Antibiotic Therapy and Treatment Failure in Patients Hospitalized for Acute Exacerbations of Chronic Obstructive Pulmonary Disease

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Context Guidelines recommend antibiotic therapy for acute exacerbations of chronic obstructive pulmonary disease (COPD), but the evidence is based on small, heterogeneous trials, few of which include hospitalized patients.

Objective To compare the outcomes of patients treated with antibiotics in the first 2 hospital days with those treated later or not at all.

Design, Setting, and Patients Retrospective cohort of patients aged 40 years or older who were hospitalized from January 1, 2006, through December 31, 2007, for acute exacerbations of COPD at 413 acute care facilities throughout the United States.

Main Outcome Measures A composite measure of treatment failure, defined as the initiation of mechanical ventilation after the second hospital day, inpatient mortality, or readmission for acute exacerbations of COPD within 30 days of discharge; length of stay, and hospital costs.

Results Of 84 621 patients, 79% received at least 2 consecutive days of antibiotic treatment. Treated patients were less likely than nontreated patients to receive mechanical ventilation after the second hospital day (1.07%; 95% confidence interval [CI], 1.06%-1.08% vs 1.80%; 95% CI, 1.78%-1.82%), had lower rates of inpatient mortality (1.04%; 95% CI, 1.03%-1.05% vs 1.59%; 95% CI, 1.57%-1.61%), and had lower rates of readmission for acute exacerbations of COPD (7.91%; 95% CI, 7.89%-7.94% vs 8.79%; 95% CI, 8.74%-8.83%). Patients treated with antibiotic agents had a higher rate of readmissions for *Clostridium difficile* (0.19%; 95% CI, 0.187%-0.193%) than those who were not treated (0.09%; 95% CI, 0.086%-0.094%). After multivariable adjustment, including the propensity for antibiotic treatment, the risk of treatment failure was lower in antibiotic-treated patients (odds ratio, 0.87; 95% CI, 0.82-0.92). A grouped treatment approach and hierarchical modeling to account for potential confounding of hospital effects yielded similar results. Analysis stratified by risk of treatment failure found similar magnitudes of benefit across all subgroups.

Conclusion Early antibiotic administration was associated with improved outcomes among patients hospitalized for acute exacerbations of COPD regardless of the risk of treatment failure.

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CHRONIC OBSTRUCTIVE PULMONARY disease (COPD) affects at least 12 million US residents and is the fourth leading cause of death in the United States.[1] Acute exacerbations of COPD are responsible for more than 600 000 hospitalizations annually, resulting in direct costs of more than $20 billion.[2] Respiratory infections appear to be the most frequent cause of COPD exacerbation, accounting for 50% to 80% of all exacerbations.[3-5] Although as many as two-thirds of these may be viral infections, COPD treatment guidelines nevertheless recommend antibiotic treatment for patients with purulent sputum and either an increase in sputum production or an increase in dyspnea.[2,6-9] The evidence supporting these recommendations comes from 11 small randomized trials demonstrating that antibiotics can reduce short-term mortality and treatment failure.[10] Patients with more severe disease, especially those receiving mechanical ventilation, appear to benefit the most.[11]

For a condition as common as acute exacerbations of COPD, evidence from randomized trials is surprisingly limited. Only 917 patients have been en-

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rolled in randomized trials, and all but 1 of these studies were conducted before 1992.[10] Little information is available to inform hospital prescribing or to select those patients most likely to benefit from therapy. To examine the association between use of antibiotics and outcomes among patients hospitalized for COPD, we conducted a retrospective cohort study in a national sample of hospitals and compared the risk of treatment failure, length of stay, and costs among patients who did or did not receive initial treatment with antibiotics.

METHODS

Setting and Patients

We conducted a retrospective cohort study of all patients hospitalized from January 1, 2006, through December 31, 2007, for acute exacerbations of COPD at 413 acute care facilities in the United States that participated in Premier's Perspective, a database developed for measuring quality and health care utilization. Participating hospitals represent all regions of the United States and are primarily small- to medium-sized nonteaching hospitals located mostly in urban areas. In addition to the information contained in the standard hospital discharge file such as *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) codes, hospital and physician information, Perspective includes a date-stamped log of all billed items, including diagnostic tests, medications, and other treatments, for individual patients. Approximately 75% of participating hospitals submit cost data; the rest submit calculated costs based on each hospital's specific cost to charge ratio.

Patients were included if they had a principal diagnosis indicating an acute exacerbation of COPD (*ICD-9-CM* codes 491.21, 491.22, 493.22) or emphysema (*ICD-9-CM* code 492.8) or a principal diagnosis of respiratory failure (*ICD-9-CM* codes 518.81, 518.84) paired with secondary diagnosis of COPD with acute exacerbations or emphysema. Other COPD codes not indicating an acute exacerbation were not included. To limit the misclassification of COPD and asthma patients, we restricted our study to patients aged 40 years or older.[12] Because mechanical ventilation initiated after hospital day 2 was an outcome of interest, we excluded patients admitted directly to the intensive care unit (ICU). 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 of fewer than 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; patients discharged within the past 30 days, and those whose attending physicians were not internists, family practitioners, hospitalists, pulmonologists, or intensivists.

