Association of Corticosteroid Dose and Route of Administration With Risk of Treatment Failure in Acute Exacerbation of Chronic Obstructive Pulmonary Disease

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Context Systemic corticosteroids are beneficial for patients hospitalized with acute exacerbation of chronic obstructive pulmonary disease (COPD); however, their optimal dose and route of administration are uncertain.

Objective To compare the outcomes of patients treated with low doses of steroids administered orally to those treated with higher doses administered intravenously.

Design, Setting, and Patients A pharmacoepidemiological cohort study conducted at 414 US hospitals involving patients admitted with acute exacerbation of COPD in 2006 and 2007 to a non–intensive care setting and who received systemic corticosteroids during the first 2 hospital days.

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 exacerbation of COPD within 30 days of discharge. Length of stay and hospital costs.

Results Of 79 985 patients, 73 765 (92%) were initially treated with intravenous steroids, whereas 6220 (8%) received oral treatment. We found that 1.4% (95% confidence interval [CI], 1.3%-1.5%) of the intravenously and 1.0% (95% CI, 0.7%-1.2%) of the orally treated patients died during hospitalization, whereas 10.9% (95% CI, 10.7%-11.1%) of the intravenously and 10.3% (95% CI, 9.5%-11.0%) of the orally treated patients experienced the composite outcome. After multivariable adjustment, including the propensity for oral treatment, the risk of treatment failure among patients treated orally was not worse than for those treated intravenously (odds ratio [OR], 0.93; 95% CI, 0.84-1.02). In a propensity-matched analysis, the risk of treatment failure was significantly lower among orally treated patients (OR, 0.84; 95% CI, 0.75-0.95), as was length of stay and cost. Using an adaptation of the instrumental variable approach, increased rate of treatment with oral steroids was not associated with a change in the risk of treatment failure (OR for each 10% increase in hospital use of oral steroids, 1.00; 95% CI, 0.97-1.03). A total of 1356 (22%) patients initially treated with oral steroids were switched to intravenous therapy later in the hospitalization.

Conclusion Among patients hospitalized for acute exacerbation of COPD low-dose steroids administered orally are not associated with worse outcomes than high-dose intravenous therapy.

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CHRONIC OBSTRUCTIVE PULMONARY disease (COPD) affects more than 6% of adults in the United States, accounts for $32 billion in direct health care costs, and is the fourth leading cause of death.[1,2] In 2006, there were approximately 600 000 hospital admissions for acute exacerbation COPD, making this 1 of the 10 leading causes of hospitalization nationwide.[3]

The mainstays of hospital care for patients with acute exacerbation of COPD include the provision of supplemental oxygen, short-acting bronchodilators, systemic corticosteroids, and usually antibiotics. Evidence supporting treatment with steroids is derived from a small number of randomized trials in which steroids were found to improve physiological measures of lung function, to reduce the risk of treatment failure, and to decrease length of stay in the hospital.[4-9] Although the benefit of steroids appears clear, the optimal dose and route of administration of these agents remain uncertain.[10,11] Based on

See also Patient Page.

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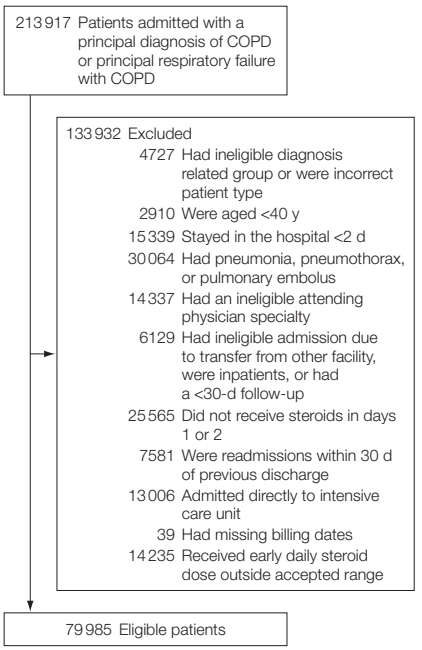
Figure 1. Patient Selection Flow Diagram



COPD indicates chronic obstructive pulmonary disease.

their high bioavailability[12] and extrapolating from studies investigating asthma and other inflammatory conditions, clinical guidelines produced by leading professional societies in the United States, the United Kingdom, and Europe recommend treatment with low doses of steroids administered orally.[13-15]

We investigated the use of corticosteroids among patients hospitalized for acute exacerbation of COPD in a large network of US hospitals and compared the outcomes of those initially treated with low doses of steroids administered orally to those in whom steroids were initially administered at higher doses intravenously.

METHODS

Setting and Patients

We conducted a retrospective cohort study using data from 414 hospitals that participate in Premier Incorporated's Perspective, a voluntary, fee-supported database developed for measuring quality and health care utilization. Participating hospitals are geographically diverse and similar to the composition of acute care hospitals nationwide and are predominantly small to midsize nonteaching facilities that serve a largely urban patient population. In addition to the information available in the standard hospital discharge file, Perspective contains a date-stamped log of all billed items, including medications, laboratory, diagnostic and therapeutic services, at the individual patient level. Three-quarters of hospitals that participate report actual costs derived from internal cost accounting systems, whereas others provide cost estimates calculated using Medicare cost to charge ratios. In 2006, the database contained the records of approximately 5.5 million hospital discharges, representing 15% of all hospitalizations nationwide.

Patients admitted to participating hospitals between January 1, 2006, and December 1, 2007, were included in our analysis if they were aged 40 years or older, had a principal diagnosis of COPD with acute exacerbation (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*] codes 491.21, 491.22, 493.22), emphysema (*ICD-9-CM*, 492.8), or if they had a principal diagnosis of respiratory failure (*ICD-9-CM* codes 518.81, 518.82, 518.84) combined with a secondary diagnosis of COPD with acute exacerbation or emphysema,[16] and were treated with systemic corticosteroids during the first 2 days of hospitalization (FIGURE 1).

