Observational Study of the Impact of Inhaled Corticosteroid Therapy on Outcomes for Patients with COPD and Hospitalized with Pneumonia

Dennis Chen, BS[1]
Marcos I. Restrepo, MD, MSc[1,3]
Michael J. Fine, MD, MSc[6,7]
Mary Jo V. Pugh, PhD[1,4]
Antonio Anzueto, MD[1,3]
Mark L. Metersky, MD[8]
Brandy Nakashima, MA[1]
Chester Good, MD[6,7]
Eric M. Mortensen, MD, MSc[1,2]

VERDICT/South Texas Veterans Health Care System[1]; Department of Medicine, Divisions of Hospital Medicine[2], Pulmonary and Critical Care Medicine[3]; and Departments of Epidemiology and Biostatistics[4]; University of Texas Health Science Center at San Antonio. Division of Pulmonary and Critical Care Medicine[8], University of Connecticut School of Medicine. VA Pittsburgh Health Care System[6] and Division of General Internal Medicine[7], Department of Medicine, University of Pittsburgh.

Word count: 2439
Key Words: inhaled corticosteroids, pneumonia, chronic obstructive pulmonary disease, mortality

Corresponding author: Eric Mortensen, MD, MSc, FACP
STVHCS/UTHSCSA
VERDICT research program (11C6)
7400 Merton Minter Boulevard
San Antonio Texas, 78229
Phone: (210)-617-5314
Fax: (210) 567-4423
Email: mortensene@uthscsa.edu

The project described was supported by Grant Number R01NR010828 from the National Institute of Nursing Research. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Nursing Research or the National Institutes of Health. This material is the result of work supported with resources and the use of facilities at the South Texas Veterans Health Care System. Dr. Restrepo is supported by a Department of Veteran Affairs Veterans Integrated Service Network 17 new faculty grant and National Health Institute Grant KL2 RR025766. Dr Copeland is supported by Veterans Health Administration Grant MRP-05-145. The funding agencies had no role in conducting the study, or role in

the preparation, review, or approval of the manuscript.

The views expressed in this article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs.

Contributions:
Funding: EMM; Conception and design: EMM, MIR AA; Analysis and interpretation: EMM, MIR, AA, DC, MJVP, MLM; Drafting the manuscript for important intellectual content: DC, MJF, AA, MIR, MJP, MLM, BN, CG.

ABSTRACT

Background: Treatment with inhaled corticosteroids (ICS) for those with chronic obstructive pulmonary disease (COPD) has been shown to be associated with an increased incidence of pneumonia. However, it is unclear if this is associated with increased mortality. The aim of this study was to examine the effects of prior ICS use on clinical outcomes for patients with COPD hospitalized with pneumonia.

Methods: We conducted a retrospective cohort study using the national administrative databases of the Department of Veterans Affairs. Eligible patients had a pre-existing diagnosis of COPD, a discharge diagnosis of pneumonia, and received treatment with one or more appropriate pulmonary medications prior to hospitalization. Outcomes included mortality, use of invasive mechanical ventilation, and vasopressor use.

Results: There were 15,768 patients (8,271 with ICS use, 7,497 no ICS use) with COPD who were hospitalized for pneumonia. There was also a significant difference for 90-day mortality (ICS: 17.3% vs. No ICS: 22.8%, $p<0.001$). Multilevel regression analyses demonstrated that prior receipt of ICS was associated with decreased mortality at 30 days (odds ratio [OR] 0.80, 95% confidence interval [CI] 0.72-0.89) and 90 days (OR 0.78, 95% CI 0.72-0.85), and decreased use of mechanical ventilation (OR 0.83, 95% CI 0.72-0.94). There was no significant association between receipt of ICS and vasopressor use (OR 0.88, 95% CI 0.74-1.04)

Conclusions: For patients with COPD**,** prior ICS use is independently associated with decreased risk of short-term mortality and use of mechanical ventilation following hospitalization for pneumonia.

Word count: 240

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the fourth most frequent cause of chronic morbidity and mortality in developed countries [1]. One of the current recommended COPD treatments by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) is inhaled corticosteroids (ICS) for symptomatic patients with a documented bronchodilator response on spirometry or for patients with forced expiratory volume in 1 second (FEV1) <50% predicted, which is indicative of moderate to severe COPD [2]. Although ICS treatment reduces the overall frequency of exacerbations of COPD [3], evidence suggests that ICS treatment is associated with an increased risk of pneumonia [4-6].