The study received an institutional review board exemption because data we received from Premier does not contain any identifiable patient information and is not considered human subjects research under federal guidelines.

Data Elements

For each patient, we extracted age, sex, race, marital and insurance status, principal diagnosis, comorbidities, and specialty of the attending physician. Patients self-report race at the time they are admitted to the hospital. Comorbidities were identified from *ICD-9-CM* 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.[13] In addition, to better assess disease severity, we recorded the presence of chronic pulmonary heart disease and the number of admissions for COPD during the 12 months before the index admission.

For each patient, we identified pharmacy or diagnostic charges for interventions that were guideline recommended (β-adrenergic and anticholinergic bronchodilators, steroids, and noninvasive positive pressure ventilation), those that are not recommended or are of uncertain benefit (methylxanthine bronchodilators, spirometry/pulmonary function testing, mucolytic medications, chest physiotherapy, sputum testing), and drugs or tests associated with severe exacerbations or end-stage COPD (loop diuretics, morphine, and arterial blood gas testing). Hospitals were categorized by region (Northeast, South, Midwest, or West), bed size, setting (urban vs rural), and teaching status.

Antibiotic Treatment and Outcome Variables

Antibiotic treatment, our main predictor variable, was defined as a minimum of 2 consecutive days of an antibiotic for acute exacerbations of COPD initiated on hospital day 1 or 2, including time spent in the emergency department. Antibiotics included first-, second-, and third-generation cephalosporins, quinolones, macrolides, tetracyclines, trimethoprim-sulfamethoxazole, and amoxicillin with or without clavulanic acid. Patients receiving other classes of antibiotics or who received only a single day of treatment on hospital day 1 or 2 were excluded from the analysis. For the purposes of the analysis, all antibiotics were considered equivalent, regardless of class, dose, duration, or route of administration. Patients whose antibiotic treatment started later than hospital day 2 were grouped with those who were not treated.

Adapting a framework used in earlier clinical trials,[14] our primary outcome was a composite measure of treatment failure, defined as the initiation of mechanical ventilation after hospital day 2, in-hospital mortality, or readmission for COPD within 30 days of discharge. Secondary outcomes included hospital costs and length of stay, as well as allergic reactions, defined by *ICD-9* codes, diarrhea and antibiotic-associated diarrhea, defined as treatment with either metronidazole or oral vancomycin initiated after hospital day 3 or readmission within 30 days for diarrhea and *Clostridium difficile*. To examine whether the association between antibiotic treatment and outcomes

varied by sputum production, dyspnea, or illness severity, we analyzed our results stratified by whether the patient underwent sputum culture or had an arterial blood gas measurement in the first 2 days, as well as the predicted risk of treatment failure in tertiles.

Statistical Analysis

Summary statistics were computed using frequencies and percentages for categorical variables and means, standard deviations, medians, and interquartile range for continuous variables. Associations between early antibiotic treatment and patient and hospital characteristics were assessed using χ^2 tests for categorical variables and z tests or Kruskal-Wallis tests for continuous variables.

We developed a series of multivariable models to evaluate the association between early antibiotic therapy and treatment failure, length of stay, and total cost. Length of stay and cost were trimmed at 3 standard deviations above the mean, and the natural log-transformed values were modeled due to extreme positive skew. To reduce the threat of selection bias, a propensity score or predicted probability of early antibiotic treatment was developed using all patient characteristics, other early treatments and tests, comorbidities, hospital and physician characteristics, and selected interaction terms.

In addition, a model to predict the risk of treatment failure risk was developed using the same strategy, while excluding information about antibiotic treatment. Logit link generalized estimating equations models were used for treatment failure and normal link models for length of stay and cost, adjusting for within-hospital correlation. The results of unadjusted, covariate-adjusted, propensity score, and covariate-adjusted models were compared. In addition, nontreated patients were matched to treated patients of similar propensity using a greedy 5 to 1 digit matching algorithm.[15] Conditional logistic models were developed using this propensity-matched subsample of patients, ad-

Table 1. Characteristics of Patients Hospitalized With Acute Exacerbations of Chronic Obstructive Pulmonary Disease