We excluded patients whose initial daily dose of corticosteroids fell outside a conventional range of treatment. This included patients who received less than 20 mg or more than 80 mg of oral prednisone and those treated intravenously at doses lower than 120 mg or higher than 800 mg of prednisone equivalents each day. Because mechanical ventilation initiated after hospital day 2 was one of our outcome measures, we excluded patients admitted directly to the intensive care unit (ICU). In addition, to focus on patients with less complicated acute exacerbation of COPD, we excluded those with a secondary diagnosis of pneumonia or pulmonary embolism. To reduce the likelihood that coding errors might be responsible for incorrectly classifying patients as having acute exacerbation of COPD, we further limited the analysis to patients whose attending physician was a family physician, general internist, hospitalist, pulmonologist, or intensivist as well as those assigned to an All Patient Refined-Diagnosis Related Group (APR-DRG version 15.0, 3M Corp, Minneapolis, Minnesota) consistent with COPD or respiratory failure. Finally, we excluded patients whose hospitalization lasted only 1 day and those who were transferred to or from another acute care facility because we could not accurately assess treatment with corticosteroid therapy. Permission to conduct the study was obtained by the institutional review board at Baystate Medical Center, where the study was conducted, and the need for written informed consent was waived.

Patient and Hospital Information

In addition to patient age, sex, race/ethnicity, and insurance status, we recorded the presence of up to 30 unique comorbidities using software provided by the Healthcare Costs and Utilization Project of the Agency for Healthcare Research and Quality based on methods described by Elixhauser et al.[17] Information about race/ethnicity was recorded by admission or triage staff of participating hospitals using hospital-defined options. Furthermore, in an effort to better characterize the underlying severity of COPD, we calculated the total number of admissions for acute exacerbation of COPD in the year prior to the index hospitalization, and used *ICD-9-CM* secondary diagnosis codes to identify the presence of chronic pulmonary heart disease. For each hospital that participated in the study, we recorded bed count, teaching status, geographic region, and whether it served an urban or rural population.

Use of Corticosteroids and Other Treatments

We reviewed detailed pharmacy charges to determine both the route and dose of systemic corticosteroids adminis-

tered during the first 2 days of hospital admission and to assess changes in steroid treatment that occurred throughout the hospitalization. Patients were categorized in the high-dose intravenous therapy group if their first recorded dose of corticosteroids was an intravenous preparation and if their maximum dose on day 1 or 2 was within the 120-mg to 800-mg range of the equivalent of prednisone, even if, as would be expected, their treatment was later transitioned to oral therapy.[18] Patients initially treated with a maximum day 1 or 2 dose of oral corticosteroids between 20 mg and 80 mg of prednisone were categorized in the low-dose oral therapy group, even if later during their hospitalization steroid therapy was intensified. The first 2 days were initiated for patient categorization because we wanted to focus on patients whose steroids were initiated at or near the time of admission and because in administrative data sets, the duration of the first hospital day includes partial days that can vary in length. Furthermore, we recorded the total duration of steroid treatment administered during the hospitalization and noted any changes in therapy.

In addition to corticosteroids, we assessed many other treatments and tests administered during the first 2 hospital days, including anticholinergic bronchodilators, short- and long-acting β_2-agonists, antibiotics, and noninvasive positive pressure ventilation. Although categorized as being of uncertain benefit in most clinical guidelines, we also assessed the use of methylxanthine bronchodilators, mucolytic agents, chest physiotherapy, sputum studies, and spirometry. Furthermore, as indirect measures of symptom severity, we recorded use of arterial blood gas testing and treatment with loop diuretics and morphine.

Outcomes

Adapting an approach used in an earlier randomized trial of steroids in acute exacerbation of COPD, our primary outcome was a composite measure of treatment failure, defined as the initiation of mechanical ventilation after the second hospital day, death during the hospitalization, or readmission for COPD within 30 days of discharge.[7] Secondary outcomes included hospital length of stay and hospital costs.

Table 1. Characteristics of Patients Included in the Study

Patient Characteristics	No. (%) of Patients			*P* Value
		Initial Steroid Therapy Administration Route		
	All Patients (N = 79 985)	Intravenous (n = 73 765)	Oral (n = 6220)	
Age, median (IQR), y	69 (60-78)	69 (60-78)	70 (59-79)	.002[a]
Female sex	49 029 (61)	45 263 (61)	3766 (61)	.20
Race/ethnicity				
White	58 523 (73)	54 455 (74)	4068 (65)	<.001
Black	8661 (11)	7473 (10)	1188 (19)	
Hispanic	2560 (3.2)	2307 (3.1)	253 (4.1)	
Other	10 241 (13)	9530 (13)	711 (11)	
Primary insurance				
Medicare traditional	49 048 (61)	45 463 (62)	3585 (58)	<.001
Medicare managed care	7487 (9.4)	6711 (9.1)	776 (13)	
Medicaid	7167 (9)	6416 (8.7)	751 (12)	
Private	12 933 (16)	12 071 (16)	862 (14)	
Self-pay, insured, or other	3350 (4.2)	3104 (4.2)	246 (4)	
Principal diagnosis				
Acute exacerbation of COPD	71 628 (90)	65 825 (89)	5803 (93)	<.001
Respiratory failure	8357 (10)	7940 (11)	417 (6.7)	
Admissions for COPD or respiratory failure in year prior				
0	56 992 (71)	52 553 (71)	4439 (71)	.15
1	13 267 (17)	12 278 (17)	989 (16)	
≥2	9726 (12)	8934 (12)	792 (13)	
Comorbidities[b]				
Hypertension	48 202 (60)	44 331 (60)	3871 (62)	<.001
Diabetes	23 004 (29)	21 035 (29)	1969 (32)	<.001
Heart failure	18 843 (24)	17 082 (23)	1761 (28)	<.001
Depression	12 545 (16)	11 536 (16)	1009 (16)	.22
Deficiency anemias	10 478 (13)	9499 (13)	979 (16)	<.001
Hypothyroidism	9740 (12)	8988 (12)	752 (12)	.83
Obesity	9578 (12)	8861 (12)	717 (12)	.26
Chronic pulmonary heart disease	6387 (8)	5870 (8)	517 (8.3)	.32
Renal failure	6221 (7.8)	5583 (7.6)	638 (10)	<.001
Peripheral vascular disease	5513 (6.9)	5102 (6.9)	411 (6.6)	.36
Neurological disorders	5012 (6.3)	4574 (6.2)	438 (7)	.009
Valvular disease	4683 (5.9)	4284 (5.8)	399 (6.4)	.05
Psychoses	3695 (4.6)	3345 (4.5)	350 (5.6)	<.001
Alcohol abuse	2689 (3.4)	2405 (3.3)	284 (4.6)	<.001
Sleep apnea	2400 (3)	2208 (3)	192 (3.1)	.68
Rheumatoid arthritis or collagen vascular disease	2244 (2.8)	2021 (2.7)	223 (3.6)	<.001
Weight loss	1860 (2.3)	1723 (2.3)	137 (2.2)	.50
Solid tumor without metastasis	1841 (2.3)	1688 (2.3)	153 (2.5)	.39
Drug abuse	1662 (2.1)	1396 (1.9)	266 (4.3)	<.001
Pulmonary circulation disease	1468 (1.8)	1369 (1.9)	99 (1.6)	.14
Liver disease	1048 (1.3)	910 (1.2)	138 (2.2)	<.001
Paralysis	789 (1)	711 (1)	78 (1.3)	.03

