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Inhaled corticosteroids and risk of pneumonia in newly diagnosed COPD

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Summary
Introduction: The use of inhaled corticosteroids (ICS) in COPD may be associated with an increased risk of pneumonia. Little is known of this risk in newly diagnosed COPD patients. The objective of this study was to determine if the use of ICS among newly diagnosed COPD patients is associated with an increased risk of pneumonia hospitalizations.
Methods: Using data from the Department of Veterans Affairs and Centers for Medicare and Medicaid Services, a nested case–control study was performed. We identified patients 65 years of age or older with a new diagnosis of COPD from 1998 to 2002. A total of 145,586 patients were identified. Cases were defined based on hospitalization for pneumonia and exposure was prior use of ICS. Up to 10 controls were matched for each case based on age, sex, month and year of the case. The association between ICS use and pneumonia was evaluated with conditional logistic regression controlling for age, comorbidities, medication classes associated with the risk of pneumonia, and markers of COPD severity.
Results: There were 13,995 cases of pneumonia. The cohort was predominantly male with an average age of 75.1 (SD = 5.4) years. The rate of pneumonia was 6.4 per 100 person-years. After adjustment for covariates, patients with current use of ICS were 1.38 (95% CI, 1.31–1.45) times more likely to have a hospitalization for pneumonia than those without current use of ICS.

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Conclusions: The use of ICS among patients with newly diagnosed COPD is associated with an increased risk of hospitalization for pneumonia.
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Introduction

Inhaled corticosteroids (ICS) are used by a large proportion of patients with chronic obstructive pulmonary disease (COPD),[1–4] however, the role of ICS in the treatment of COPD continues to evolve. Although clinical studies have shown improved outcomes such as decrease in acute exacerbations of COPD with the use of ICS,[5–10] more recently, ICS use in COPD has also been associated with an increase in the rate of pneumonia.[7,8,10,11]

The Towards a Revolution in COPD Health study found a significant increase in the rate of pneumonias in those receiving fluticasone alone (18.3%) and those receiving fluticasone and salmeterol in combination (19.6%) compared to placebo (12.3%).[7] Other studies evaluating the effect of fluticasone and salmeterol, in combination, versus salmeterol alone or tiotropium alone on COPD exacerbations also found an increase in the rate of pneumonia in the fluticasone containing regimen.[8,10,11] In a recent Canadian study using health databases to evaluate the risk of pneumonia hospitalizations and the use of ICS in pneumonia, there was a 1.7-fold increase in the rate of pneumonias in those receiving ICS.[12] Meta-analyses to assess the effects of ICS on the risk of pneumonia in COPD patients have shown conflicting results. A meta-analysis evaluating the risks and benefits of adjunctive ICS therapy in severe/very severe COPD also found an increased risk of pneumonia in those receiving ICS (RR, 1.68, 95% CI 1.28–2.21).[13] Another meta-analysis to determine adverse events in patients with stable COPD compared to nonsteroid inhaled therapy found that patients receiving ICS therapy had a relative risk of pneumonia of 1.34 (95% CI, 1.03–1.75).[14] However, the most recent meta-analysis evaluating the use of a specific ICS, budesonide, for up to 12 months only did not show increased risk of pneumonia in patient with COPD.[15]

Unlike asthma, where ICS has an established role, the use of ICS in COPD is becoming more unclear. The reduction in acute exacerbations of COPD with the use of ICS has been questioned due to improper statistical techniques used in studies to come to this conclusion.[16,17] To help clarify the role of ICS, we need to better understand the risks associated with its use in various COPD populations, especially as it relates to serious pneumonias that require hospitalization. Those with newly diagnosed COPD are likely to have more limited long-term exposure and possibly less severe disease. Understanding the risk to benefit ratio of ICS in this population is essential prior to recommending and/or initiating therapy with ICS. The objective of this study was to determine if the use of ICS among newly diagnosed COPD patients is associated with an increased risk of serious pneumonias.