	No. (%) of Patients				
		Antibiotic Treatment Status			
		All Patients		Propensity-Matched[a]	
Characteristic	Overall (N = 84 621)	Early (n = 67 229)	Late/None (n = 17 392)	Early (n = 17 052)	Late/None (n = 17 052)
Age, median (IQR), y	69 (60-78)	69 (60-78)	70 (60-79)	70 (61-79)	70 (61-79)
Female sex	51 256 (61)[b]	40 502 (60)[b]	10 754 (62)[b]	10 635 (62)	10 550 (62)
Race/ethnicity					
White	60 232 (71)	48 975 (73)	11 257 (65)	11 730 (69)	11 110 (65)
Black	9914 (12)	7153 (11)	2761 (16)	2408 (14)	2626 (15)
Hispanic	2746 (3)	2201 (3)	545 (3)	598 (4)	535 (3)
Other	11 729 (14)	8900 (13)	2829 (16)	2316 (14)	2781 (16)
Primary insurance					
Medicare traditional	51 845 (61)	41 140 (61)	10 705 (62)	10 578 (62)	10 524 (62)
Medicare managed care	7904 (9)	6236 (9)	1668 (10)	1770 (10)	1634 (10)
Medicaid	7680 (9)	6087 (9)	1593 (9)	1533 (9)	1537 (9)
Private	13 441 (16)	10 820 (16)	2621 (15)	2510 (15)	2575 (15)
Self-pay/uninsured/other	3751 (4)	2946 (4)	805 (5)	661 (4)	782 (5)
Principal diagnosis					
Acute exacerbation of COPD	76 505 (90)	60 927 (91)	15 578 (90)	15 211 (89)	15 343 (90)
Respiratory failure	8116 (10)	6302 (9)	1814 (10)	1841 (11)	1709 (10)
Admissions for COPD or respiratory failure in year prior, No.					
0	61 227 (72)	49 112 (73)	12 115 (70)	11 848 (69)	11 885 (70)
1	13 552 (16)	10 640 (16)	2912 (17)	2864 (17)	2871 (17)
≥2	9842 (12)	7477 (11)	2365 (14)	2340 (14)	2296 (13)
Comorbidities[c]					
Hypertension	51 455 (61)	40 514 (60)	10 941 (63)	10 755 (63)	10 683 (63)
Diabetes	24 780 (29)	19 316 (29)	5464 (31)	5511 (32)	5306 (31)
Heart failure	20 433 (24)	15 089 (22)	5344 (31)	5399 (32)	5137 (30)
Depression	12 766 (15)	10 148 (15)	2618 (15)	2649 (16)	2578 (15)
Deficiency anemias	10 944 (13)	8325 (12)	2619 (15)	2556 (15)	2549 (15)
Hypothyroidism	10 328 (12)	880 (12)	2248 (13)	2321 (14)	2211 (13)
Obesity	10 235 (12)	7767 (12)	2468 (14)	2458 (14)	2375 (14)
Renal failure	6687 (7.9)	4919 (7.3)	1768 (10)	1813 (11)	1684 (10)
Peripheral vascular disease	5910 (7.0)	4564 (6.8)	1346 (7.7)	1335 (7.8)	1321 (7.7)
Neurological disorders	5272 (6.2)	4120 (6.1)	1152 (6.6)	1140 (6.7)	1138 (6.7)
Valvular disease	5246 (6.2)	3910 (5.8)	1336 (7.7)	1274 (7.5)	1279 (7.5)
Psychoses	3939 (4.7)	3046 (4.5)	893 (5.1)	871 (5.1)	877 (5.1)
Alcohol abuse	2954 (3.5)	2290 (3.4)	664 (3.8)	651 (3.8)	640 (3.8)
Sleep apnea	2528 (3.0)	1943 (3.0)	585 (3.0)	609 (4.0)	560 (3.0)
Rheumatoid arthritis or collagen vascular	2334 (2.8)	1862 (2.8)	472 (2.7)	480 (2.8)	466 (2.7)
Solid tumor without metastasis	1923 (2.3)	1519 (2.3)	404 (2.3)	381 (2.2)	395 (2.3)
Weight loss	1887 (2.2)	1425 (2.1)	462 (2.7)	473 (2.8)	444 (2.6)
Drug abuse	1879 (2.2)	1401 (2.1)	478 (2.7)	402 (2.4)	454 (2.7)
Pulmonary circulation disease	1400 (1.7)	1025 (1.5)	375 (2.2)	377 (2.2)	337 (2.0)
Liver disease	1136 (1.3)	867 (1.3)	269 (1.5)	240 (1.4)	255 (1.5)
Metastatic cancer	808 (1.0)	609 (0.9)	199 (1.1)	193 (1.1)	190 (1.1)
Paralysis	799 (0.9)	622 (0.9)	177 (1.0)	169 (1.0)	172 (1.0)
Chronic blood loss anemia	487 (0.6)	357 (0.5)	130 (0.7)	140 (0.8)	126 (0.7)

Abbreviations: COPD, chronic obstructive pulmonary disease; IQR, interquartile range.
[a] Each patient without initial antibiotic treatment matched on propensity with 1 antibiotic-treated patient 17 052 of 17 392 (98%) matched.
[b] Has 1 missing value.
[c] Additional comorbidities evaluated in models but not reported in tables include lymphoma, AIDS, polycythemia.

justed for persistent imbalance of covariates. An additional analysis for treatment failure was conducted, excluding cases of asthma plus COPD with acute exacerbation (*ICD-9* code 493.22).

