Inhaled Corticosteroids and Risk of Recurrent Pneumonia: A Population-Based, Nested Case-Control Study

Dean T. Eurich,1,2 Colin Lee,3 Thomas J. Marrie,4 and Sumit R. Majumdar1,2,5
1Department of Public Health Sciences, School of Public Health, and 2ACHORD, 2-040 Li Ka Shing Center, University of Alberta, Edmonton; 3Leslie L. Dan Faculty of Pharmacy, University of Toronto, Ontario; 4Department of Medicine, Faculty of Medicine, Dalhousie University, Halifax, Nova Scotia, and 5Department of Medicine, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Canada

Background. Studies have suggested an increased risk of pneumonia with inhaled corticosteroid (ICS) use, although this association is inconsistent. We evaluated the risk of recurrent pneumonia associated with ICS use in a high-risk population of individuals who survived an episode of pneumonia.

Methods. Clinical and 5-year follow-up data were collected on all adults aged ≥65 years with pneumonia over a period of 2 years. Using a nested case-control design, first cases (patients with recurrent pneumonia ≥30 days after initial episode) and then controls (free of pneumonia and matched on age, sex, and chronic obstructive pulmonary disease [COPD]) were identified. ICS use was classified as never, past (remote, only before initial pneumonia), or current. Our primary outcome measure was recurrent pneumonia assessed using conditional multivariate logistic regression after adjustment of demographics and clinical data.

Results. During 5 years of follow-up, 653 recurrent pneumonia cases were matched with 6244 controls; mean age was 79 (SD, 8) years, 3577 (52%) were male, 2652 (38%) had COPD, and 2294 (33%) ever used ICS. Overall, 123 of 870 (14%) current ICS users had recurrent pneumonia compared to 395 of 4603 (9%) never-users (adjusted odds ratio, 1.90; 95% confidence interval, 1.45–2.50; P < .001; number need to harm = 20). Conversely, there was no association between past (remote) use of ICS and pneumonia: 9% of past users versus 9% never-users (P = .36).

Conclusions. ICS use was associated with a 90% relative increase in the risk of recurrent pneumonia among high-risk pneumonia survivors. This should be considered when prescribing ICS and when deciding which patients might need more intensive follow-up.

Keywords. corticosteroids; pneumonia; elderly; ICS.

Community-acquired pneumonia (CAP) is a common illness in the elderly and accounts for one-third of all hospitalizations in older adults, as well as up to a 2-fold increased risk of recurrent pneumonia [1–4]. Numerous risk factors are associated with its development, including age, previous pneumonia, chronic comorbidities including asthma and COPD, and poor functional status [5]. Increasing attention has been focused on the potential risk associated with certain medications such as proton pump inhibitors, antipsychotics, and, in particular, inhaled corticosteroids (ICSs) [6, 7].

ICSs are often used to treat asthma and its variants, chronic obstructive pulmonary disease (COPD), bronchiectasis, and conditions related to hyperactive airway disease that manifest as a chronic cough. ICSs continue to be widely used, although some studies suggest a link between ICS use and pneumonia risk [8–16]. The Towards a Revolution in COPD Health (TORCH) trial was one of the earliest studies suggesting this risk where a 6% higher rate of CAP among inhaled fluticasone propionate users versus placebo was observed [8]. Subsequently, 2 meta-analyses of randomized controlled trials (RCTs) confirmed an increased risk (34%–57%) of...
CAP with ICS use [9, 10]. Conversely, 2 similar meta-analyses did not show this association [11, 12]. Data from observational studies have also been inconsistent, with studies reporting 38%–70% increases in risk [13–15], whereas others show no association [16]. Collectively, the current literature is inconclusive; the majority of RCTs were not designed with pneumonia as a pre-specified or adjudicated endpoint, and most observational studies were not population-based, had a relatively short follow-up time, and were unable to adjust for important covariates, such as smoking history, immunization status, or premorbid functional status [13–16]. Perhaps, and most notably, the risk of pneumonia in the previous studies was relatively low, mostly ranging from 3% to 16%, and may have limited the ability to detect this association where one existed.

