Recurrent Community-acquired Pneumonia in Patients Starting Acid-suppressing Drugs

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\textbf{ABSTRACT}

\textbf{BACKGROUND:} Several studies suggest that proton pump inhibitors (PPIs) and histamine 2-receptor antagonists (H2s) increase risk of community-acquired pneumonia. To test this hypothesis, we examined a prospective population-based cohort predisposed to pneumonia: elderly patients (≥65 years) who had survived hospitalization for pneumonia.

\textbf{METHODS:} This study featured a nested case-control design where cases were patients hospitalized for recurrent pneumonia (≥30 days after initial episode) and controls were age, sex, and incidence-density sampling matched but never had recurrent pneumonia. PPI/H2 exposure was classified as never, past, or current use before recurrent pneumonia. The association between PPI/H2s and pneumonia was assessed using multivariable conditional logistic regression.

\textbf{RESULTS:} During 5.4 years of follow-up, 248 recurrent pneumonia cases were matched with 2476 controls. Overall, 71 of 608 (12\%) current PPI/H2 users had recurrent pneumonia, compared with 130 of 1487 (8\%) nonusers (adjusted odds ratio [aOR] 1.5; 95\% confidence interval [CI], 1.1-2.1). Stratifying the 608 current users according to timing of PPI/H2 initiation revealed incident current-users (initiated PPI/H2 after initial pneumonia hospitalization, \(n = 303\)) bore the entire increased risk of recurrent community-acquired pneumonia (15\% vs 8\% among nonusers, aOR 2.1; 95\% CI, 1.4-3.0). The 305 prevalent current-users (PPI/H2 exposure before and after initial community-acquired pneumonia hospitalization) were equally likely to develop recurrent pneumonia as nonusers (aOR 0.99; 95\% CI, 0.63-1.57).

\textbf{CONCLUSION:} Acid-suppressing drug use substantially increased the likelihood of recurrent pneumonia in high-risk elderly patients. The association was confined to patients initiating PPI/H2s after hospital discharge. Our findings should be considered when deciding to prescribe these drugs in patients with a recent history of pneumonia.

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\textbf{KEYWORDS:} Acid-suppression therapy; Pneumonia; Prospective cohort

Community-acquired pneumonia is a common and costly condition, particularly in the elderly, where the incidence is 18-50 cases per 1000 subjects.\textsuperscript{1-3} Recently, acid-suppressing medication use (ie, proton pump inhibitors [PPI] and histamine 2-receptor antagonists [H2]) has been associated with a 1.5- to 2-fold increased risk of community-acquired pneumonia.\textsuperscript{4,7} This elevated risk has important implications for the elderly because PPI/H2 use is common, with 10\%-20\% prescribed PPI/H2s at some juncture and up to 5\% taking these medications regularly.\textsuperscript{8} In addition, many PPI/H2s do not require a prescription, resulting in increased and unmonitored use. Although generally effective for symptom relief and relatively inexpensive,\textsuperscript{8} such increased and widespread use makes issues of population-based safety even more critical.
The mechanisms by which acid suppression might increase the risk of community-acquired pneumonia have not been fully elucidated, but changes in gastric pH can alter normal gastrointestinal and oropharyngeal flora, leading to decreased elimination of, or increased colonization by, various pathogens. Indeed, elevation of gastric pH by acid suppression agents promotes proliferation of bacteria, particularly Gram-positive organisms commonly found in the mouth and oropharynx. Gastric acid has a major putative role in protecting against infection and therefore, its attenuation provides a plausible mechanism to explain why patients consuming PPI/H2s might be at increased risk of community-acquired pneumonia.

Four previous studies have suggested an association between PPI/H2 use and pneumonia, but all have been limited by the lack of important but rarely captured clinical data (e.g., functional status), short follow-ups, and some degree of selection bias as populations studied are inherently very low risk for developing pneumonia. As such, the association between PPI/H2 use and pneumonia has been difficult to ascertain and remains controversial. Given the importance of this question, we designed a study to evaluate the independent association between PPI/H2 use and pneumonia with the intent of overcoming limitations of previous studies. Specifically, our study was drawn from a population-based cohort of patients with detailed clinical and medication information to fully characterize PPI/H2s use for all subjects and prospectively followed for 5 years.