Table 2. Setting and Treatment of Patients With Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Characteristic	No. (%) of Participants				
		Antibiotic Treatment Status			
		All Participants		Propensity-Matched[a]	
	Overall (N = 84 621)	Early (n = 67 229)	Late/None (n = 17 392)	Early (n = 17 052)	Late/None (n = 17 052)
No. of beds					
0-200 (n = 144)	16 048 (19)	13 163 (20)	2885 (17)	2993 (18)	2834 (17)
201-300 (n = 79)	14 431 (17)	11 510 (17)	2921 (17)	2827 (17)	2898 (17)
301-500 (n = 126)	30 924 (37)	24 835 (37)	6089 (35)	5891 (35)	5989 (35)
≥501 (n = 64)	23 218 (27)	17 721 (26)	5497 (32)	5341 (31)	5331 (31)
Rural setting (n = 95)	14 524 (17)	12 484 (19)	2040 (12)	2241 (13)	2014 (12)
Region					
South (n = 201)	43 639 (52)	35 281 (52)	8358 (48)	7963 (47)	8227 (48)
Midwest (n = 77)	16 659 (20)	13 415 (20)	3244 (19)	3258 (19)	3145 (18)
Northeast (n = 54)	14 563 (17)	10 590 (16)	3973 (23)	3927 (23)	3889 (23)
West (n = 64)	9760 (12)	7943 (12)	1817 (10)	1904 (11)	1791 (11)
Teaching hospital (n = 111)	29 016 (34)	22 023 (33)	6993 (40)	6759 (40)	6781 (40)
Attending specialty					
Internal medicine or hospitalist	55 122 (65)	44 109 (66)	11 013 (63)	10 899 (64)	10 830 (64)
Family or general medicine	18 213 (22)	14 576 (22)	3637 (21)	3657 (21)	3560 (21)
Pulmonologist	10 902 (13)	8305 (12)	2597 (15)	2436 (14)	2518 (15)
Critical care or intensivist	384 (0)	239 (0)	145 (1)	60 (0)	144 (1)
Admission source					
Emergency department	67 434 (80)	53 711 (80)	13 723 (79)	13 484 (79)	13 543 (79)
Non–health care facility	14 421 (17)	11 452 (17)	2969 (17)	2924 (17)	2909 (17)
Transfer from health care facility	1262 (1)	949 (1)	313 (2)	320 (2)	289 (2)
Transferred from court or jail or not available	1504 (2)	1117 (2)	387 (2)	324 (2)	311 (2)
Early therapies and tests[b]					
Steroids					
None	9057 (11)	5961 (9)	3096 (18)	3130 (18)	2815 (17)
Intravenous	68 899 (81)	56 467 (84)	12 432 (71)	11 882 (70)	12 405 (73)
Oral	6665 (8)	4801 (7)	1864 (11)	2040 (12)	1832 (11)
Anticholinergic bronchodilator and/or short-acting β_2 agonist	64 990 (77)[c]	53 168 (79)[c]	11 822 (68)[c]	12 721 (75)	11 712 (69)
Long-acting β_2-agonist	31 370 (37)[c]	25 546 (38)[c]	5824 (34)[c]	6470 (38)	5756 (34)
Noninvasive ventilation	5692 (7)	4411 (7)	1281 (7)	1362 (8)	1250 (7)
Methylxanthine bronchodilators	8511 (10)	6979 (10)	1532 (9)	1715 (10)	1517 (9)
Mucolytic medications	1634 (2)	1394 (2)	240 (1)	281 (2)	234 (1)
Chest physiotherapy	2029 (2)	1805 (3)	224 (1)	210 (1)	224 (1)
Sputum test	6697 (8)	6201 (9)	496 (3)	495 (3)	496 (3)
Spirometry	3833 (5)	2916 (4)	917 (5)	1069 (6)	851 (5)
Arterial blood gas	36 517 (43)	29 860 (44)	6657 (38)	7023 (41)	6509 (38)
Brain natriuretic peptide tests	46 303 (55)	36 831 (55)	9472 (54)	10 016 (59)	9249 (54)
Morphine	6700 (8)	5261 (8)	1439 (8)	1553 (9)	1390 (8)
Loop diuretics	29 563 (35)	22 827 (34)	6736 (39)	7311 (43)	6550 (38)

[a] Each patient without initial antibiotic treatment matched on propensity with 1 antibiotic-treated patient 17 052 of 17 392 (98%) matched.
[b] Early indicates that treatment was initiated by day 2 of hospital stay.
[c] Has 54 missing values from hospitals not reporting bronchodilators.