Given the clinical importance of this question and the need to reconcile the conflicting results of previous studies, we evaluated the association between ICS use and recurrent pneumonia in a very high-risk population: patients ≥65 years of age who survived a clinically confirmed episode of pneumonia. Unlike previous studies in populations with a relatively low risk of pneumonia or with potentially quite varying susceptibility to pneumonia [13–16], our population cohort was clinically defined and uniformly high risk for pneumonia with up to 5 years of prospective follow-up. We hypothesized that current ICS use would be independently associated with an increased risk of recurrent pneumonia.

**METHODS**

**Setting and Subjects**

Our prospective population-based clinical registry [17–20] contains comprehensive data on all 6874 patients ≥17 years of age with CAP seen in all 7 emergency departments and 6 hospitals serving the Edmonton (Canada) health region between 2000 and 2002. CAP was defined as the presence of radiographic confirmation according to the treating physician and at least 2 of the following: cough, pleurisy, shortness of breath, temperature >38°C, and crackles or bronchial breathing on auscultation. All patients were managed according to a validated clinical CAP pathway. The only patients excluded from the registry were those with tuberculosis and/or cystic fibrosis, those who were immunocompromised (including chronic glucocorti-coid exposures defined as >10 mg/day prednisone equivalents for at least 3 months prior to presentation), those who were pregnant or nursing, and those who had been recently hospitalized. The Health Research Ethics Board of the University of Alberta approved the study (Pro00004999).

**Data Collection and Measurements**

Trained research nurses collected all data [17, 18], including sociodemographics, comorbidities, prescription medications, premorbid functional status, and the well-validated Pneumonia Severity Index (PSI), with data collection necessarily more limited for outpatients compared to inpatients [20].

All postdischarge individual health service data were ascertained through linkage to various provincial health services (eg, emergency department visits, hospitalizations) and vital statistics databases through 31 March 2006 [3, 19]. All health services are recorded in International Classification of Diseases (ICD) codes, and all discharge coding was conducted by trained coders at each site and was routinely validated through a central agency in Canada [21]. In addition, prescription drug dispensations were recorded for all registrants aged ≥65 years whereby validity is routinely evaluated through computerized processing.

**Nested Case-Control Population**

Our study population consisted of all patients ≥65 years of age who survived their initial CAP hospitalization or emergency department visit (n = 2900). Because patients ≥65 years of age are at substantially increased risk of recurrent CAP [22], these patients may be most susceptible to the potential impact of ICS use. Moreover, restricting to patients ≥65 years of age allowed for the full characterization of postdischarge ICS use that is otherwise only captured in those ≥65 years of age within the province. We excluded 137 patients (5%) whom we could not link to the administrative databases. In addition, to ensure sufficient follow-up for the occurrence of repeat (that is, return) CAP and to exclude healthcare-associated pneumonia, all patients who were readmitted with pneumonia, died, or were otherwise censored within 30 days of discharge were excluded (284 [10%]).

Using a nested-case control approach [20], all subjects with recurrent pneumonia were considered cases and matched on age (5-year bands), male sex, COPD history, and pre pneumonia ICS use to controls using conventional risk set sampling (ie, incident density sampling) [23, 24]. Based on considerations of statistical power, with a risk estimate in prior studies of at least 40% [13–15] and a 2-sided α of 0.05, we selected up to 10 controls per case to ensure >80% power to the study. In fact, post hoc, our study had 84% power. All controls had the same duration of follow-up and were “at risk” for the outcome of interest (ie, actively followed, alive, and event free prior to the matched case index date). By convention, controls were selected with replacement (that is, a subject can be a control subject for several cases across time points) and given an analogous index date as their matched case using the sttoc command in Stata. Previous studies have shown that sampling without replacement within this design can lead to substantial bias [23, 25]. Furthermore, matching with replacement allows controls to be selected that may be more similar to the case (as all available controls may be eligible at a given time period) and help to reduce bias and confounding; however, there is a tradeoff in that replacement...
reduces the number of unique observations in the study, thereby increasing the variance of the estimator [26].