**METHODS**

**Subjects and Setting**

Between 2000 and 2002, all community-acquired pneumonia patients admitted to all 6 hospitals in Edmonton, Alberta, Canada were enrolled in a clinical registry and treated according to a validated clinical pathway for community-acquired pneumonia management. The population-based cohort and data collection methods are described in detail elsewhere. Briefly, data were collected prospectively on all 3415 patients >17 years of age admitted with community-acquired pneumonia. Subjects were excluded if they had tuberculosis, cystic fibrosis, were immunocompromised, or were pregnant. Trained research nurses prospectively collected data using standardized abstraction forms, and patients were followed until discharge. Clinical characteristics (age, sex, comorbidities, smoking, and premorbid functional status) and prescription medication use in the week before admission were collected. In addition, the Pneumonia Severity Index, a validated measure of the severity of pneumonia-specific illness at presentation based on a weighted sum of 3 demographic variables, 5 comorbidities, 5 physical findings, and 7 laboratory tests, also was calculated on all patients.

**Clinical Significance**

- Acid-suppressing drugs (proton pump inhibitors/histamine 2-receptor antagonists) substantially increase the likelihood of recurrent community-acquired pneumonia in high-risk elderly patients.
- This association, however, is confined to patients newly starting acid suppression drugs (proton pump inhibitors/histamine 2-receptor antagonists) after hospital discharge.
- These findings should be considered when deciding to prescribe these drugs in patients with a recent history of pneumonia.

**Study Sample**

Our source population consisted of all subjects ≥65 years of age who survived their initial community-acquired pneumonia hospitalization (n = 1950). We restricted our cohort to this age group for 2 reasons. First, subjects aged ≥65 years are at substantially higher risk for community-acquired pneumonia than younger subjects and, therefore, may be most susceptible to the hypothesized adverse effects of PPI/H2s. Second, the administrative databases provide information to fully characterize PPI/H2s use for all subjects aged ≥65 years. We excluded 104 (5%) subjects whom we could not link to the administrative databases. To ensure that repeat (that is, return) community-acquired-pneumonia-related hospitalizations were unrelated to the initial community-acquired pneumonia hospitalization, we excluded 49 (2%) subjects with community-acquired-pneumonia-related hospitalizations recurring within 30 days postdischarge. For all analyses, the cohort entry date was defined as the discharge date of initial community-acquired pneumonia.
hospitalization. All postdischarge hospital service data and prescription claim data were extracted from cohort entry until event of interest, death, coverage termination, or March 31, 2006 for all eligible subjects.

Outcomes (Pneumonia Requiring Hospitalization)
Our primary outcome of interest was the first community-acquired pneumonia hospitalization ≥30 days after cohort entry. This was defined as a hospital admission with a most responsible discharge diagnosis of 480.0-487.7 (using International Classification of Diseases [ICD]-9-CM values) or J10-J18 (using ICD-10-CA values). These ICD diagnostic codes have high accuracy (98% sensitivity and 97% specificity) for identifying pneumonia when compared with medical charts and have been used in numerous pneumonia studies. The admission date of first community-acquired pneumonia recurrence was defined as the index date.

Exposure (Proton Pump Inhibitor or Histamine-2 Receptor Antagonist Use)
The exposure of interest was current use of PPIs (omeprazole, pantoprazole, lansoprazole, rabeprazole) or H2s (ranitidine, cimetidine, famotidine), defined as at least one dispensation record within 90 days before the index date (or analogous date for matched control subjects). Past PPI/H2 use was defined as PPI/H2 use in the week before initial community-acquired pneumonia hospitalization only or PPI/H2 dispensation records ending more than 90 days before the recurrent community-acquired pneumonia event. Nonuse (reference group for all analyses) was defined by no record of PPI/H2 use either before initial community-acquired pneumonia hospitalization or during the postdischarge observation period. In a secondary analysis, we stratified current PPI/H2 users into those initiating PPI/H2 use after initial community-acquired pneumonia hospitalization (incident current users) and those who were using PPI/H2s before the initial community-acquired pneumonia hospitalization (prevalent current users). We did not have access to over-the-counter PPI/H2 use.

Nested Case-control Analysis
As others have, we used a nested case-control analysis to evaluate the association between PPI/H2 use and risk of community-acquired pneumonia to reduce confounding by indication and account for time-varying changes in PPI/H2 exposure over time. All cohort subjects with the primary outcome of interest were considered cases. Each case subject was matched on age (5-year bands) and sex, with up to 10 controls using incident density sampling (ie, risk set sampling). In incident density sampling, to be eligible as a control, subjects must have the same duration of follow-up and be “at risk” for the event (ie, actively followed, alive, and event free before case index). By convention, from this pool of “at risk” subjects, controls were selected one subject at a time for each case with replacement (that is, a subject can be a control subject for several cases) and given an analogous index date as their matched case. Incidence density sampling produces odds ratios that are unbiased estimates of the rate ratios. Up to 10 controls were chosen based on considerations of statistical power and efficiency that generally improve by using up to 10 control subjects.