Methods

This study was approved by the Institutional Review Board at the Hines VA Hospital, Jesse Brown VA Medical Center, and the University of Illinois at Chicago.

Study design and cohort

We conducted a nested case–control study in a cohort of Veterans Affairs (VA) patients with COPD. VA administrative data was used to identify patients 65 years of age or older with a diagnosis of COPD (ICD-9 codes 491.x, 492.x, 496) from October 1, 1998 to September 30, 2002. The date of diagnosis or entry date was defined as the following: (1) the discharge date of a hospitalization with COPD as a primary diagnosis, or (2) date of the second outpatient clinic visit with a COPD diagnosis within a one year period. To ensure that we included patients with a new diagnosis of COPD and not those with COPD who were new to the VA, patients also required at least one encounter in the VA within one year prior to the entry date. Exclusion criteria included the following: (1) a diagnosis of COPD one year prior to the entry date to capture new cases, and (2) a concomitant diagnosis of asthma (ICD-9 code 493.x). Patients meeting all criteria were followed until their first hospitalization for pneumonia, death, or until September 30, 2003. Once the patients to be included were identified, a combination of VA administrative and Centers for Medicare and Medicaid Services (CMS) data was used to identify the case, exposure, and covariates.

Case definition and controls

A case was defined as a hospitalization with a primary diagnosis of pneumonia (International classification of diseases, 9th version (ICD-9) code 480.x to 486.x, and 487.0) during the follow-up period. The date of the hospitalization was called the event date. Death within 30 days of the event was identified. For each case identified, up to 10 control patients matched for age (within 5 years) and sex were selected at random from those who entered the cohort in the same month and year as the case patient. The control patients had to be at risk on the date of the corresponding case and this date was defined as the event date for the control patients.

Exposure

Exposure was defined as the use of inhaled corticosteroids (ICS) prior to the event date. ICS included orally inhaled beclomethasone, budesonide, flunisolide, fluticasone, and triamcinolone. Doses were converted to beclomethasone equivalents[18] and cumulative exposure was calculated. The average daily dose was calculated for each patient and categorized into low ($\leq$1000 μg per day), moderate ($>$1000–$\leq$2000 μg per day), and high ($>$2000 μg per day) doses. Exposure was also categorized based on timing of ICS exposure as well as dose of ICS exposure, and the interaction between time and dose. Exposure time was divided into 90 day interval prior to the event. Current use was defined as use within 90 days prior to the event date.

Covariates

Covariates included were age, comorbidities, medication classes associated with the risk of pneumonia, and severity of COPD. Comorbidities were determined by a combination of diagnostic codes and dispensing of prescriptions associated with particular disorders at any time from a year prior to entry date to the event date. ICD-9 codes were used to identify diabetes mellitus, hypertension, chronic kidney disease, chronic liver disease, heart disease (i.e. heart failure and coronary artery disease), cancer, alcoholism, substance abuse, depression, mental health disorders, dementia, and other lung diseases (i.e. cystic fibrosis with pulmonary manifestations, pneumoconiosis, and bronchiectasis). Prescription dispensing of various classes of medication were used to identify gastrointestinal disease (i.e. histamine antagonists, proton pump inhibitors) and hyperlipidemia (i.e. 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors).

Prescriptions of classes of medications that could be associated with the risk of pneumonia were also included. These included central nervous system medications (i.e. sedatives, hypnotics, barbiturates, benzodiazepines, anticonvulsants, and antiparkinson therapy) and immunosuppressant/disease modifying antirheumatic drugs (i.e. cyclophosphamide, chlorambucil, methotrexate, cyclosporine, azathioprine, cyclosporine, tacrolimus, muromonab-cd3, anti-malarials, antirheumatic gold compounds, sulfasalazine).