[a] Calculated by Kruskal-Wallis test.
[b] Additional comorbidities evaluated in models but not reported in tables include: polycythemia, AIDS, metastatic cancer, lymphoma, and blood loss anemia.

Table 2. Setting and Treatment of Patients Included in the Study

	No. (%) of Patients			
		Initial Steroid Therapy Administration Route		
	All Patients (N = 79 985)	Intravenous (n = 73 765)	Oral (n = 6220)	*P* Value
Hospital characteristics				
No. of beds				
≤200	15 042 (19)	14 175 (19)	867 (14)	<.001
201-300	13 987 (18)	13 240 (18)	747 (12)	
301-500	29 427 (37)	27 211 (37)	2216 (36)	
>500	21 529 (27)	19 139 (26)	2390 (38)	
Population served				
Rural	13 564 (17)	12 882 (18)	682 (11)	<.001
Urban	66 421 (83)	60 883 (83)	5538 (89)	
Region				
South	41 554 (52)	39 312 (53)	2242 (36)	<.001
Midwest	15 858 (20)	14 594 (20)	1264 (20)	
Northeast	12 457 (16)	10 713 (15)	1744 (28)	
West	10 116 (13)	9146 (12)	970 (16)	
Teaching status				
Nonteaching	52 629 (66)	49 811 (68)	2818 (45)	<.001
Teaching	27 356 (34)	23 954 (33)	3402 (55)	
Attending specialty				
Internal medicine or hospitalist	52 148 (65)	47 754 (65)	4394 (71)	<.001
Family or general medicine	16 724 (21)	15 560 (21)	1164 (19)	
Pulmonary medicine	10 810 (14)	10 184 (14)	626 (10)	
Critical care or intensivist	303 (0.4)	267 (0.4)	36 (0.6)	
Early therapies and tests[a]				
Total steroid dose in first 2 hospital days, in mg prednisone equivalents, median (IQR)		600 (350-781)	60 (40-120)	
Antibiotics	60 566 (76)	56 390 (76)	4176 (67)	<.001
Anticholinergic bronchodilator and/or short-acting β_2-agonist[b]	63 257 (79)	58 179 (79)	5078 (82)	<.001
Long acting β_2-agonist[b]	31 102 (40)	28 693 (39)	2409 (41)	.09
Noninvasive ventilation	5861 (7.3)	5526 (7.5)	335 (5.4)	<.001
Methylxanthine bronchodilators	8516 (11)	8081 (11)	435 (7)	<.001
Mucolytic medications	1641 (2.1)	1553 (2.1)	88 (1.4)	<.001
Chest physiotherapy	2207 (2.8)	2065 (2.8)	142 (2.3)	.02
Sputum testing	7136 (8.9)	6758 (9.2)	378 (6.1)	<.001
Spirometry	3436 (4.3)	3061 (4.1)	375 (6)	<.001
Arterial blood gas	36 643 (46)	34 448 (47)	2195 (35)	<.001
Brain natriuretic peptide	44 951 (56)	41 577 (56)	3374 (54)	.001
Morphine	6544 (8.2)	5989 (8.1)	555 (8.9)	.03
Loop diuretics	28 201 (35)	25 794 (35)	2407 (39)	<.001
Patient outcomes				
Late ventilation, after day 2	941 (1.2)	866 (1.2)	75 (1.2)	.82
Readmission for COPD within 30 d[c]	6911 (8.8)	6392 (8.8)	519 (8.4)	.34
In-hospital mortality	1080 (1.4)	1018 (1.4)	62 (1)	.01
Treatment failure[d]	8671 (11)	8032 (11)	639 (10)	.13
Length of stay, median (IQR), d	4 (3-6)	4 (3-6)	4 (2-5)	<.001[e]
Total cost, median (IQR), US $	5021 (3516-7529)	5056 (3536-7578)	4639 (3327-6980)	<.001[e]

Abbreviations: COPD, chronic obstructive pulmonary disease, IQR, interquartile range.
[a] Early indicates that the treatment was initiated by day 2 of hospital stay.
[b] Has 52 missing values from hospitals not reporting bronchodilators.
[c] Among 78 905 survivors.
[d] Death, late ventilation, 30-d COPD readmission.
[e] Calculated by Kruskal-Wallis test.