Despite several studies demonstrating that patients with COPD have an increased likelihood of developing pneumonia when receiving ICS [4-8], it remains unclear if ICS use is associated with adverse medical outcomes for patients with COPD. Prior studies examining the effect of COPD on pneumonia-related mortality have lead to conflicting conclusions [9-11]. Two systematic reviews examining the use of ICS therapy to manage COPD found no significant differences in mortality [4, 5]. Another study comparing COPD exacerbation rates between patients being treated with either salmeterol or a combination of salmeterol and fluticasone demonstrated that all-cause mortality was similar for patients hospitalized with pneumonia regardless of prior ICS use [6]. However, they did find increased mortality for ICS users with pneumonia within 30-days of hospitalization. Another recent study showed that ICS use was associated with

lower 30-day and 90-day mortality following pneumonia, however this study was not able to examine other clinically relevant outcomes or assess the effects of other appropriate respiratory medications received [12].

The aim of our study was to examine the association between prior ICS use and clinical outcomes, including mortality, need for mechanical ventilation, and vasopressors, in patients with COPD hospitalized with pneumonia. Our hypothesis was that prior ICS use would not be associated with worse clinical outcomes for patients with COPD hospitalized for pneumonia, after adjusting for potential confounders.

METHODS

We conducted a retrospective cohort study utilizing the national administrative databases of the Department of Veterans Affairs Health Care System to examine treatments and outcomes for elderly patients hospitalized with pneumonia. The VA databases are the repositories of clinical and administrative data from the more than 150 VA hospitals and 850 clinics [13]. The Institutional Review Board of the University of Texas Health Science Center at San Antonio approved this study.

Inclusion and Exclusion Criteria

We identified all patients who had a VA hospital stay during fiscal years 2002-2007 (Oct 2001-Sep 2007) with a primary discharge diagnosis of pneumonia (International Classification of Diseases, ninth revision (ICD-9) codes 480.0–483.99 or 485–487.0) or a secondary discharge diagnosis of pneumonia with a primary diagnosis of respiratory failure (ICD-9 code 518.81) or sepsis (ICD-9 code 038.xx) [14-16]. We included patients in this study if they (1) were 65 or older on the date of hospital presentation, (2) had at least 1 year of VA outpatient care prior to admission, (3) had received at least 1 dose of antibiotics within 48 hours of admission, and (4) had a prior diagnosis of COPD (ICD-9 codes 490-492,496) with use of at least one of the following respiratory medications during the 30-day period prior to hospitalization: any form of β-agonist, theophylline, tiotropium, or ipratropium bromide. For patients with multiple hospitalizations, we only assessed the first admission during the study period.

We excluded patients with history of asthma (ICD-9 codes 493.xx) and those who were treated with outpatient oral corticosteroids within 90-days prior to hospital admission.

Data

This study used demographic, utilization, and clinical data from the National Patient Care Database, pharmacy data from the VA Decision Support System and Pharmacy Benefits Management group, and mortality data from the VA vital status file. Encrypted patient identifiers were used to link the information from each database.

We obtained demographic information (age, sex, race, marital status) from inpatient and outpatient data files. We categorized race as white, black, other, and missing. We used ICD-9 codes for tobacco use (305.1, V15.82), attendance at a smoking cessation clinic, and/or use of medications for the treatment of nicotine dependence (Zyban, nicotine replacement, or varenicline) to identify recent tobacco use. We utilized information on the VA means test as a surrogate for income.

We assessed the presence of comorbid conditions using data from inpatient and outpatient administrative data using the Charlson-Deyo system to assign a comorbidity score for preexisting conditions [18-20]. The Charlson-Deyo comorbidity score is based on 19 comorbid conditions, each of which has an associated prognostic weight ranging from 1 to 6.

The primary independent variable of interest was the prior use of inhaled corticosteroids. We defined patients as current users of a given medication if they received a prescription within 90-days of the date of hospitalization. We classified the following medications as ICS: inhaled forms of triamcinolone, fluticasone, budesonide, beclamethasone and flunisolide.