Severity of COPD was determined by a combination of number of dispensed prescriptions of respiratory medications (i.e. short-acting β-agonists, ipratropium, long-acting β-agonists, and theophylline) and antibiotics (excluding those prescribed 30 days prior to the event date), average daily dose of oral corticosteroids, count of primary care visits, count of emergency department visits, and number of acute exacerbations of COPD. All were measured in the year before the event date, except oral corticosteroids which was measured 180 days prior to the event date. Acute exacerbations of COPD were identified using a combination of inpatient, outpatient, and pharmacy data. Exacerbations were defined based on the presence of an ICD-9 code related to COPD and/or specific to an exacerbation (ICD-9 490, 491, 491.0, 491.1, 491.2, 491.21, 491.22, 491.8, 491.9, 492.x) with one of the following: (1) an inpatient hospitalization; (2) an emergency department visit; or (3) an outpatient visit with either an oral steroid or antibiotic prescription dispensed within five days of the visit with less than a 30 day supply. Outpatient visits that included a diagnosis for infections other than respiratory infections (e.g. cellulitis) were not included as an exacerbation. Exacerbations were assumed to last 30 days and after 30 days a new acute exacerbation could be identified.[19,20]

Statistical analysis

Conditional logistic regression was used to determine the association between ICS exposure and the risk of hospitalization for pneumonia in patients with COPD. Odds ratios and 95% confidence intervals were used to quantify the risk of hospitalization with pneumonia in adjusted and unadjusted conditional logistic regression models. Adjusted models included the covariates listed above. Conditional logistic regression was also used to estimate odds ratios. Separate odds ratios were also estimated for interaction between current use of ICS (90 days) and oral corticosteroids. Recent use of oral corticosteroids was defined as having oral drugs dispensed between 31 and 90 days before the event date, as more recent use at time of pneumonia may be due to worsening COPD. All statistical analysis was performed using STATA version 9.2 (StataCorp., College Station, TX).

Sensitivity analysis

To account for chronic oral corticosteroid use as a marker of severity of COPD, we ran a sensitivity analysis excluding these patients. As it is sometimes difficult to discern chronic oral corticosteroid dispensing from daily dose prescriptions to be taken as steroid bursts, we defined chronic oral use of corticosteroids in the following two ways using a medication possession ratio (MPR). The MPR is the ratio of the number of days supply of medication dispensed over the six month time frame. A patient was considered to be receiving chronic oral corticosteorids if six months prior to the event, the following was noted: (1) MPR of $\geq$0.8 and an average daily dose of $\geq$10 mg/day, and (2) an MPR of $\geq$0.5 and an average daily dose of $\geq$20 mg/day. The conditional logistic regression model was again used adjusting for covariates used in the original analysis.

Results

A total of 145,586 were included in the cohort. From this cohort, a total of 13,995 cases were matched to 131,591 controls (average of 9.4 controls/case). The population was predominantly male (cases = 99.1%, controls = 99.8%) and the average age was 75.4 (SD = 5.6) years for the cases and 75.0(SD = 5.4) years for the controls. The baseline characteristics of the case and control subjects are shown in Table 1. The average duration of follow-up was 1.49 (SD = 1.11) years per person. During 217,558 person-years of follow-up, the rate of hospitalization for pneumonia (cases) was 6.4 cases per 100 person-years.

The average daily dose of ICS and oral corticosteroids stratified by days prior to the event are shown in Table 2. A total of 21.7% of case patients were exposed to ICS 90 days prior to the hospitalization for pneumonia compared to 16.0% of the control patients ($p < 0.001$). The majority of the patients using ICS 90 days prior were using low doses ($\leq$1000 μg/day). Table 3 shows the adjusted odds ratio of hospitalization for pneumonia associated with ICS use. After adjustment for covariates, patients with current use of ICS (90 days) were 1.38 (95% CI, 1.31−1.45) times more likely to have a hospitalization for pneumonia than those without current use of ICS. A dose−response relationship or a relationship based on time of use was not noted. When stratified by time of use and dose, those with current and low dose of ICS were most likely to be hospitalized with pneumonia (OR = 1.51, 95% CI 1.41−1.62). Table 4 shows the adjusted odds ratio of hospitalization for pneumonia associated with ICS and oral corticosteroid use. When

Table 1 Characteristics of cases of pneumonia and matched controls.