Analysis

Summary statistics were constructed using frequencies and proportions for categorical data, and means, medians, and interquartile ranges for continuous variables. We compared the characteristics of patients who initially received high-dose intravenous therapy with those in whom steroids were administered at low doses orally. χ^2, z, or Kruskal-Wallis tests were used to assess the relationship between choice of therapy and the initiation of mechanical ventilation after the second hospital day, in-hospital mortality, 30-day readmission, the composite measure of treatment failure, length of stay, hospital costs, and any potential confounders.

We developed a series of multivariable regression models to assess the independent effect of initial choice of steroid administration on the composite measure of treatment failure, length of stay, and costs while adjusting for principal diagnosis, all patient and hospital characteristics, and other early diagnostic tests and treatments. 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. Generalized estimating equations (SAS PROC GENMOD; SAS Institute Inc, Cary, North Carolina) were used to account for the clustering of patients within hospitals. Logit-link models were used for treatment failure and identity-link models and for the log-transformed length of stay and cost.

We developed a nonparsimonious regression model for initial steroid therapy, using GEE modeling with a logit-link (SAS PROC GENMOD) to produce a propensity score for initial treatment with low-dose oral steroids. The model included all patient and hospital characteristics, attending specialty, all other early treatments and diagnostic tests, and selected interaction terms. The model produced a propensity score for each patient reflecting his/her probability of initial treatment with low doses of steroids administered orally. This score was then included as

a covariate in the previous models for treatment failure, length of stay and costs. Then, using a greedy 5 to 1 digit match algorithm, we matched each patient who received initial low-dose oral therapy with a patient in the high-dose intravenous group with a similar propensity for oral treatment.[19] The matched cohort was evaluated for differences for each of the potential confounding factors, and conditional logistic regression was used to assess the association between choice of steroid use and treatment failure, while adjusting for any remaining differences between groups ($P < .05$).

To address the threat of residual confounding by indication, in which sicker patients might preferentially be given higher-dose intravenous treatment, we developed a model combining an ecologic, or grouped treatment variable, with individual-level covariates and outcomes.[20] This is an adaptation of the instrumental variable approach, a technique with an extensive track record in econometrics and growing use in health care.[21,22] Using this approach, each patient was assigned a probability of treatment with low-dose oral steroids that was equivalent to the rate of low-dose oral therapy at the hospital where they received care—the group rate. We then repeated the GEE model for treatment failure, substituting the hospital rate of treatment in place of individual treatment. This approach attempts to answer the question, "Is treatment at an institution where low-dose oral steroids are used more frequently associated with better or worse outcomes, regardless of how a particular patient is treated?" Grouping treatment at the hospital level in this way has the advantage of largely bypassing the issue of confounding by indication at the patient level, yet in contrast to a traditional ecologic analysis is able to account for patient-level covariates and outcomes.

As a sensitivity analysis to assess the effect of modeling structure, we repeated the final models in a hierarchical structure with SAS PROC GLIMMIX including a random hospital effect.

All significance tests were 2-sided, with a .05 significance level. The study was powered to detect an odds ratio (OR) of 1.2 or larger. With approximately 80 000 cases, 92% in 1 treatment group and adjusting for clustering within hospitals, we had more than 90% power to detect a treatment failure difference from 10% to 11.8%. All analyses were carried out using SAS software version 9.1.

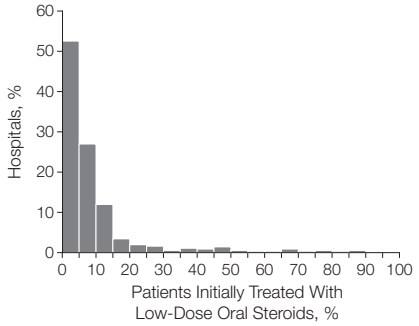
RESULTS

Of 79 985 patients who met our enrollment criteria (Figure 1), 71 628 (90%) had a principal diagnosis of COPD and 8357 (10%) had a principal diagnosis of respiratory failure. The median age was 69 years, 61% were women, 73% were white, and Medicare was the most common form of health insurance (TABLE 1). Hypertension, diabetes, heart failure, and depression were the most frequently recorded comorbidities, and chronic pulmonary heart disease was present in 8% of patients. Overall, 17% had 1 admission for COPD in the year before the index hospitalization, and 12% had 2 or more. Sixty-six percent of patients were cared for at nonteaching facilities, 19% at hospitals with fewer than 201 beds, and 27% at hospitals operating more than 500 beds. Eighty percent were admitted directly from the emergency department, and general internists and family physicians were the attending of record for 86% of cases (TABLE 2). The median length of stay was 4 days, median costs were $5021, and 3 out of 10 patients were hospitalized for 6 days or longer. A total of 941 patients (1.2%) had mechanical ventilation initiated after the second hospital day, 1080 (1.4%) died during the hospitalization, and 6911 (9%) were readmitted for COPD within 30 days of discharge. Overall, 8671 patients (11%) experienced the composite measure of treatment failure.

Use of Corticosteroids and Other Therapies

In total, 73 765 patients (92%) were initially treated with high doses of steroids administered intravenously, while 6220 (8%) began low doses of steroids given orally. Expressed in prednisone equivalents, the median total dose administered during the first 2 hospital days was 600 mg in the high-dose intravenous group, and 60 mg among those given lower-dose steroids orally. The 25th to 75th percentile day 1 and 2 dose ranges in the 2 groups of patients was 350 mg to 781 mg in the high-dose intravenous group and 40 mg to 120 mg in the low-dose oral group. Across the 388 hospitals that contributed 20 or more patients to the study, the use of oral steroids as an initial treatment strategy varied modestly. The median rate of initial low-dose oral steroid treatment was 5%, rates varied from 3% to 9% across the 25th to 75th percentile, and 1% of hospitals started half or more of patients with low doses of steroids orally (FIGURE 2).