To further control for potential confounding, we calculated each patient's count of unique drugs in each of the following classes for drugs filled/refilled within 90-days of presentation: cardiac medications, respiratory medications (other than ICS), and diabetic medications. Previous research has demonstrated that using the count of these medication classes is preferable to adjusting for the individual medications [21].

Outcomes

The primary outcomes for this study were 30-day and 90-day mortality. We chose these time periods for follow-up, because previous research demonstrated that mortality within 30-days is primarily pneumonia-related while mortality between 60 and 90 days is more frequently due to comorbid conditions [22]. Mortality was assessed through January 1, 2008 using the VA vital status file. Previous studies have demonstrated that this data source has a sensitivity of ~98% for veterans' deaths [23]. Secondary outcomes were use of invasive mechanical ventilation and vasopressor support during hospitalization.

Statistical Analyses

We used bivariate statistics to test the associations of demographic and clinical characteristics and mortality. Categorical variables were analyzed using the $\chi 2$ test, and continuous variables were analyzed using Student's *t* test. Due to the large sample size, we defined statistical significance using a two-tailed $p<0.01$.

For our primary analyses, we used generalized linear mixed-effect models with the patient's hospital as a random effect. We created separate models for each of the outcomes of interest, with ICS use and potential confounders as the independent variables. We included variables as potential confounders in the models if we hypothesized a priori that they would be associated with the severity of COPD or the outcome of interest. Potential confounders included in the models of mortality were age, gender, race, marital status, socioeconomic status, number of primary care visits within 1 year prior to admission, classes of medications, nursing home status, current tobacco use, the Charlson composite score, ICU admission, and receipt of guideline concordant antibiotics [24]. Classes of medications were cardiac, diabetic, and other respiratory drugs. In addition, we determined the most common respiratory medicine regimes and then repeated our primary analyses including only patients who received those regimes +/- ICS (e.g. for the short acting beta agonist (SABA) + ipratropium group we included only patients who used SABA + ipratropium +/- ICS but no other respiratory medications).

To analyze time-to-death for patients by receipt of ICS, we used Cox proportional hazard models to estimate and graph the baseline survivor functions after adjusting for the potential confounders used in the mortality analyses.

All analyses were performed using STATA 10 (College Station, Texas).

RESULTS

In the entire VA system, during the study period of fiscal years 2002-2007, there were 962,408 admissions for those > 65 years of age of which 66,531 were for pneumonia. A total of 15,768 patients admitted to 122 VA hospitals met all study eligibility criteria. Of these, 8,271 (52.5%) patients received ICS and 7,497(47.5%) did not receive ICS within 90-days of presentation. Among ICS users, the most commonly prescribed medications were flunisolide (51.2% of all ICS prescribed), fluticasone (27.8%), and triamcinolone (19.8%). In the cohort, 98.4% of all patients were male, mean age was 76.5 years (standard deviation 6.4 years) and 52.5% were married. Comparisons of patient characteristics stratified by prior ICS use revealed few clinically significant differences between the two groups (Table 1). Patients with ICS use were less likely to have cancer or current tobacco use, and were more likely to be married, receiving long acting beta agonist and/or tiotropium therapy.

For this cohort, 1,859 (11.8%) patients died within 30 days, and 3,139 patients (19.9%) within 90 days. Table 2 shows outcomes by ICS use. There were significant differences in both 30-day mortality (ICS users 10.2% vs. non- users 13.6%, $p<0.001$) and 90-day mortality (ICS users 17.3% vs. non-users 22.8%, $p<0.001$). Patients who received ICS were significantly less likely to need mechanical ventilation (ICS users 5.9% vs. non-users 7.3%, $p=0.001$), but there was no significant difference in the need for vasopressors.

In the multilevel regression analyses (Table 3), after adjusting for potential confounders, prior receipt of ICS was associated with decreased 30-day mortality (Odds Ratio [OR] 0.80, 95% Confidence Interval [CI] 0.72-0.89), and 90-day mortality (OR 0.78, 95% CI 0.72-0.85). In addition, patients who had received ICS were less likely to require invasive mechanical ventilation (OR 0.83, 95% CI 0.72-0.94) but there was no significant association with need for vasopressors (OR 0.88, 95% CI 0.74-1.04.) When we exclude those patients with cancer we found similar results: 30-day mortality (OR 0.75, 95% CI 0.68-0.82), 90-day mortality (OR 0.78, 95% CI 0.73-0.85), mechanical ventilation (OR 0.94, 95% CI 0.82-1.08), and vasopressors (OR 0.91, 95% CI 0.78-1.07.)

