suggest that antibiotics in addition to steroids are effective in improving short-term outcomes for patients hospitalized with AE-COPD.

Acknowledgments

Authors contributions: Dr Stefan had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Dr Stefan: contributed to study conception and design, analysis and interpretation of data, drafting the manuscript for important intellectual content, and reading and approving the final manuscript.
Dr Rothberg: contributed to study conception and design, analysis and interpretation of data, drafting the manuscript for important intellectual content, and reading and approving the final manuscript.
Dr Shieh: contributed to analysis and interpretation of data and reading and approving the final manuscript.
Dr Pekow: contributed to study conception and design, analysis and interpretation of data, drafting the manuscript for important intellectual content, and reading and approving the final manuscript.
Dr Lindenauer: contributed to study conception and design, analysis and interpretation of data, drafting the manuscript for important intellectual content, and reading and approving the final manuscript.
Financial/nonfinancial disclosures: The authors have reported to *CHEST* that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.
Role of sponsors: The content of this publication is solely the responsibility of the authors and does not represent the official views of National Institutes of Health or the National Cancer Institute.

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