	Case subjects	Control subjects
Number	13,995	131,591
Age(yr), mean (SD)	75.4 (5.6)	75.0 (5.4)
Gender, % male	99.1	99.8
Comorbidities		
Diabetes, %	32.2	27.9
Hypertension, %	76.0	76.9
Kidney disease, %	12.1	7.0
Liver disease, %	2.0	1.2
Heart disease %	66.1	55.2
Cancer, %	41.0	35.2
Alcohol abuse, %	5.0	3.8
Substance abuse, %	23.7	20.4
Depression, %	18.7	15.0
Mental health, %	8.0	5.2
Dementia, %	5.4	3.5
Other lung diseases, %	2.7	2.2
Central nervous system drugs, %	15.9	11.8
Gastrointestinal drugs, %	46.3	41.3
Hyperlipidemia drugs, %	32.1	36.5
Immunosuppressive drugs, %	0.8	0.5
≥1 COPD exacerbation, 1 year prior, %	42.8	21.2
Mean (SD)	1.13 (2.41)	0.46 (1.49)
Antibiotic Use 1 year prior to event, number of prescriptions, Mean (SD)	1.11 (2.42)	0.76 (1.85)
Medication use 180 days prior to event date		
LABA, %	11.5	8.7
SABA, %	52.3	41.7
IPRA, %	34.2	24.0
THEO, %	7.9	5.4
Oral corticosteroids (%)	17.1	7.9
Health care utilization		
PCP visits, mean (SD)	7.0 (7.8)	6.4 (7.0)
ED visits, mean (SD)	0.7 (1.9)	0.3 (1.3)
Hospitalizations, mean (SD)	1.1 (1.6)	0.4 (1.0

LABA, long-acting bronchodilators; SABA, short-acting bronchodilators; IPRA, ipratropium; THEO, theophylline; PCP, primary care visits; ED, emergency department visits.

Table 2 Oral and inhaled corticosteroid use prior to date of hospitalization for pneumonia or day at risk for pneumonia.

	Cases	Controls	*p*-Value
ICS use			
Average daily dose, μg/day, mean (SD)			
90 days	344.4 (989.0)	265.3 (879.9)	<0.001
91–180 days	155.6 (471.0)	124.0 (425.7)	<0.001
181–270 days	93.5 (303.5)	75.5 (268.0)	<0.001
271–365 days	65.9 (219.5)	52.9 (195.0)	<0.001
1 year	213.7 (556.9)	168.1 (503.9)	<0.001
Oral steroid use, mean (SD)			
No. of prescriptions, 90 days	0.3 (0.8)	0.1 (0.5)	<0.001
No. of prescriptions, 91–180 days	0.1 (0.5)	0.1 (0.4)	<0.001
Ave daily dose (mg/day), 31–90 days	1.2 (5.4)	0.4 (3.1)	<0.001
Ave daily dose (mg/day), 91–180 days	0.7 (4.3)	0.3 (1.8)	<0.001
Cumulative dose (mg), 31–90 days	108.6 (487.0)	38.8 (278.5)	<0.001
Cumulative dose (mg), 91–180 days	123.2 (782.0)	45.6 (331.1)	<0.001

stratified by use of oral and inhaled corticosteroids, those with current use of inhaled and oral corticosteroids were the most likely to have a hospitalization for pneumonia (OR = 1.70, 95% CI 1.51–1.90). Association of pneumonia and oral corticosteroids was stronger than with ICS alone and the recent use of both had a stronger relationship then the use of one alone. However, after excluding those with chronic oral corticosteroids use, the OR was 1.39 (95% CI 1.19–1.62) after excluding those with an MPR ≥0.8 and average daily dose ≥10 mg/day and 1.43 (95% CI, 1.22–1.66) after excluding those with an MPR ≥0.5 and average daily dose ≥20 mg/day.