Figure 2. Percentage of Patients Initially Treated With Low-Dose Oral Steroids at 388 Hospitals Contributing 20 or More Patients to the Study



When compared with those in the high-dose intravenous group, patients treated with low-dose oral steroids were marginally older, included a lower proportion of white patients, and were less likely to have private insurance (Table 2). Patients treated with low doses of orally administered steroids had a greater number of comorbidities, including diabetes, heart failure, anemia, and renal failure. When compared with those initially treated intravenously, they were less likely to receive early treatment with antibiotics, methylxanthine bronchodilators, to un-

dergo arterial blood gas analysis, and to receive noninvasive ventilation in the first 2 hospital days (Table 2). Treatment with low-dose orally administered steroids was more common in the Northeast, at larger hospitals, and those with teaching programs. A total of 1.4% (95% confidence interval [CI], 1.3%-1.5%) of patients initially treated with intravenous steroids died during the hospitalization and 10.9% (95% CI, 10.7%-11.1%) experienced the composite treatment failure outcome, whereas 1.0% (95% CI, 0.7%-1.2%) of orally treated patients died during the hospitalization and 10.3% (95% CI, 9.5%-11.0%) experienced the composite outcome. A total of 1356 patients (22%) initially treated with low-dose oral steroids were later switched to intravenous therapy. More than 92% of patients received treatment throughout their entire hospital stay, including 90% receiving low-dose and 92% receiving high-dose treatment intravenously.

Table 3. Characteristics of Patients in the Propensity-Matched Sample[a]

Patient Characteristics	No. (%) of Patients: Initial Intravenous Therapy (n = 6201)	No. (%) of Patients: Initial Oral Therapy (n = 6201)	*P* Value
Age, median (IQR), y	70 (60-79)	70 (59-79)	.01[b]
Female sex	3801 (61)	3753 (61)	.38
Race/ethnicity			
White	4489 (72)	4061 (65)	<.001
Black	738 (12)	1183 (19)	
Hispanic	213 (3.4)	252 (4.1)	
Other	761 (12)	705 (11)	
Primary insurance			
Medicare traditional	3722 (60)	3572 (58)	.005
Medicare managed care	690 (11)	773 (12)	
Medicaid	653 (11)	750 (12)	
Private	880 (14)	860 (14)	
Self-pay, uninsured, or other	256 (4.1)	246 (4.0)	
Principal diagnosis			
Acute exacerbation of COPD	5800 (94)	5785 (93)	.59
Respiratory failure	401 (6.5)	416 (6.7)	
Admissions for COPD or Respiratory Failure in year prior, No.			
0	4538 (73)	4428 (71)	.08
1	940 (15)	986 (16)	
≥2	723 (12)	787 (13)	
Comorbidities[c]			
Hypertension	3841 (62)	3859 (62)	.74
Diabetes	1972 (32)	1961 (32)	.83
Heart failure	1855 (30)	1751 (28)	.04
Depression	1040 (17)	1006 (16)	.41
Deficiency anemias	991 (16)	971 (16)	.62
Hypothyroidism	828 (13)	748 (12)	.03
Obesity	788 (13)	714 (12)	.04
Chronic pulmonary heart disease	569 (9.2)	512 (8.3)	.07
Renal failure	628 (10)	637 (10)	.79
Peripheral vascular disease	435 (7.0)	410 (6.6)	.37
Neurological disorders	429 (6.9)	435 (7.0)	.83
Valvular disease	473 (7.6)	396 (6.4)	.007
Psychoses	374 (6.0)	348 (5.6)	.32
Alcohol abuse	252 (4.1)	283 (4.6)	.17
Sleep apnea	205 (3.3)	190 (3.1)	.44
Rheumatoid arthritis or collagen vascular disease	261 (4.2)	219 (3.5)	.05
Weight loss	140 (2.3)	134 (2.2)	.71
Solid tumor without metastasis	156 (2.5)	152 (2.5)	.82
Drug abuse	155 (2.5)	264 (4.3)	<.001
Pulmonary circulation disease	98 (1.6)	107 (1.7)	.53
Liver disease	114 (1.8)	137 (2.2)	.14
Paralysis	74 (1.2)	77 (1.2)	.81
Metastatic cancer	67 (1.1)	51 (0.82)	.14

[a] Each orally treated patient matched on propensity with 1 intravenously treated patient 6201 of 6220 (99.7%) of orally treated cases were matched.
[b] Calculated by Kruskal-Wallis test.
[c] Additional comorbidities evaluated in models but not reported in tables include polycythemia, AIDS, lymphoma, and blood loss anemia.

Results of Multivariable Analyses

Overall, 99.7% of patients treated with low-dose steroids administered orally were successfully matched to a patient with a similar propensity who was treated with high-dose steroids administered intravenously (TABLE 3 and TABLE 4). In this propensity-matched cohort, the majority of covariates were well balanced, and after conditional regression was applied to control for remaining differences between the groups, patients treated with oral steroids had a lower risk of treatment failure (OR, 0.84; 95% CI, 0.75-0.95), shorter length of stay (ratio, 0.90; 95% CI, 0 0.88-0.91), and lower hospital costs (ratio, 0.91; 95% CI, 0.89-0.93; TABLE 5).

In models that adjusted for patient, hospital, and physician characteristics, including the propensity for treatment with low doses of steroids given orally, the early use of other treatments and diagnostic tests, and selected interaction terms, the risk of treatment failure among patients given low doses of steroids orally was not significantly different from those treated with high-dose steroids intravenously (OR, 0.93; 95% CI, 0.84-1.02). Patients treated with low doses of steroids administered orally had shorter lengths of stay (ratio, 0.92; 95% CI,

0.91-0.94) and lower costs (ratio, 0.93; 95% CI, 0.91-0.94; Table 5).

Finally, when individual patients were assigned a probability of initial treatment with low-dose steroids given orally equal to the hospital rate where they received care, each 10% increase in the hospital rate of low-dose oral steroids was associated with no change in the odds of treatment failure (OR, 1.00; 95% CI, 0.97-1.03; Table 5).