To reduce the threat of residual selection bias due to unmeasured confounders not directly addressed through propensity adjustment,[16] we used a variation of the instrumental variable approach, in which the actual treatment for each patient is replaced by the hospital treatment rate.[17] Grouping treatment at the hospital level bypasses the issue of confounding by indication, yet in contrast to a traditional ecological analysis accounts for patient-level covariates and outcomes. Finally, in sensitivity analyses, we ran hierarchical models as an alternative method to account for potential effects of hospital clustering.

For each model, adjusted odds ratios (ORs) for treatment failure, or ratio of length of stay and cost with associated 95% confidence intervals (CIs) for antibiotic treatment were calculated. All significance tests were 2-sided, with a .05 significance level. The study was powered to detect a difference in rare outcomes. For example, with more than 84 000 cases and approximately 80% in 1 group, we had more than 85% power to detect a mortality difference from 1.0% to 1.3%. All analyses were performed using SAS version 9.1 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Of the 213 917 admissions for acute exacerbations of COPD during the study period, 84 621 were included in our sample (eFigure available at http://www.jama.com). The median age was 69 years; 61% were women and 71% were white (TABLE 1). Ninety percent of patients had a principal diagnosis of obstructive chronic bronchitis with acute exacerbation and 10% had respiratory failure. The most common comorbid conditions were hypertension, diabetes mellitus, and congestive heart failure. Twenty-eight percent had been admitted at least once in the preceding 12 months. In-hospital mortality was 1.2% while 10% of patients experienced the composite measure of treatment failure. Mean length of stay was 4.8 days.

Seventy-nine percent of patients received at least 2 consecutive days of an-

tibiotic treatment beginning on day 1 or 2 of hospitalization, most commonly with a quinolone (60%), a cephalosporin (37%), or a macrolide (38%). An additional 6% of patients received antibiotic therapy at some point during hospitalization and were included with the nontreated patients. Compared with patients who did not receive initial treatment with an antibiotic, treated patients were younger, more likely to have private insurance, and to be white. They were more likely to be from hospitals that were smaller, southern, rural, and nonteaching (TABLE 2). Treated patients also had less comorbidity and had fewer admissions in the preceding 12 months. They were more likely to receive guideline concordant interventions, including steroids and bronchodilators, to have an arterial blood gas, and to receive guideline discordant interventions, including methyxanthine and mucolytic agents and chest physiotherapy. They were less likely to receive loop diuretics, morphine, and noninvasive positive pressure ventilation.

Compared with patients not receiving antibiotics in the first 2 days, antibiotic-treated patients were less likely to be receive mechanical ventilation after the second hospital day (1.07% vs 1.80%), had lower inpatient mortality (1.04% vs 1.59%), a lower incidence of treatment failure (9.77% vs 11.75%), and lower rates of readmission for acute exacerbations of COPD (7.91% vs 8.79%; TABLE 3). Antibiotic-treated patients had somewhat fewer allergic reactions (0.13% vs 0.20%) but a higher incidence of readmissions for *C difficile* diarrhea (0.19% vs 0.09%). Patients treated with and without antibiotics had similar lengths of stay, but patients treated with antibiotics had lower costs (Table 3).

Propensity-matching balanced many of the differences in comorbidities among the 2 groups of patients (Table 1), but compared with those who did not receive antibiotics in the first 2 hospital days, those treated with antibiotics were still more likely to be white; from rural hospitals; more likely to be insured by Medicare; had more congestive heart failure, diabetes, and renal failure; and received more methyxanthines, short- and long-acting bronchodilators, steroids, morphine, and loop diuretics. They were also more likely to have an arterial blood gas analysis, brain natriuretic protein tests, and spirometry. Most of these differences were clinically nonsignificant in magnitude, but the study's large sample size rendered the differences statistically significant.