Exposure
To define ICS use, patients were categorized into mutually exclusive categories: (1) current use; (2) past use; (3) never use. Current ICS use was defined as at least 1 dispensation for an ICS (ie, beclomethasone, fluticasone, or budesonide, the only ICS agents on the provincial formulary) 90 days prior to the date of their recurrent (index) pneumonia or the analogous “pseudo–index date” for the matched controls. Past use was defined as patients who used ICS in the week before the initial pneumonia or had dispensations for ICS after their initial pneumonia that ended >90 days prior to the index date of the recurrent pneumonia or matched index date for the controls. Patients who did not use ICS in the week before their initial CAP event and who did not have any dispensations for ICS were considered never-users (reference group). In addition, we further subcategorized all current ICS users as those newly initiating ICS after initial pneumonia (incident current users) and those using ICS before and after initial CAP event (prevalent current users).

Outcomes
The primary study outcome was first occurrence of any pneumonia ≥30 days from the date of the initial pneumonia discharge. Emergency department visits or hospitalizations with a most responsible discharge diagnosis of pneumonia were identified based on well-validated (98% sensitivity and 97% specificity) ICD-9 codes of 480.0–487.7 or ICD-10 codes J10–J18 [27, 28]. For analyses, the date of first recurrent CAP was defined as the index date.

Statistical Analysis
Our primary analysis was a single multivariable conditional logistic regression model to estimate the independent association between ICS use (a single variable composed of our mutually exclusive categories of current, past, and never exposed) and recurrent pneumonia adjusted for numerous confounding factors, including comorbidities, smoking, premorbid functional status, nursing home residence, up-to-date vaccinations [18, 19], total prescription medications, and the PSI.

Sensitivity Analyses
To evaluate the robustness of our study results, we conducted numerous sensitivity analyses. First, to ensure the use of 10 controls was not inflating the statistical significance of our results, we repeated our analyses using only 1 control per case. Second, as ICSs are mostly prescribed to patients with COPD, we stratified all analyses by history of COPD. In addition, we adjusted for the severity of COPD based on the use of ≥3 of the following: use of home oxygen therapy, tiotropium, nedocromil, ipratropium, short-acting β2 agonists, long-acting β2 agonists, theophylline products, leukotriene receptor antagonists, and oral steroids ≥10 mg/day. Third, we used commonly defined methods [29] to construct a propensity score for ICS use postdischarge (c statistic = 0.81 for model with >90 variables; details available upon request) and included this in our base-case multivariate model. Fourth, we excluded all patients who initiated ICS use 14 days prior to the recurrent pneumonia to reduce protopathic bias (ie, ICS use initiated for respiratory tract symptoms [eg, cough or shortness of breath] due to an [as of yet] undiagnosed pneumonia versus similar symptoms related to some form of exacerbation of reactive airways). Fifth, we limited recurrent pneumonia cases to only those with the most severe pneumonia requiring admission to hospital. Sixth, we repeated all analysis with additional matching criteria on initial site of treatment (inpatient vs outpatient), history of asthma, preneumonia oral corticosteroid use, and pneumonia severity according to the PSI. Seventh, to ensure that the use of prednisone postdischarge was not affecting our results, we adjusted for the daily use of ≥10 mg of prednisone in our analyses, excluded all patients receiving prednisone postdischarge, and repeated our analyses. Last, as a tracer condition analysis, we repeated all analyses with calcium channel blockers as our exposure of interest, and with heart failure as our outcome of interest. To our knowledge, there should be no association between the use of calcium channel blockers and recurrent pneumonia, nor with ICS use and heart failure exacerbation. All analyses were completed with Stata SE, version 12 (StataCorp, College Station, Texas).

RESULTS
Our study included 2479 elderly patients who survived their initial episode of CAP. Overall, 656 (26%) had recurrent (ie, repeat) CAP ≥30 days after their initial pneumonia; the mean time to recurrence was 1.4 (SD, 1.2) years over 5.4 years of follow-up. We successfully matched 653 (99%) cases to 6244 controls (90% of cases having 10 controls). Of the available 1823 controls, 1547 (85%) were included in at least 1 risk set. Mean age was 79 (SD, 8) years, 3577 (52%) were male, 4402 (64%) were treated as inpatients, 2652 (38%) had COPD, and 2294 (33%) had ever used ICSs (Tables 1 and 2). Overall, cases were similar to controls except that cases had more severe initial pneumonia and were more likely to have been hospitalized (Table 1).