We then restricted the multilevel models to patients who received the two most common combinations of respiratory medications (Table 4) with the reference group being those not receiving ICS in order to determine the impact of other pulmonary medications. For the group that received short acting beta agonist and ipratropium +/- ICS (total n= 11,696), ICS use was not significantly associated with worsening of any of the clinical outcomes, and receipt of ICS was associated with improved 90-day mortality, and less need for mechanical ventilation, but not 30-day mortality or vasopressor use. For those who received short acting beta agonist, ipratropium, and a long acting beta-agonist +/- ICS (total n=1,851) there were no significant associations with the outcomes of interest.

DISCUSSION

In this study, we found that among patients hospitalized for pneumonia, those with a pre-existing diagnosis of COPD and prior ICS use had significantly lower rates of 30- and 90-day mortality and use of mechanical ventilation. In addition, when we compared those who receive a given regime of pulmonary medications +/- ICS we found no association with worse outcomes. Several studies have demonstrated that ICS use is associated with an increased incidence of pneumonia [4-8], however our research did not demonstrate a significant association between ICS use and increased mortality after pneumonia.

Although ICS use has been shown to reduce the frequency of exacerbations and improve quality of life in patients with COPD [25], studies have consistently shown an increased risk of pneumonia for those receiving ICS as part of therapy for COPD [4-8, 26, 27]. Unfortunately the randomized control studies of ICS use in COPD were limited by no formal definition of pneumonia, and by the small number of patients who developed pneumonia, so they were unable to address whether mortality is increased for those patients on ICS who do develop pneumonia. To date, only Ernst et al. [6] has shown an association between increased pneumonia-related mortality and receipt of ICS. Malo de Molina et al., using a similar but less extensive and detailed database, demonstrated that receipt of ICS was associated with decreased 30- and 90-day mortality for those patients with COPD hospitalized with pneumonia [12].

Our study found that ICS use in patients with COPD hospitalized with pneumonia was associated with decreased mortality. One potential explanation for these findings is the effect of corticosteroids on the inflammatory response. ICS have been shown to reduce both non-specific inflammation and neutrophil influx into the lungs [28-31]. It might be expected that reducing the inflammatory response would negatively impact clinical outcomes, but evidence suggests that an excessive inflammatory response may have harmful effects during an infection [32]. ICS treatment may suppress the inflammatory response during the acute infection, blocking an excessive inflammatory response and the related harmful effects. Similarly, excessive neutrophil sequestration in the lungs may cause a variety of lung diseases and injuries [33, 34]. The presence of microorganisms during pneumonia leads to increased leukocyte migration. This effect may be counterbalanced by ICS treatment, preventing excess sequestration and subsequent lung injury. Another possible explanation for our findings is that ICS treatment may reduce bacterial load. Reduction of bacterial load by ICS has been demonstrated in a mouse model of lung infection where inhaled fluticasone proprionate reduced the invasion of airway epithelial cells by *Streptococcus pneumonia* and *Haemophilus influenza* [35].

Although our study was a large database analysis and subject to the recognized limitations of such studies, we carefully assembled our cohort from complete patient discharge data to avoid ascertainment bias. Our sample was predominantly men due to

our use of VA administrative data, and it is possible that women may have differential responsiveness to ICS as compared to men. Due to the lack of pulmonary function data in these databases, we had to rely upon ICD-9 codes and medication use to define COPD. However a recent paper demonstrated that 80% of VA patients with an ICD-9 code of COPD had pulmonary function tests consistent with COPD [17]. In addition, the proportion of COPD patients in each GOLD class group utilizing COPD medications increases by class, with 59% of GOLD class 1-2 ,and 91% of class 3-4, utilizing these medications [17]. Prior studies have also demonstrated that clinicians frequently treat patients without this data [36]. We believe that those with exposure to ICS would be much more likely to have pulmonary function tests confirming COPD diagnosis, more likely to have severe COPD, and therefore be at high risk of death as compared to those who do not meet spirometry criteria for COPD. In addition, we are unable to examine the impact of ICS use upon the incidence of hospitalization for pneumonia, and therefore are unable to determine if this might impact our results. We are also unable to explicitly examine issues regarding adherence and quality of care due to the data sources. Finally, as in any non-experimental study, we are unable to state that the use of ICS in COPD patients reduces mortality.