Table 3. Unadjusted Outcomes by Antibiotic Exposure

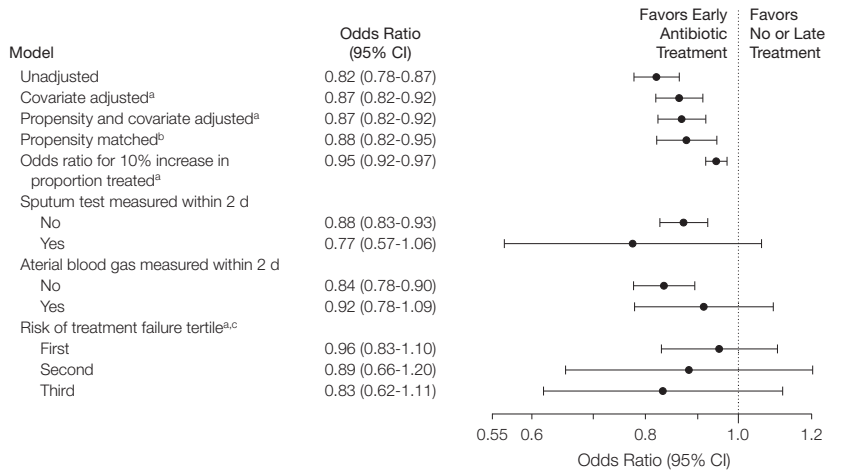
Patient Outcomes	No. (%) [95% Confidence Interval] Early Antibiotics (n = 67 229)	No/Late Antibiotics (n = 17 392)	*P* Value
Late ventilation, after day 2	721 (1.07) [1.06-1.08]	313 (1.80) [1.78-1.82]	<.001
In-hospital mortality	700 (1.04) [1.03-1.05]	277 (1.59) [1.57-1.61]	<.001
Treatment failure[b]	6571 (9.77) [9.75-9.80]	2043 (11.75) [11.70-11.79]	<.001
Allergic reaction	88 (0.13) [0.13-0.13]	35 (0.20) [0.19-0.19]	.03
Clostridium difficile testing after hospital day 2	1172 (1.74) [1.73-1.75]	280 (1.61) [1.59-1.63]	.23
Antibiotics for presumed *C difficile* diarrhea	603 (0.90) [0.89-0.90]	147 (0.85) [0.83-0.86]	.52
Diarrhea diagnosis	1124 (1.67) [1.66-1.68]	293 (1.68) [1.67-1.70]	.91
Readmission within 30 d			
COPD[a]	5321 (7.91) [7.89-7.94]	1528 (8.79) [8.74-8.83]	<.001
Diarrhea[a]	152 (0.23) [0.22-0.23]	22 (0.13) [0.12-0.13]	.01
C difficile diarrhea[a]	129 (0.190) [0.187-0.193]	15 (0.090) [0.086-0.094]	.003
	Median (Interquartile Range)		
Length of stay, d			
All patients	4 (3-6)	4 (3-6)	.16[c]
Excluding patients with values >3 SDs from overall patient mean	4 (3-6)	4 (3-6)	.013
Total cost, US $[d]			
All patients	4925 (3496-7261)	5084 (3547-7652)	<.001[c]
Excluding patients with values >3 SDs from overall patient mean	4881 (3479-7135)	5012 (3522-7451)	<.001

Abbreviation: COPD, chronic obstructive pulmonary disease.
[a] Among 83 644 survivors.
[b] Death, late ventilation, 30-d COPD readmission.
[c] Calculated by Kruskal-Wallis test.
[d] Excludes 760 with missing values.

Antibiotic Use and Treatment Failure—Results of Multivariable Analyses

In the base analysis accounting only for within-hospital clustering, patients treated with antibiotics had an OR for treatment failure of 0.82 (95% CI, 0.78-0.87) compared with untreated patients (FIGURE 1). Adjustment for propensity for antibiotic treatment and other covariates attenuated the apparent effect of antibiotics by a small amount (OR, 0.87; 95% CI, 0.82-0.92). Results were similar using a hierarchical model (eTable available at http://www.jama.com). In the propensity-matched sample, the OR was similar: 0.88 (95% CI, 0.82-0.95). Hospital prescribing rates varied from 0% to 100%, although most hospitals had rates between 65% and 95% (FIGURE 2). When individual patients were assigned a probability of initial treatment with antibiotics equal to the hospital rate where they received care, each 10% increase in the hospital rate of treatment (eg, from 70% to 80%) was associated with a 5% reduction in the odds of treatment failure (OR, 0.95; 95% CI, 0.92-0.97). Removing patients with a diagnosis code of asthma plus COPD with acute exacerbation (*ICD-9* code 493.22) strengthened the covariate-adjusted association be-

Figure 1. Treatment Failure for Early Antibiotic Treatment vs Late or No Treatment



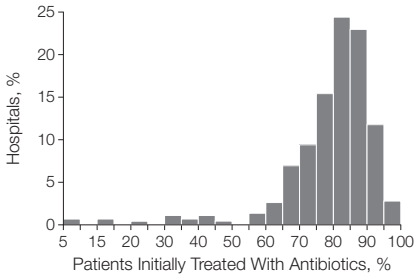
Subgroup analyses are presented according to whether patients had a sputum test or arterial blood gas measurement on hospital day 1 or 2 and also by risk tertile for treatment failure.

[a] Covariates include age group, sex, insurance, respiratory failure as a principle diagnosis, attending physician specialty, admission source, prior year admissions for acute exacerbation chronic obstructive pulmonary disease, region, chronic pulmonary heart disease, hypertension, heart failure, pulmonary circulation disease, metastatic cancer, arthritis, obesity, weight loss, deficiency anemia, hypothyroid, depression, psychoses, alcohol abuse, and day 1 or 2 initiation of long-acting β_2 agonists, bilevel positive airway pressure or continuous positive airway pressure, methylxanthine bronchodilators, oral or intravenous steroids, morphine, loop diuretics, arterial blood gas measurements, brain natriuretic peptide, pulmonary function tests, and selected interaction terms.