In those hospitalized with pneumonia, 16.4% died within 30 days of being hospitalized ($n = 2290$). The 30 day mortality for those with current use of ICS was 13.3% and for those without current use of ICS was 17.2% ($p < 0.001$). The 30 day mortality for those with current use of oral corticosteroids was 19.8% and for those without current use was 15.9% ($p < 0.001$).

Discussion

We found that within a cohort of patients with newly diagnosed COPD, the current use of ICS was associated with an increased risk of being hospitalized for pneumonia. This finding is consistent with prior studies.[7,10,12,13] However, our study was unique in evaluating this association in patients with a recent diagnosis of COPD, thus a limited long-term exposure to corticosteroid agents. This may explain the lack of a dose–response relationship that was seen in the study by Ernst et al.[12] Most of the patients receiving ICS in our study, were receiving doses equivalent to beclomethasone <1000 μg/day (equivalent to fluticasone <500 μg/day), whereas in the Ernst et al. study, the majority of the patients were receiving doses equivalent to fluticasone 500–999 μg/day possibly indicating more mild disease in our cohort.

The meta-analysis by Sin et al. did not find an increased risk of pneumonia in those using inhaled budesonide for COPD. However, the observation period was relatively short at one year compared to other studies. The study duration

Table 3 Unadjusted and adjusted odds ratios of hospitalizations for pneumonias associated with inhaled corticosteroid use.

	Cases (%)	Controls (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Number	13,995	131,591		
ICS use				
No use in past year	70.5	77.7	1.00	1.00
Current use (last 90 days)	21.7	16.0	1.51 (1.45–1.58)	1.38 (1.31–1.45)
Low dose (≤1000 μg/day)	9.0	6.0	1.66 (1.56–1.77)	1.51 (1.41–1.62)
Medium dose (>1000 to ≤2000 μg/day)	5.4	4.3	1.40 (1.29–1.52)	1.28 (1.18–1.39)
High dose (>2000 μg/day)	7.3	5.7	1.43 (1.34–1.53)	1.30 (1.21–1.41)
Past use, %				
91–180 days	3.4	2.8	1.32 (1.20–1.46)	1.21 (1.09–1.34)
181–270 days	2.5	1.9	1.48 (1.32–1.65)	1.39(1.23–1.56)
271–365 days	1.9	1.5	1.36 (1.20–1.55)	1.31 (1.14–1.50)
Use and dose				
Current use and low dose (90 days, ≤1000 μg/day)	9.0	6.0	1.66 (1.56–1.77)	1.51 (1.41–1.62)
Current use and high dose (90 days, >1000 μg/day)	12.7	10.0	1.42 (1.34–1.50)	1.29 (1.22–1.37)
Past use and low dose (91–365 days, ≤1000 μg/day)	5.6	4.5	1.37 (1.27–1.48)	1.27 (1.17–1.38)
Past use and high dose (91–365 days, >1000 μg/day)	2.2	1.7	1.39 (1.23–1.57)	1.31 (1.15–1.49)

and follow-up in the other meta-analyses were 6–40 months[14] and 6–36 months.[13] Due to the seasonal variation in the incidence of community acquired pneumonia a longer follow-up period may have noted more cases of pneumonia.[21] The average years of follow-up per person, or time to pneumonia, was 1.49 years in our study with the endpoint being pneumonia hospitalization, death, or one year after the final date of the inclusion period. This would have resulted in various follow-up periods for those with pneumonia. However, the controls were matched on date of entry and assigned the same end date as the case and therefore would have similar follow-up time. Therefore, the risk of pneumonia in terms of observation time included in the analysis would be similar between cases and controls.''

Similar to other studies, our study did not find an increased risk of death in those using ICS.[13,14] Our study showed lower 30 day mortality in those receiving current ICS compared to those not receiving current ICS. This may suggest that pneumonia associated with the use of ICS may be less severe than pneumonia not associated with ICS use.[21] ICS, which can increase risk of pneumonia, may also decrease severity of the pneumonia by decreasing the level of inflammation. An alternative explanation may be that those using ICS may have better COPD disease control at the time of the pneumonia diagnosis. Future studies are needed to further refine this relationship.