Estimates of treatment effect for oral vs intravenous steroids from hierarchical models were virtually identical to those obtained from GEE modeling.

COMMENT

In this large observational study, we found that, in sharp contrast to the recommendations contained in leading clinical guidelines,[13-15] the vast majority of patients hospitalized for acute exacerbation of COPD were initially treated with high doses of corticosteroids administered intravenously. This practice does not appear to be associated with any measurable clinical benefit and at the same time exposes patients to the risks and inconvenience of an intravenous line, potentially unnecessarily high doses of steroids, greater hospital costs, and longer lengths of stay.

Following several small trials conducted over more than a decade, the effectiveness of corticosteroid therapy for patients hospitalized with acute exacerbation of COPD was convincingly established in 1999 through a multicenter trial at the Department of Veterans Affairs (VA) in which a total of 271 patients were randomized to receive placebo or 2 weeks or 8 weeks of steroid treatment.[7] The protocol called for 125 mg of methylprednisolone to be given intravenously every 6 hours for 72 hours, followed by 60 mg of prednisone once daily orally on days 4 through 7. Investigators found that corticosteroid treatment led to more rapid improvements in lung function, a reduced risk of treatment failure (primarily in the form of decreased need for retreatment with steroids following discharge), and shorter hospital

Table 4. Setting and Treatment of Patients in the Propensity-Matched Sample[a]

	No. (%) of Patients		
	Initial Intravenous Therapy (n = 6201)	Initial Oral Therapy (n = 6201)	*P* Value
Hospital characteristics			
No. of beds			
≤200	999 (16)	862 (14)	.002
201-300	717 (12)	746 (2)	
301-500	2235 (36)	2209 (36)	
>500	2250 (36)	2384 (38)	
Population served			
Rural	764 (12)	679 (11)	.02
Urban	5522 (89)	5437 (88)	
Region			
South	2549 (41)	2239 (36)	<.001
Midwest	1092 (18)	1261 (20)	
Northeast	1382 (22)	1737 (28)	
West	1178 (19)	964 (16)	
Teaching status			
Nonteaching	2814 (45)	3101 (50)	<.001
Teaching	3100 (50)	3387 (55)	
Attending specialty			
Internal medicine or hospitalist	4299 (69)	4386 (71)	<.001
Family or general medicine	1334 (22)	1154 (19)	
Pulmonary medicine	551 (8.9)	625 (10)	
Critical care or intensivist	17 (0.27)	36 (0.58)	
Early therapies and tests[b]			
Total steroid dose in first 2 hospital days (in mg prednisone equivalents), median (IQR)	556 (313-781)	60 (40-120)	
Antibiotics	4140 (67)	4167 (67)	.61
Anticholinergic bronchodilator and/or short-acting β_2-agonist	4648 (75)	5068 (82)	<.001
Long-acting β_2-agonist	2421 (40)	2404 (41)	.29
Noninvasive ventilation	308 (5.0)	333 (5.4)	.31
Methylxanthine bronchodilators	507 (8.2)	435 (7.0)	.02
Mucolytic medications	108 (1.7)	87 (1.4)	.13
Chest physiotherapy	144 (2.3)	141 (2.3)	.86
Sputum testing	439 (7.1)	378 (6.1)	.03
Spirometry	288 (4.6)	370 (6.0)	.001
Arterial blood gas	2174 (35)	2191 (35)	.75
Brain natriuretic peptide	3478 (56)	3369 (54)	.05
Morphine	518 (8.4)	553 (8.9)	.26
Loop diuretics	2531 (41)	2398 (39)	.02
Patient outcomes			
Late ventilation, after day 2	65 (1.1)	75 (1.2)	.40
Readmission for COPD within 30 d[c]	574 (9.4)	516 (8.4)	.06
In-hospital mortality	90 (1.5)	61 (1.0)	.02
Treatment failure[d]	706 (11.4)	635 (10)	.04
Length of stay, median (IQR), d	4 (3-6)	3 (2-5)	<.001
Total cost, median (IQR), US$	5189 (3612-7617)	4610 (3309-6854)	<.001

Abbreviations: COPD, chronic obstructive pulmonary disease; IQR, interquartile range.
[a] Each orally treated patient matched on propensity with 1 intravenously treated patient, 6201 of 6220 (99.7%) of orally treated cases were matched.
[b] Early indicates that therapy was initiated by day 2 of hospital stay.
[c] Among 6111 survivors with initial intravenous and 6140 survivors with initial oral therapy.
[d] Death, late ventilation, 30-d COPD readmission.

Table 5. Association Between Low-Dose Oral Steroid Therapy vs High-Dose Intravenous Therapy and Outcomes in Acute Exacerbation of Chronic Obstructive Pulmonary Disease

Model	Treatment Failure, OR (95% CI)	Ratio (95% CI)	
		Length of Stay	Total Cost
Unadjusted[a]	0.91 (0.83-1.00)	0.92 (0.91-0.93)	0.92 (0.91-0.93)
Propensity score– and covariate-adjusted[b,c]	0.93 (0.84-1.02)	0.92 (0.91-0.94)	0.93 (0.91-0.94)
Matched sample adjusted for unbalanced covariates[d]	0.84 (0.75-0.95)	0.90 (0.88-0.91)	0.91 (0.89-0.93)
Group treatment for 10% increase in hospital proportion oral steroids, covariate adjusted[b,c]	1.00 (0.97-1.03)		