In conclusion, we showed that prior outpatient therapy with ICS was associated with significantly lower 30- and 90-day mortality in patients with COPD who were hospitalized with pneumonia, after adjusting for potential confounders. Additional

studies are needed to confirm the safety and efficacy of these medications in patients with COPD and for those who develop pneumonia while utilizing them.

REFERENCES

1. Murray, C.J. and A.D. Lopez, *Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study.* Lancet, 1997. **349**(9063): p. 1436-42.
2. Pauwels, R.A., A.S. Buist, P. Ma, et al., *Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: National Heart, Lung, and Blood Institute and World Health Organization Global Initiative for Chronic Obstructive Lung Disease (GOLD): executive summary.* Respir Care, 2001. **46**(8): p. 798-825.
3. Calverley, P., R. Pauwels, J. Vestbo, et al., *Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial.* Lancet, 2003. **361**(9356): p. 449-56.
4. Drummond, M.B., E.C. Dasenbrook, M.W. Pitz, et al., *Inhaled corticosteroids in patients with stable chronic obstructive pulmonary disease: a systematic review and meta-analysis.* Jama, 2008. **300**(20): p. 2407-16.
5. Singh, S., A.V. Amin, and Y.K. Loke, *Long-term use of inhaled corticosteroids and the risk of pneumonia in chronic obstructive pulmonary disease: a meta-analysis.* Arch Intern Med, 2009. **169**(3): p. 219-29.
6. Ernst, P., A.V. Gonzalez, P. Brassard, et al., *Inhaled corticosteroid use in chronic obstructive pulmonary disease and the risk of hospitalization for pneumonia.* Am J Respir Crit Care Med, 2007. **176**(2): p. 162-6.

7. Almirall, J., I. Bolibar, X. Balanzo, et al., *Risk factors for community-acquired pneumonia in adults: a population-based case-control study.* Eur Respir J, 1999. **13**(2): p. 349-55.

8. Farr, B.M., C.L. Bartlett, J. Wadsworth, et al., *Risk factors for community-acquired pneumonia diagnosed upon hospital admission. British Thoracic Society Pneumonia Study Group.* Respir Med, 2000. **94**(10): p. 954-63.

9. Rello, J., A. Rodriguez, A. Torres, et al., *Implications of COPD in patients admitted to the intensive care unit by community-acquired pneumonia.* Eur Respir J, 2006. **27**(6): p. 1210-6.

10. Restrepo, M.I., E.M. Mortensen, J.A. Pugh, et al., *COPD is associated with increased mortality in patients with community-acquired pneumonia.* Eur Respir J, 2006. **28**(2): p. 346-51.

11. Tejerina, E., F. Frutos-Vivar, M.I. Restrepo, et al., *Prognosis factors and outcome of community-acquired pneumonia needing mechanical ventilation.* J Crit Care, 2005. **20**(3): p. 230-8.

12. Malo de Molina, R., E.M. Mortensen, M.I. Restrepo, et al., *Inhaled corticosteroid use is associated with lower mortality for subjects with chronic obstructive pulmonary disease and hospitalized with pneumonia.* Eur Respir J, 2010.

13. Brown, S.H., M.J. Lincoln, P.J. Groen, et al., *VistA--U.S. Department of Veterans Affairs national-scale HIS.* Int J Med Inform, 2003. **69**(2-3): p. 135-56.

14. Marrie, T.J., H. Durant, and E. Sealy, *Pneumonia--the quality of medical records data.* Med Care, 1987. **25**(1): p. 20-4.

15. Whittle, J., M.J. Fine, D.Z. Joyce, et al., *Community-acquired pneumonia: can it be defined with claims data?* American Journal of Medical Quality, 1997. **12**(4): p. 187-93.