Main Analysis
Crude and adjusted odds ratios were estimated using conditional logistic regression. In addition to our matching variables (age, sex), we adjusted for numerous potential confounding factors, including comorbidities (heart failure, chronic obstructive pulmonary disease, neuropsychiatric illness), smoking status, premorbid functional status, nursing home residence, Pneumonia Severity Index, total number of prescription medications, use of gastric motility agents, and drug therapies possibly requiring gastric protection (eg, corticosteroids, antiplatelets, antiplatelet agents, nonsteroidal anti-inflammatory drugs). All analyses were completed with Stata SE, version 10 (Stata, College Station, Tex).

Sensitivity Analyses
To evaluate the robustness of our observations, we prespecified several sensitivity analyses. First, we varied our “current user” definition to at least one dispensation record within 180 days or 30 days before the index date. Second, we restricted all analyses to those using PPIs exclusively within the cohort. Insufficient subjects (n = 54) were available to evaluate H2 users alone. Third, we included the 49 cases of community-acquired pneumonia that occurred within 30 days postdischarge of the initial community-acquired pneumonia hospitalization. Fourth, we excluded all patients initiating PPI/H2 within 14 days of recurrent pneumonia to reduce the chance of protopathic bias (ie, PPI/H2s initiated for abdominal or upper gastrointestinal tract symptoms, which are, in fact, symptoms related to undiagnosed pneumonia). Last, to further control for confounding, we constructed a propensity score (more than 60 variables, available upon request) for PPI/H2 use after initial community-acquired pneumonia hospitalization and included this in our multivariable models. The propensity score is an alternative method for estimating treatment effects when treatment assignment is not random, but can be assumed to be unconfounded, by balancing observed characteristics between treatment groups and thereby reducing selection bias.

RESULTS
Population Characteristics
Our study population consisted of 1797 subjects who survived their initial community-acquired pneumonia hospitalization. Average age was 79.4 (SD 7.9) years, 917 (51%) were male, 170 (9%) had functional impairment, 414 (23%) resided in a nursing home, and the majority had severe pneumonia (class IV or V and therefore, have the highest morbidity rates and are at the highest risk for mortality). During more than 5 years of follow-up (mean 3.0 [SD 1.7]
years), 248 (14%) subjects were readmitted to the hospital for community-acquired pneumonia ≥30 days after initial community-acquired pneumonia hospitalization (ie, cases) (Figure 1). These 248 cases were successfully matched to 2476 controls with >99% of cases matched to 10 controls (only 2 cases had <10 control subjects: 7 and 9 controls, respectively). There were few differences between cases and controls for most characteristics; however, cases were more likely to have functional status impairment compared with controls (Table 1).

**Association between PPI/H2 Use and Outcomes**

Among the 248 cases and 2476 controls, 71 (29%) and 537 (22%), respectively, were current PPI/H2 users. Overall, 71 of 608 (12%) current PPI/H2 users had another hospitalization for community-acquired pneumonia, compared with 130 of 1617 (8%) nonusers (4% absolute difference; unadjusted odds ratio [OR] 1.53; 95% confidence interval [CI], 1.12-2.08; \(P = .008\)) (Table 2). After adjustment, the risk of recurrent community-acquired pneumonia was significantly higher for PPI/H2 use within 90 days of the index date compared with nonuse (adjusted OR [aOR] 1.51; 95% CI, 1.10-2.07; \(P = .01\)). In contrast, no association between past PPI/H2 use and recurrent community-acquired pneumonia was observed (47 of 499 [9%] vs 130 of 1617 [8%]; aOR 1.10; 95% CI, 0.76-1.57; \(P = .62\)) (Table 2, Figure 2).

Stratified analysis of current PPI/H2 use suggested a substantial difference in risk, depending on the timing of PPI/H2 initiation. Among current users (n = 608), 305 (50%) were prevalent current users and 303 (50%) were incident current users. Incident current PPI/H2 use was associated with a 2-fold increased risk of recurrent community-acquired pneumonia (46 of 303 [15%] vs 8%; aOR 2.05; 95% CI, 1.42-2.97; \(P < .001\)), with no observed risk associated with prevalent current PPI/H2 use compared with nonuse (25 of 305 [8%] vs 8%; aOR 0.99; 95% CI, 0.63-1.57; \(P = .66\)) (Figure 2). Further, direct comparison within the current use group indicated that incident current users had a substantially higher risk for recurrent community-acquired pneumonia compared with prevalent current users (15% vs 8%; aOR 2.07; 95% CI, 1.22-3.49; \(P = .007\)).