A major strength of our study is the large number of cases and more complete healthcare information as data from CMS was included. As U.S. veterans over the age of 65 qualify for Medicare benefits from the government in addition to VA benefits, care may be provided outside of the VA Healthcare system. Hospitalization for pneumonia may be urgent or emergent with use of the closest medical facility, which may not be a VA hospital. CMS data allows up to capture this health care utilization outside of the VA. At baseline, the case patients appeared to have more severe respiratory disease compared to the control patients as evidenced by a larger proportion having an acute COPD exacerbation, using respiratory medications and having at least one dispensing of oral corticosteroids, and having increased health care utilization prior to the pneumonia hospitalization. To address the possibility of confounding by indication, we adjusted for these differences in the severity of disease. We also conducted a sensitivity analysis excluding those who were considered chronic oral corticosteroid users. Aside from the severity of disease, comorbidities and other risk factors for pneumonia were accounted for by ICD-9 codes as well as specific pharmaceutical agents that could be associated with pneumonia. After these adjustments and sensitivity analysis, there was still an independent association between the risk of pneumonia and current use of ICS.

Our study does have some limitations. First, similar to previous studies the diagnosis of pneumonia; we could not radiographically confirm a diagnosis of pneumonia. However, not all cases of pneumonia requiring pharmacotherapy are evident on chest radiographs as evidenced by studies comparing high resolution computed tomography and chest radiographs[22] and laboratory evaluations in those with clinical or radiographic diagnosis of pneumonia.[23] In addition, it seems unlikely that a patient hospitalized with a diagnosis of pneumonia would not have a confirmatory test by way of chest radiographs or computed tomography. Our definition was a hospitalization with a primary diagnosis of pneumonia. Second, the medication data is indicative of medication dispensed and not necessarily used. Third, assessment of lung function was not used in the diagnosis of COPD. To strengthen the likelihood of COPD, we included patients hospitalized with a primary diagnosis of COPD or those with at least two outpatient visits for COPD. Fourth, we did not have smoking histories and the

Table 4 Unadjusted and adjusted odds ratios of hospitalizations for pneumonias associated with inhaled and oral corticosteroid use.

	Cases (%)	Controls (%)	Unadjusted OR	Adjusted OR
Number	13,995	131,591		
(−) Oral steroids (31−90 days), (−) ICS (90 days)	71.2	80.8	1	1
(−) Oral steroids (31−90 days), (+) ICS (90 days)	17.7	14.4	1.42 (1.35−1.48)	1.37 (1.30−1.44)
(+) Oral steroids (31−90 days), (−) ICS (90 days)	7.1	3.2	2.57 (2.39−2.76)	1.64 (1.50−1.80)
(+) Oral steroids (31−90 days), (+) ICS (90 days)	4.0	1.6	2.84 (2.58−3.12)	1.70 (1.51−1.90)
(−) Oral steroids (31−180 days), (−) ICS (90 days)	69.0	79.4	1	1
(−) Oral steroids (31−180 days), (+) ICS (90 days)	16.6	13.8	1.41 (1.35−1.48)	1.38 (1.31−1.45)
(+) Oral steroids (91−180 days), (−) ICS (90 days)	2.1	1.4	1.79 (1.59−2.02)	1.25 (1.10−1.43)
(+) Oral steroids (91−180 days), (+) ICS (90 days)	1.1	0.7	1.87 (1.58−2.21)	1.26 (1.05−1.52)

possibility remains that our associations are confounded by tobacco use. Finally, although we controlled for severity using measured data, there is the potential for confounding based on unmeasured variables.

In conclusion, we found an increase in the risk of hospitalization for pneumonia associated with the use of ICS in patients with newly diagnosed COPD. We did not find an increased rate of death from pneumonia related to current ICS use. The risk of severe pneumonia should be considered when starting even low doses of ICS in patients with a recent diagnosis of COPD.

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Conflicts of interest

Min Joo has no conflicts of interest to disclose.

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