ICS Use and Recurrent Pneumonia
Among the 653 cases, 123 (19%) were current ICS users compared to 747 (12%) of 6244 controls. Overall, 123 of 870 (14%) current users of ICS had a recurrent CAP compared to 395 (9%) ICS never-users (5% absolute risk difference; number
needed to harm = 20; unadjusted odds ratio [OR], 1.92; 95% confidence interval [CI], 1.48–2.50; Table 2). After adjustment, the risk of recurrent pneumonia remained at near-identical magnitude and statistically significant for current ICS use (adjusted OR [AOR], 1.90; 95% CI, 1.45–2.50). Conversely, no association between the past use of ICS and recurrent pneumonia was observed: 135 (9%) of past users compared to 395 (9%) never-users (AOR, 1.15; 95% CI, 0.85–1.55; Table 2, Figure 1).

Prevalent Versus Incident ICS Use and Recurrent Pneumonia
Further stratification by the type of current ICS use resembled the main analysis. Among 870 current users, 418 (48%) were prevalent current users and 452 (52%) were incident current users. Both prevalent current use (57 of 418 [14%]; AOR, 2.10, 95% CI, 1.26–3.50; P = .004) and incident current use (66 of 452 [15%]; AOR, 1.85, 95% CI, 1.37–2.50; P < .001) were associated with a statistically significant increased risk of recurrent pneumonia compared with ICS never-users (395 of 4603 [9%]) (Figure 1).

Sensitivity Analysis
First, our results were nearly identical in analyses using only 1 control per case (current ICS use: AOR, 1.91; 95% CI, 1.27–2.86; P = .002). Second, results were similar in analyses restricted to patients with a history of COPD (12% of current ICS users had recurrent pneumonia compared to 8% of never-users; AOR, 1.72; 95% CI, 1.17–2.55; P = .006) and in those without a history of COPD (16% of current ICS users compared to 9% of never-users: AOR, 2.31; 95% CI, 1.53–3.49; P < .001 and P = .4 for interaction between COPD and current ICS use) (Figure 2). Further adjustment for severity of COPD provided nearly identical results (AOR, 1.77; 95% CI, 1.33–2.34) and there was no statistically significant or clinically important interaction between COPD severity and ICS use (P = .10). Third, addition of a propensity for ICS use postdischarge resulted in nearly identical results (AOR, 1.90; 95% CI, 1.44–2.50; P < .001). Fourth, fifth, and sixth, analyses that excluded all patients initiating ICS use 14 days prior to event (634 cases: AOR, 1.50; 95% CI, 1.12–2.00; P = .007) or recurrent pneumonia “cases” to only those requiring hospitalization (330 cases: AOR, 1.62; 95% CI, 1.10–2.39; P = .015) or that entailed further matching criteria (551 cases: AOR, 1.92; 95% CI, 1.38–2.69; P < .001) did not materially alter our results (Figure 2). Seventh, adjustment for daily use of ≥10 mg of prednisone (AOR, 1.91; 95% CI, 1.46–2.52) did not alter our results, with no interaction between ICS use and prednisone use noted (P = .75), nor did exclusion of all patents receiving prednisone postdischarge (495 cases: AOR, 2.14; 95% CI, 1.52–3.01). Last, in a set of tracer analyses, no association between past (P = .5) or current calcium channel blocker use (P = .1) and recurrent pneumonia was observed, nor was any association between past ICS use (P = .6) or current ICS use (P = .6) and heart failure–related admissions observed.

DISCUSSION
Among a population-based cohort of uniformly high-risk elderly patients who survived an episode of pneumonia, we observed a near 2-fold relative increase in risk (5% absolute risk increase) of recurrent pneumonia among patients currently using ICSs compared to nonusers. This association was observed irrespective of whether a person initiated ICS use prior to or after hospitalization for initial pneumonia, suggesting that...
any current exposure to ICSs may be associated with an increase in pneumonia risk. Furthermore, the associations were robust to numerous analytic approaches and sensitivity analyses.