**Sensitivity Analyses**

The risk of recurrent community-acquired pneumonia associated with current PPI/H2 use was nearly identical to our main results when the exposure definition was changed to a PPI/H2 dispensation record within 180 days before index (85 of 735 [12%] current PPI/H2 users had recurrent community-acquired pneumonia compared with 130 of 1617 [8%] nonusers [aOR 1.49; 95% CI, 1.10-2.01; \(P < .001\)]) or 30 days before index (43 of 376 [12%] current PPI/H2 users had recurrent community-acquired pneumonia compared with 130 of 1617 [8%] nonusers [aOR 1.54; 95% CI, 1.06-2.23; \(P = .02\)]). Results also were comparable in analyses restricted to PPI users only: 59 of 497 (12%) current PPI users had recurrent community-acquired pneumonia, compared with 126 of 1503 (8%) of nonusers (aOR 1.45; 95% CI, 1.03-2.04; \(P = .035\)). Similar to our main findings, the risk of recurrent community-acquired pneumonia was isolated to incident current PPI use (41 of 288 [14%] vs 8%; aOR 1.83; 95% CI, 1.24-1.70; \(P = .002\)) with no observed risk associated with prevalent current PPI use compared with nonuse (18 of 209 [9%] vs 8%; aOR 0.95; 95% CI,

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**Figure 1** Cumulative incidence for community-acquired pneumonia readmission according to acid-suppressing drug use.
Analyses that included the 49 additional cases of community-acquired pneumonia (ie, 297 total cases) that occurred within 30 days postdischarge from initial community-acquired pneumonia hospitalization (aOR 1.57; 95% CI, 1.17-2.13; \( P = .003 \)) or excluded all patients initiating PPI/H2s within 14 days of the index event (aOR 1.39; 95% CI, 1.01-1.93; \( P = .045 \)) did not substantively change our results. Finally, analyses that included a propensity score (c-statistic for propensity model 0.79) further increased the magnitude and statistical significance of the observed association (aOR 1.63; 95% CI, 1.17-2.28; \( P = .004 \)).

**DISCUSSION**

Our prospective, population-based cohort followed high-risk elderly patients after hospitalization for community-acquired pneumonia for more than 5 years. We observed a statistically significant 51% increase in the risk of recurrent community-acquired pneumonia for current PPI/H2 users compared with nonusers. Importantly, our results also suggest that the increased risk of recurrent community-acquired pneumonia was isolated to incident “new users” of PPI/H2s. Initiating a PPI/H2 after hospitalization for pneumonia was associated with about a 7% absolute increase and 2-fold relative increase in the risk of recurrent community-acquired pneumonia when compared with either patients who had never used these drugs or those who continued use before and after their initial pneumonia hospitalization.

Our results are broadly consistent with 4 previous observational studies of this issue.4-7 The first study conducted in a cohort of Dutch patients suggested that acid suppression therapy was associated with a 60%-70% increased risk of community-acquired pneumonia.4 This was followed by a Danish study that observed a 50% increased risk of community-acquired pneumonia associated with PPI therapy.5 Unlike previous studies, researchers using data from the United Kingdom failed to observe an overall association between current use of PPI/H2s and community-acquired pneumonia;6 however, they did find (and discounted on the basis of a lack of plausible mechanism) a significant association between very recent initiation of PPI/H2s and community-acquired pneumonia similar to what we reported. Most recently, a second United Kingdom study reported a 55% increased risk of community-acquired pneumonia associated with PPI therapy.7 Unlike previous studies, researchers using data from the United Kingdom failed to observe an overall association between current use of PPI/H2s and community-acquired pneumonia similar to what we reported.