16. Aronsky, D., P.J. Haug, C. Lagor, et al., *Accuracy of administrative data for identifying patients with pneumonia.* Am J Med Qual, 2005. **20**(6): p. 319-28.

17. Joo, M.J., T.A. Lee, B. Bartle, et al., *Patterns of Healthcare Utilization by COPD Severity: A Pilot Study.* Lung, 2008. **186**(5): p. 307-12.

18. Deyo, R.A., D.C. Cherkin, and M.A. Ciol, *Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases.* J Clin Epidemiol, 1992. **45**(6): p. 613-9.

19. Southern, D.A., H. Quan, and W.A. Ghali, *Comparison of the Elixhauser and Charlson/Deyo methods of comorbidity measurement in administrative data.* Med Care, 2004. **42**(4): p. 355-60.

20. Charlson, M., T.P. Szatrowski , J. Peterson, et al., *Validation of a combined comorbidity index.* J Clin Epidemiol, 1994. **47**(11): p. 1245-1251.

21. Schneeweiss, S., J.D. Seeger, M. Maclure, et al., *Performance of comorbidity scores to control for confounding in epidemiologic studies using claims data.* Am J Epidemiol, 2001. **154**(9): p. 854-64.

22. Mortensen, E.M., C.M. Coley, D.E. Singer, et al., *Causes of death for patients with community-acquired pneumonia: results from the Pneumonia Patient Outcomes Research Team cohort study.* Arch Intern Med, 2002. **162**(9): p. 1059-64.

23. Sohn, M.W., N. Arnold, C. Maynard, et al., *Accuracy and completeness of mortality data in the Department of Veterans Affairs.* Popul Health Metr, 2006. **4**: p. 2.

24. Mandell, L.A., R.G. Wunderink, A. Anzueto, et al., *Infectious diseases society of america/american thoracic society consensus guidelines on the management of community-acquired pneumonia in adults.* Clin Infect Dis, 2007. **44 Suppl 2**: p. S27-72.

25. Calverley, P.M., J.A. Anderson, B. Celli, et al., *Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease.* N Engl J Med, 2007. **356**(8): p. 775-89.

26. Kardos, P., M. Wencker, T. Glaab, et al., *Impact of salmeterol/fluticasone propionate versus salmeterol on exacerbations in severe chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 2007. **175**(2): p. 144-9.

27. Wedzicha, J.A., P.M. Calverley, T.A. Seemungal, et al., *The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide.* Am J Respir Crit Care Med, 2008. **177**(1): p. 19-26.

28. Barnes, N.C., Y.S. Qiu, I.D. Pavord, et al., *Antiinflammatory effects of salmeterol/fluticasone propionate in chronic obstructive lung disease.* Am J Respir Crit Care Med, 2006. **173**(7): p. 736-43.

29. Llewellyn-Jones, C.G., T.A. Harris, and R.A. Stockley, *Effect of fluticasone propionate on sputum of patients with chronic bronchitis and emphysema.* Am J Respir Crit Care Med, 1996. **153**(2): p. 616-21.

30. Sin, D.D., P. Lacy, E. York, et al., *Effects of fluticasone on systemic markers of inflammation in chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 2004. **170**(7): p. 760-5.

31. van Overveld, F.J., U.A. Demkow, D. Gorecka, et al., *Inhibitory capacity of different steroids on neutrophil migration across a bilayer of endothelial and bronchial epithelial cells.* Eur J Pharmacol, 2003. **477**(3): p. 261-7.

32. Lekkou, A., M. Karakantza, A. Mouzaki, et al., *Cytokine production and monocyte HLA-DR expression as predictors of outcome for patients with community-acquired severe infections.* Clin Diagn Lab Immunol, 2004. **11**(1): p. 161-7.

33. Kambas, K., M.M. Markiewski, I.A. Pneumatikos, et al., *C5a and TNF-alpha up-regulate the expression of tissue factor in intra-alveolar neutrophils of patients with the acute respiratory distress syndrome.* J Immunol, 2008. **180**(11): p. 7368-75.

34. Zemans, R.L., S.P. Colgan, and G.P. Downey, *Transepithelial migration of neutrophils: mechanisms and implications for acute lung injury.* Am J Respir Cell Mol Biol, 2009. **40**(5): p. 519-35.