Our results are broadly consistent with and confirm 5 earlier studies suggesting an increased risk of pneumonia with ICS use [9, 10, 13–15]. Two previous meta-analyses in COPD patients found a significant 34%–57% increase in the risk of pneumonia with ICS use [9, 10], and observational studies have also suggested an 11%–70% increased risk [13–15]. Conversely, our work refutes 3 earlier studies that did not find such an association. One individual patient data meta-analysis was restricted to budesonide use alone and included studies with a relatively short ICS exposure [11], whereas the second study mostly consisted of unpublished manufacturer-sponsored studies of budesonide and included both the asthmatic and pediatric populations [12]. The third study of 5245 patients that did not find an association between ICS use and pneumonia may have been underpowered (AOR, 1.29 within a 90-day exposure window) due to stratification of ICS use into several subgroups of different therapeutic combinations [16].

Most of these studies, whether RCTs or observational in nature, have been restricted to COPD patients and included populations at relatively lower risk for pneumonia. More importantly, the previous literature had important limitations.

Table 2. Risk of Community-Acquired Pneumonia According to Exposure of Inhaled Corticosteroid Therapy, by Conditional Logistic Regression

<table>
<thead>
<tr>
<th>ICS Use</th>
<th>Controls (n = 6244), No. (%)</th>
<th>Cases (n = 653), No. (%)</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>4208 (67)</td>
<td>396 (61)</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Past</td>
<td>1289 (21)</td>
<td>135 (21)</td>
<td>1.23 (.92–1.65)</td>
<td>1.15 (.85–1.55)</td>
</tr>
<tr>
<td>Current (within 90 d)</td>
<td>747 (12)</td>
<td>123 (19)</td>
<td>1.92 (1.47–2.50)</td>
<td>1.90 (1.45–2.50)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; ICS, inhaled corticosteroid; OR, odds ratio.

* Adjusted for comorbidities, total medications, oral corticosteroid use, use of proton pump inhibitors or histamine receptor antagonists, vaccinations, smoking status, nursing home residence, functional status, and pneumonia severity index.

Primary Analysis

Current ICS Use

Past ICS Use

Secondary Analysis

Incident ICS Use

Prevalent ICS Use

Figure 1. Adjusted odds ratios of pneumonia associated with inhaled corticosteroid use. Abbreviation: ICS, inhaled corticosteroid.
Prior meta-analysis studies mainly consisted of RCTs that were not specifically designed to evaluate predefined pneumonia outcomes [9–12]. In addition, the observational studies, for the most part, did not have the ability to account for important confounding factors such as smoking history, clinical data, immunizations, or functional status [13–16]. We believe that our work, in the context of these prior studies, is able to overcome some of these limitations and confirm the findings that suggest that the risk of pneumonia is increased among those currently using ICSs. Furthermore, we were able to extend the risk of ICS use to a common (and previously unstudied, to our knowledge) group of patients—those who survived an episode of pneumonia but remain at much higher risk of recurrent pneumonia than the general population.

Despite some strengths, several limitations of the current study should be acknowledged. First, some may consider that our study population was atypical in that all patients had previously survived an episode of pneumonia. In fact, given their high risk of pneumonia (26% over 5 years), we consider this a strength as it provides a clinically defined and uniform study population. Second, the diagnosis of recurrent pneumonia could not be confirmed clinically nor radiographically. Third, we do not know the indication for ICS use; for those with asthma or COPD we do not have any spirometric data, and our marker of severity for those with COPD was based on utilization patterns that may not fully capture disease severity. Fourth, we could not determine a dose response as the prescription database utilized in this study did not provide data regarding ICS daily doses. Fifth, we did not have the power to examine differences between the various ICS agents and could not convert all ICSs to standardized beclomethasone equivalents.

**CONCLUSIONS**

In this study, ICS use was independently associated with a significant 90% increased risk of pneumonia in high-risk patients who had previously survived an episode of pneumonia. Until there is better and more consistent evidence on this topic, our findings should be considered when deciding to continue or initiating new prescriptions for ICSs in patients who survive an episode of pneumonia and when trying to identify those patients who might benefit from more intensive follow-up.

**Notes**

**Author contributions.** All authors contributed to the conception and design. D. T. E., C. L., and S. R. M. contributed to the analysis and interpretation of data. D. T. E. and C. L. drafted the article, all authors revised it.

![Figure 2. Sensitivity analyses for pneumonia associated with inhaled corticosteroid use. Abbreviations: CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid.](https://academic.oup.com/cid/article-abstract/57/8/1138/529900/fig2)
critically for important intellectual content, and all authors provided final approval of the version to be published. All authors had full access to all of the data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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