[b] Covariates include race, insurance status, respiratory failure as principal diagnosis, attending physician specialty, region, population served, chronic pulmonary heart disease, heart failure, diabetes, hypothyroid, renal failure, drug abuse, and day 1 or 2 initiation of anticholinergic or short-acting β_2 agonists, long-acting β_2 agonists, methylxanthine bronchodilators, bilevel positive airway pressure or continuous positive airway pressure, oral or intravenous steroids, morphine, loop diuretics, mucolytic medications, arterial blood gases, brain natriuretic peptide, and pulmonary function tests.

[c] Risk of treatment failure tertiles are first: 0.008-0.059; second: 0.060-0.102; third: 0.103-0.838.

Figure 2. Antibiotic Treatment in the Hospital Sample



tween antibiotic use and treatment failure (OR, 0.85; 95% CI, 0.80-0.91).

We also explored whether the association between antibiotic administration and outcome varied according to disease severity (indicated by risk of treatment failure), increased or purulent sputum (indicated by sputum culture on hospital day 1 or 2), or severe dyspnea (indicated by an arterial blood gas measurement on hospital day 1 or 2). The OR for treatment failure comparing patients who did and did not receive initial antibiotics, stratified by tertile of treatment failure from lowest to highest risk, was 0.96 for patients at lowest risk, 0.89 for those at intermediate risk, and 0.83 for those at highest risk ($P = .08$ for trend). There were no statistical differences in the effect of antibiotic treatment on patients who received early sputum culture compared with those who did not (OR, 0.77 vs OR, 0.88; $P = .41$) or those who had an early arterial blood gas measurement compared with those who did not (OR, 0.92 vs OR, 0.84; $P = .09$).

Costs and Length of Stay

In multivariable analysis, the association between antibiotic use and costs and length of stay were less consistent than they were for treatment failure. In unadjusted analyses, the median antibiotic use was $4925 (interquartile range, $3496-$7261) for those treated with antibiotics vs $5084 (interquartile range, $3547-$7652) for those who were not treated with antibiotics (Table 3). However, in models accounting for within-hospital correlation and in covariate and propensity-adjusted models, the antibiotic group had higher costs than the nonantibiotic group (FIGURE 3). This difference was also seen in the propensity-adjusted model but was not significant in the propensity-matched model. A similar pattern was seen for length of stay.

COMMENT

In this observational study of 84 621 patients admitted to 413 hospitals for acute exacerbation of COPD, the administration of antibiotics was associated with a 13% decrease in the risk of treatment failure. There was also a decrease in inpatient mortality and late mechanical ventilation. Antibiotic use was not associated with an increase in allergic reactions or treatment for antibiotic-associated diarrhea, but it was associated with readmission for diarrhea and *C difficile*. Moreover, our results do not support restriction of antibiotics to hospitalized patients with purulent sputum and increased sputum production or dyspnea.

Knowledge about the effectiveness of antibiotics in the management of acute exacerbations of COPD remains limited by the lack of strong evidence. Recommendations contained in current guidelines were initially derived from a 1995 meta-analysis containing only 265 inpatients.[18] A more recent meta-analysis identified 9 studies involving inpatients, including 4 that measured short-term mortality and 4 that measured treatment failure.[10] The mortality analysis was heavily influenced by a single Tunisian study of 93 ICU patients showing a 78% reduction in mortality among patients treated with antibiotics.[19] The other 3 studies demonstrated a similar effect, but it was not statistically significant. In the studies that measured treat-

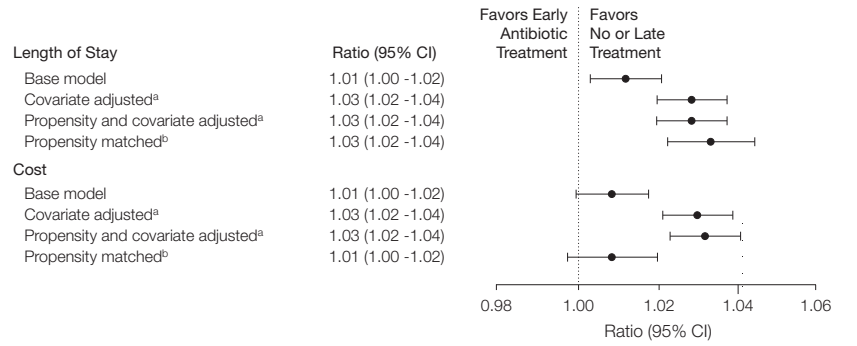
ment failure, antibiotics reduced treatment failure by half, but treatment failure, defined as no improvement or death following treatment, reached almost 60% in the placebo group, compared with only 12% in our study. In contrast, a recent small randomized trial of patients hospitalized for acute exacerbations of COPD found that compared with placebo, doxycycline did not improve clinical outcomes at 30 days.[20]

Our study has several limitations. First, its observational design makes it vulnerable to selection bias. We attempted to overcome this with rigorous multivariable adjustment, including the propensity for treatment and by using an adaptation of the instrumental variable approach, but we cannot exclude the possibility of residual confounding. However, it seems likely that patients with more severe disease would be more likely to receive antibiotics, and thus bias the results away from any observed benefit from antibiotic treatment. In fact, patients treated with antibiotics were more likely to receive corticosteroids or have an arterial blood gas analysis, both signs of more severe illness.