Abbreviations: CI, confidence interval; OR, odds ratio.
[a] Accounting for within-hospital clustering.
[b] Covariates included in all models: age group, sex, race/ethnicity, insurance status, respiratory failure principal diagnosis, attending physician specialty, region, teaching status, chronic pulmonary heart disease, diabetes, hypertension, depression, hypothyroid, deficiency anemia, obesity, peripheral vascular disease, arthritis, weight loss, blood loss, congestive heart failure, metastatic cancer, psychoses, alcohol abuse, and day 1 or 2 initiation of long acting β_2-agonists, noninvasive ventilation, antibiotics, arterial blood gas, brain natriuretic peptide, loop diuretics, methylzanthine bronchodilators, morphine, mucolytic medications, pulmonary function tests, prior year admissions for chronic obstructive pulmonary disease, and selected interaction terms.
[c] Additional covariates in length of stay and cost models: population served, hospital bed count, sleep apnea, valve disease, neurologic disorders, renal failure, paralysis, liver disease, solid tumor, lymphoma, drug use, day 1 or 2 initiation of chest physiotherapy, sputum tests, anticholinergic, or short acting β_2-agonists.
[d] Age group, race/ethnicity, insurance status, attending physician specialty, hospital bed count, population served, region, teaching status, obesity, heart failure, valve disease, drug use, hypothyroidism, day 1 or 2 initiation of short acting β_2-agonists, loop diuretics, methylxanthine bronchodilators, sputum testing, or spirometry.

stays, and they found that prolonged steroid tapers had no clinical benefit.

Although direct evidence from head-to-head trials is limited, most clinical guidelines recommend treatment with 20 mg to 60 mg of prednisone once daily administered orally rather than the higher doses of intravenously administered methylprednisolone as described in the VA trial. These recommendations are supported by the high bioavailability of orally administered corticosteroids,[12] small trials demonstrating the efficacy of low-dose oral steroids for treating acute exacerbation of COPD,[6,9] and multiple studies among patients with acute exacerbations of asthma showing equivalency between oral- and intravenous-based strategies.[23-25] Moreover, when compared with intravenous therapy, oral administration has several advantages, including lower nursing costs, decreased risk of line-related infections and complications, and reduced pain and immobility.[26-30]

When treating acute exacerbation of COPD specifically, the oral and intravenous routes of steroid administration were recently compared in a randomized trial involving 435 patients at a single hospital in the Netherlands.[31] Investigators there found that 60 mg of prednisone administered daily produced a similar clinical benefit whether administered intravenously or orally; however, patients treated by the intravenous route incurred greater hospital costs. Our findings extend those of De Jong and colleagues[31] by asking a more pertinent question for physicians practicing in the United States; namely whether higher doses of steroids given intravenously offer any advantage over low-dose oral therapy. Because high-dose intravenous therapy is so common and because patients with COPD are hospitalized frequently for exacerbations, our findings have a significant potential to alter practice, potentially reducing costs, complications, and lowering the risks of steroid-associated adverse events.[32]

What factors might explain the large discrepancy between the recommendations found in guidelines and current physician practice? Among a number of possibilities, we suspect that a lack of knowledge of pharmacokinetics, a gut instinct that higher doses are more effective than lower doses, and possibly utilization review programs that require the presence of an intravenous line to justify continued hospitalization at an acute care level are all implicated. In addition, some patients may initially receive high-dose intravenous therapy after the real or perceived failure of low-dose oral therapy started in the ambulatory setting.

The primary limitation of this study is its observational design. Treatment assignment was not random, and physician decisions regarding the choice of high-dose intravenous and low-dose oral therapy may have been influenced by initial illness severity. We found some evidence to support this view; on the one hand, patients in the low-dose oral therapy group were older and had a greater number of comorbidities; however, they were also less likely to undergo early arterial blood gas analysis and less likely to receive early treatment with antibiotics. In addition, although we recorded information about a large number of patient, hospital, physician, and treatment factors, our study was based on highly detailed hospital claims, not direct clinical measurements, and therefore we were not able to adjust for measures of lung function, such as the forced expiratory volume in the first, second, or the partial pressure of carbon dioxide in arterial blood. Furthermore, although we used robust statistical techniques to minimize the threat of selection bias, including propensity adjustment and matching, these approaches are primarily designed to control for imbalances in the distribution of measured confounders. To address our concern about residual biases due to unmeasured factors, we applied a form of instrumental variable analysis in which all patients treated at the same hospital were assigned an identical probability of treatment with low-dose oral steroids equal to the hospital rate of initial oral therapy. This approach is attractive because, although it does not control for differences in the management skills at hospitals that might be associated with the choice of therapy, it largely overcomes the problem of confounding by indication at the patient level. Finally, our analysis was limited to patients initially cared for out-

side of the intensive care unit, and our results should not be generalized to more severely ill patients.

As an initial treatment strategy for patients with acute exacerbation of COPD, low doses of steroids administered orally were not associated with worse outcomes than high doses of steroids administered intravenously. In light of the greater risks and higher costs associated with high-dose intravenous treatment, opportunities may exist to improve care by promoting greater use of low-dose steroids given orally. Given the large numbers of patients hospitalized with COPD each year in the United States, a clinical trial comparing these 2 approaches to management would be valuable.

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Study concept and design: Lindenauer, Pekow, Benjamin, Rothberg.
Acquisition of data: Lindenauer.
Analysis and interpretation of data: Lindenauer, Pekow, Lahti, Lee, Rothberg.
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Administrative, technical, or material support: Lindenauer, Benjamin.
Study supervision: Lindenauer, Pekow, Rothberg.
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REFERENCES