35. Barbier, M., A. Agusti, and S. Alberti, *Fluticasone propionate reduces bacterial airway epithelial invasion.* Eur Respir J, 2008. **32**(5): p. 1283-8.

36. Lee, T.A., B. Bartle, and K.B. Weiss, *Spirometry use in clinical practice following diagnosis of COPD.* Chest, 2006. **129**(6): p. 1509-15.

Table 1: Patient Demographic and Clinical Characteristics by the Use of Outpatient Inhaled Corticosteroids

	Inhaled Corticosteroids Used Prior to Hospitalization		
Variable	**Yes N = 8,271 (%)**	**No N = 7,497 (%)**	**p-value**
Age in years, mean (SD)	76.3 (6.32)	76.8 (6.46)	<0.001
Male	8,142 (98.4)	7,375 (98.4)	0.74
Race			
White	7,262 (87.8)	6,424 (85.7)	
Black	642 (7.8)	741 (9.9)	
Other	76 (0.9)	77 (1.0)	
Missing	291 (3.5)	255 (3.4)	<0.001
Married	4,549 (53.7)	3,930 (46.4)	<0.001
Smoker	3,947 (47.7)	3,776 (50.4)	<0.001
Alcohol abuse	346 (4.2)	401 (5.4)	<0.001
Drug abuse	98 (1.2)	109 (1.5)	0.14
Preexisting Comorbid Conditions			
Congestive Heart Failure	2,468 (29.8)	2,308 (30.8)	0.20
Peripheral vascular disorders	1,337 (16.2)	1,291 (17.2)	0.08
Hemiplegia or paraplegia	82 (1.0)	102 (1.4)	0.03
Diabetes, uncomplicated	2,345 (28.4)	2,121 (28.3)	0.93
Diabetes, complicated	652 (7.9)	586 (7.8)	0.88
Renal disease	870 (10.5)	874 (11.7)	0.02
Moderate or severe liver disease	19 (0.2)	25 (0.3)	0.22
Mild liver disease	60 (0.7)	58 (0.8)	0.73
Peptic ulcer disease	311 (3.8)	268 (3.6)	0.54
AIDS	15 (0.2)	9 (0.1)	0.32
Metastatic cancer	261 (3.2)	328 (4.4)	<0.001
Malignancy	2,038 (24.6)	2,047 (27.3)	<0.001
Leukemia	151 (1.8)	147 (2.0)	0.53
Rheumatoid arthritis/ Collagen vascular diseases	163 (2.0)	149 (2.0)	0.94
Cerebrovascular disease	1,258 (15.2)	1,258 (16.8)	0.007
Myocardial infarction	592 (7.2)	588 (7.8)	0.10
Dementia	247 (3.3)	162 (2.0)	< 0.001

Diabetes medications, mean (SD)	0.19 (0.49)	0.18 (0.48)	0.23
Cardiovascular medications, mean (SD)	1.30 (1.41)	1.49 (1.39)	<0.001
Respiratory medications			
Ipratroprium	5,646 (68.3)	5,291 (70.6)	0.002
Long acting beta-agonists	1,952 (23.6)	671 (9.0)	<0.001
Tiotroprium	406 (4.9)	131 (1.8)	<0.001
Theophylline	898 (10.8)	626 (8.4)	<0.001

Table 2: Univariate Outcomes by the Prior Receipt of ICS

Variable	ICS Use Prior to Hospitalization		p-value
	Yes N = 8,271 (%)	No N = 7,497 (%)	
30-day mortality	841 (10.2)	1,018 (13.6)	<0.001
90-day mortality	1,430 (17.3)	1,709 (22.8)	<0.001
Mechanical ventilation	491 (5.9)	544 (7.3)	0.001
Vasopressors	302 (3.7)	318 (4.2)	0.06

Abbreviations: ICS- Inhaled corticosteroids

Table 3: Results of Multilevel Regression Models After Adjusting for Potential Confounders*

Outcome	Odds Ratio	95% Confidence Interval
30-day mortality	0.80	0.72 – 0.89
90-day mortality	0.78	0.72 – 0.85
Mechanical ventilation	0.83	0.72 – 0.94
Vasopressors	0.88	0.74 – 1.04

*after adjusting for age, gender, race, marital status, socioeconomic status, classes of medications, nursing home status, current tobacco use, Charlson composite score, ICU admission, and receipt of guideline concordant antibiotics.