Second, our study used administrative data, and therefore we could not directly adjust for physiological differences between treated and untreated patients. However, we did adjust for prior admissions for COPD as well as for additional treatments the patients received, assuming that many of these treatments, including the need for arterial blood gas testing and steroids, reflected the clinicians' assessment of disease severity.

Finally, no validated method exists for identifying patients with acute exacerbations of COPD through administrative data review. It is possible that some of the patients in our study did not have acute exacerbations of COPD. To maximize the specificity, we chose to include only *ICD-9* codes that represent acute exacerbations of COPD, and the high rate of intravenous steroid use suggests that patients were, in fact, experiencing acute exacerbations of COPD. Excluding patients with combined asthma and COPD diagnoses, further strengthened the observed associations.

Figure 3. Association of Early Antibiotic Treatment vs Late or No Treatment With Cost and Length of Stay



The base model and all others account for clustering within hospital. See corresponding footnotes a and b in Figure 1 for definitions of covariates.

Our study also has a number of strengths. It was conducted in a nationally representative sample of hospitals and included a large number of patients cared for under real-world conditions, and our detailed data set enabled us to adjust for numerous patient characteristics and treatments that could confound the relationship between antibiotic treatment and outcome. Finally, almost 90% of our patients received treatment with corticosteroids. This is important because the only randomized antibiotic trials in which all patients received corticosteroids did not find any benefit from antibiotics.[20,21]

Chronic obstructive pulmonary disease is an important cause of recurrent hospitalization, morbidity, and mortality, and the number of patients with COPD is expected to increase in the coming years. Although published guidelines recommend antibiotics for acute exacerbations of COPD, practice patterns demonstrate that physicians are slow to adopt these guidelines.[22] In our sample, less than 80% of patients received antibiotics in the first 2 days of hospitalization, leaving considerable room for improvement.

One reason that not all patients receive antibiotics may be that the guidelines recommend antibiotics only for patients with purulent or increased sputum production, based on the work of Anthonisen et al.[11] In the past 2 decades, there has been little progress toward identifying which patients benefit from antibiotics. We could not identify a group that did not benefit from antibiotics, although our ability to detect clinical findings was limited. Our treatment-failure model suggested that patients with less severe disease might derive less benefit, but we lacked power to prove it. In our sample, patients receiving antibiotics appeared to have the more severe exacerbations, judging by the other therapies they received. Nevertheless, patients who received antibiotics had lower mortality than those who did not. If physicians' decisions to use antibiotics were based on their clinical impressions of patient illness, then these impressions appear not to have been sufficiently discriminative.

At the same time, we found little evidence of harm associated with antibiotic prescribing—we noted no increase in allergic reactions and only a slight increase in readmissions with *C difficile* diarrhea. Patients receiving antibiotics may have a slightly longer length of stay or may have experienced other unmeasured

complications. For example, we had no way of measuring the acquisition of antibiotic-resistant bacteria.

These 2 findings, that all patient groups seemed to benefit from therapy and that harms were minimal, support the notion that all patients hospitalized with acute exacerbations of COPD should be prescribed antibiotics. This recommendation, however, is not consistent with the fact that roughly 50% of COPD patients do not have a bacterial etiology for their exacerbation. Identifying these patients remains a challenge, because sputum cultures do not distinguish between active infection and colonization. New bacterial infections may cause exacerbations[23] and are associated with increases in inflammatory markers, such as procalcitonin, whereas colonization is not.[24] Recently, Stolz et al[25] demonstrated that withholding antibiotics from COPD patients with normal procalcitonin resulted in comparable health outcomes with 32% less antibiotic use. Such studies are promising, but until more data are available, routine use of antibiotics for acute exacerbations of COPD may be appropriate.

Author Contributions: Drs Rothberg and Pekow had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Rothberg, Pekow, Brody, Skiest, Lindenauer.
Acquisition of data: Lindenauer.
Analysis and interpretation of data: Rothberg, Pekow, Lahti, Skiest, Lindenauer.
Drafting of the manuscript: Rothberg, Pekow, Lahti, Brody.
Critical revision of the manuscript for important intellectual content: Pekow, Skiest, Lindenauer.
Statistical analysis: Pekow, Lahti.
Administrative, technical, or material support: Skiest, Lindenauer.
Study supervision: Pekow, Lindenauer.
Financial Disclosures: None reported.
Online-Only Material: An eFigure and eTable are available at http://www.jama.com.
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