1. National Center for Health Statistics Fast Stats Chronic obstructive pulmonary disease (COPD) includes: chronic bronchitis and emphysema [Web page]. http://www.cdc.gov/nchs/fastats/copd.htm. Accessed April 23, 2010.
2. National Institutes of Health NHLBI. Morbidity and mortality chartbook on cardiovascular, lung, and blood disorders. 2009. http://www.nhlbi.nih.gov/resources/docs/cht-book.htm. Accessed April 23, 2010.
3. Healthcare Cost and Utilization Project [Web page]. Agency for Healthcare Research and Quality. http://hcupnet.ahrq.gov/ Accessed April 23, 2010.
4. Albert RK, Martin TR, Lewis SW. Controlled clinical trial of methylprednisolone in patients with chronic bronchitis and acute respiratory insufficiency. *Ann Intern Med*. 1980;92(6):753-758.
5. Bullard MJ, Liaw SJ, Tsai YH, Min HP. Early corticosteroid use in acute exacerbations of chronic airflow obstruction. *Am J Emerg Med*. 1996;14(2):139-143.
6. Davies L, Angus RM, Calverly PM. Oral corticosteroids in patients admitted to hospital with exacerbations of chronic obstructive pulmonary disease: a prospective randomised controlled trial. *Lancet*. 1999;354(9177):456-460.
7. Niewoehner DE, Erbland ML, Deupree RH, et al. Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. *N Engl J Med*. 1999;340(25):1941-1947.
8. Shortall SP, Blum J, Oldenburg FA, Rodgerson L, Branscombe JM, Harrow EM. Treatment of patients hospitalized for exacerbations of chronic obstructive pulmonary disease: comparison of an oral/metered-dose inhaler regimen and an intravenous/nebulizer regimen. *Respir Care*. 2002;47(2):154-158.
9. Thompson WH, Nielson CP, Carvalho P, Charan NB, Crowley JJ. Controlled trial of oral prednisone in outpatients with acute COPD exacerbation. *Am J Respir Crit Care Med*. 1996;154(2 pt 1):407-412.
10. Singh JM, Palda VA, Stanbrook MB, Chapman KR. Corticosteroid therapy for patients with acute exacerbations of chronic obstructive pulmonary disease. *Arch Intern Med*. 2002;162(22):2527-2536.
11. Walters JA, Gibson PG, Wood-Baker R, Hannay M, Walters EH. Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2009;(1):CD001288.
12. Al-Habet S, Rogers HJ. Pharmacokinetics of intravenous and oral prednisolone. *Br J Clin Pharmacol*. 1980;10(5):503-508.
13. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) [Web site]. http://www.goldcopd.org. Accessed April 23, 2010.
14. National Collaborating Centre for Chronic Conditions. Chronic obstructive pulmonary disease: national clinical guideline for management of chronic obstructive pulmonary disease in adults in primary and secondary care. *Thorax*. 2004;59(suppl 1):1-232.
15. Celli BR, MacNee W; ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper [a published correction appears in *Eur Respir J*. 2006;27(1):242]. *Eur Respir J*. 2004;23(6):932-946.
16. Stein BD, Bautista A, Schumock G, et al. Specificity of *ICD-9* diagnosis codes for identifying patients hospitalized for COPD. *Am J Respir Crit Care Med*. 2009;179:A2159.
17. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. *Med Care*. 1998;36(1):8-27.
18. Vondracek SF, Hemstreet BA. Retrospective evaluation of systemic corticosteroids for the management of acute exacerbations of chronic obstructive pulmonary disease. *Am J Health Syst Pharm*. 2006;63(7):645-652.
19. Parsons L. Reducing bias in a propensity score matched-pair sample using greedy matching techniques. Paper presented at: Proceedings of the Twenty-sixth Annual SAS Users Group International Conference; April 22-25, 2001; Long Beach, CA.
20. Johnston SC, Henneman T, McCulloch CE, van der Laan M. Modeling treatment effects on binary outcomes with grouped-treatment variables and individual covariates. *Am J Epidemiol*. 2002;156(8):753-760.
21. McClellan M, McNeil BJ, Newhouse JP. Does more intensive treatment of acute myocardial infarction in the elderly reduce mortality? analysis using instrumental variables. *JAMA*. 1994;272(11):859-866.
22. Stukel TA, Fisher ES, Wennberg DE, Alter DA, Gottlieb DJ, Vermeulen MJ. Analysis of observational studies in the presence of treatment selection bias: effects of invasive cardiac management on AMI survival using propensity score and instrumental variable methods. *JAMA*. 2007;297(3):278-285.
23. Harrison BD, Stokes TC, Hart GJ, Vaughan DA, Ali NJ, Robinson AA. Need for intravenous hydrocortisone in addition to oral prednisolone in patients admitted to hospital with severe asthma without ventilatory failure. *Lancet*. 1986;1(8474):181-184.
24. Jónsson S, Kjartansson G, Gislason D, Helgason H. Comparison of the oral and intravenous routes for treating asthma with methylprednisolone and theophylline. *Chest*. 1988;94(4):723-726.
25. Ratto D, Alfaro C, Sipsey J, Glovsky MM, Sharma OP. Are intravenous corticosteroids required in status asthmaticus? *JAMA*. 1988;260(4):527-529.
26. Tager IB, Ginsberg MB, Ellis SE, et al. An epidemiologic study of the risks associated with peripheral intravenous catheters. *Am J Epidemiol*. 1983;118(6):839-851.
27. Creditor MC. Hazards of hospitalization of the elderly. *Ann Intern Med*. 1993;118(3):219-223.
28. Maki DG, Ringer M. Risk factors for infusion-related phlebitis with small peripheral venous catheters: a randomized controlled trial. *Ann Intern Med*. 1991;114(10):845-854.
29. Brown CJ, Williams BR, Woodby LL, Davis LL, Allman RM. Barriers to mobility during hospitalization from the perspectives of older patients and their nurses and physicians. *J Hosp Med*. 2007;2(5):305-313.
30. Maki DG, Kluger DM, Crnich CJ. The risk of bloodstream infection in adults with different intravascular devices: a systematic review of 200 published prospective studies. *Mayo Clin Proc*. 2006;81(9):1159-1171.
31. de Jong YP, Uil SM, Grotjohan HP, Postma DS, Kerstjens HAM, van den Berg JWK. Oral or IV prednisolone in the treatment of COPD exacerbations: a randomized, controlled, double-blind study. *Chest*. 2007;132(6):1741-1747.
32. McEvoy CE, Niewoehner DE. Adverse effects of corticosteroid therapy for COPD: a critical review. *Chest*. 1997;111(3):732-743.