Table 4- Results of Multilevel Regression Analyses by the Most Common Pulmonary Medications Received*

	Clinical Outcomes Odds Ratio (95% CI)			
Pulmonary medications prescribed	**30-day mortality**	**90-day mortality**	**MV**	**Vasopressors**
SABA+IPRA	1.0	1.0	1.0	1.0
SABA+ IPRA + ICS	0.82 (0.67 - 1.0)	0.78 (0.66 - 0.93)	0.64 (0.48 - 0.86)	0.80 (0.57 - 1.13)
SABA+ IPRA + LABA	1.0	1.0	1.0	1.0
SABA+ IPRA + LABA+ICS	0.88 (0.56 - 1.38)	0.99 (0.67 - 1.46)	1.08 (0.60 - 1.9)	1.42 (0.61 - 3.3)

Abbreviations: CI – confidence interval, SABA- Short acting beta agonist, IPRA- ipratropium bromide, ICS- inhaled corticosteroid, LABA- long acting beta agonist, , MV- mechanical ventilation

*After adjusting for age, gender, race, marital status, socioeconomic status, classes of medications, nursing home status, current tobacco use, Charlson composite score, ICU admission, and receipt of guideline concordant antibiotics

Figure 1- Survival curves for patients with COPD hospitalized with pneumonia by use of ICS versus non-use (p<0.0001) after adjusting for potential confounders

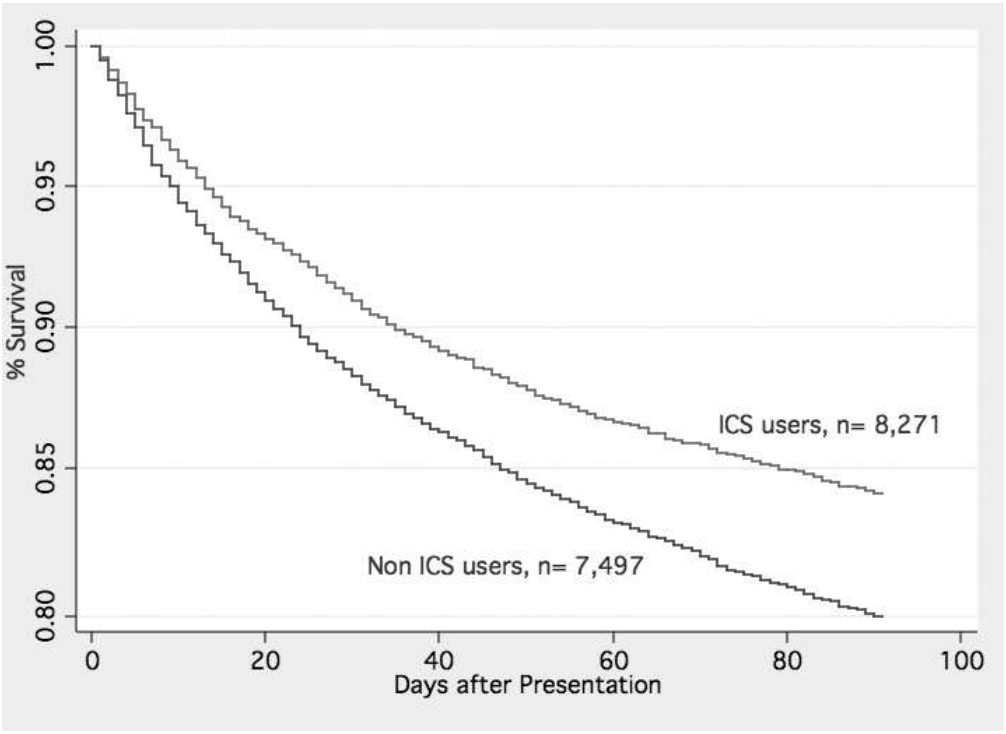

Figure 1- Survival curves for patients with COPD hospitalized with pneumonia by use of ICS versus non-use (p<0.0001) after adjusting for potential confounders
252x183mm (72 x 72 DPI)