Table 1  Characteristics of Case Subjects and Matched Controls with Community-acquired Pneumonia

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control n = 2476</th>
<th>Case n = 248</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td>79.3 ± 7.8</td>
<td>79.3 ± 7.8</td>
</tr>
<tr>
<td>Male</td>
<td>1200 (48%)</td>
<td>120 (48%)</td>
</tr>
<tr>
<td>Previous co-morbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>640 (26)</td>
<td>74 (30)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>933 (38)</td>
<td>95 (38)</td>
</tr>
<tr>
<td>Neuropsychiatric illness</td>
<td>497 (20)</td>
<td>42 (17)</td>
</tr>
<tr>
<td>Five or more medications</td>
<td>448 (18)</td>
<td>52 (21)</td>
</tr>
<tr>
<td>Agents possibly requiring gastric protection*</td>
<td>971 (39)</td>
<td>97 (39)</td>
</tr>
<tr>
<td>Motility agents</td>
<td>80 (3)</td>
<td>9 (4)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>1079 (44)</td>
<td>103 (42)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>1018 (41)</td>
<td>107 (43)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>379 (15)</td>
<td>38 (15)</td>
</tr>
<tr>
<td>Nursing home resident</td>
<td>522 (21)</td>
<td>53 (21)</td>
</tr>
<tr>
<td>Premorbid functional status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Independent mobility</td>
<td>2294 (93)</td>
<td>220 (89)</td>
</tr>
<tr>
<td>Wheelchair/prosthesis</td>
<td>121 (5)</td>
<td>14 (6)</td>
</tr>
<tr>
<td>Bedridden</td>
<td>61 (2)</td>
<td>14 (6)</td>
</tr>
<tr>
<td>Pneumonia Severity Index</td>
<td></td>
<td></td>
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<tr>
<td>Class I or II</td>
<td>122 (5)</td>
<td>10 (4)</td>
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<tr>
<td>Class III</td>
<td>513 (21)</td>
<td>46 (19)</td>
</tr>
<tr>
<td>Class IV</td>
<td>1289 (52)</td>
<td>142 (57)</td>
</tr>
<tr>
<td>Class V</td>
<td>552 (22)</td>
<td>50 (20)</td>
</tr>
</tbody>
</table>

*Corticosteroids, antiplatelet, antiplatelet agents, nonsteroidal anti-inflammatory drug therapy.

Table 2  Risk of Community-acquired Pneumonia According to Exposure of PPI/H2 Therapy

<table>
<thead>
<tr>
<th>Proton pump inhibitor or H2 antagonist use</th>
<th>Control n = 2476</th>
<th>Case n = 248</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>1487 (60)</td>
<td>130 (52)</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Current (within 90 days)</td>
<td>537 (22)</td>
<td>71 (29)</td>
<td>1.53 (1.12-2.08)</td>
<td>1.51 (1.10-2.07)</td>
</tr>
<tr>
<td>Past</td>
<td>452 (18)</td>
<td>47 (19)</td>
<td>1.20 (0.84-1.71)</td>
<td>1.10 (0.76-1.57)</td>
</tr>
</tbody>
</table>

PPI = proton pump inhibitor; H2 = histamine 2-receptor antagonist; OR = odds ratio; CI = confidence interval.

Conditional Logistic Regression: *Adjusted for comorbidities, total medications, use of agents possibly requiring gastric protection, motility agents, smoking status, nursing home residence, functional status, and pneumonia severity index.
prevalent current users did not. Collectively, these data suggest that community-acquired pneumonia risk may diminish over time with continued acid-suppressive therapy.

Is there a plausible mechanism whereby acid suppression might predispose patients to pneumonia? Because PPIs (and to a lesser extent, H2s) provide early relief of acid-related symptoms by suppressing acid within 24-48 hours of ingestion, it could permit rapid bacterial re-colonization and overgrowth soon after starting therapy. In vulnerable patients, such as frail elderly patients, these sudden changes in bacterial growth could promote infection. We admit that this is speculative, and we were unable to find any literature to support or refute this premise. Nevertheless, in one of the previous observational studies, PPI use increased the risk of community-acquired pneumonia associated with gastric pathogens but not airborne pathogens. The mechanism is, perhaps, less important than the fact that now 5 studies have demonstrated that the risk of pneumonia associated with PPI/H2 use occurs soon after starting these medications.

Our study has several distinct strengths that overcome some limitations of previous studies. For example, our 5-year observation period is longer than other studies and we had robust and detailed clinical data to adjust for potential confounding. Most important, we selected a population at very high and relatively uniform risk of pneumonia, given that all patients were elderly and had already survived an episode of community-acquired pneumonia. This is in contrast to previous studies where the overall risk of community-acquired pneumonia was considerably lower and patients who developed community-acquired pneumonia were more likely to have other predispositions to pneumonia.

There are, however, a number of limitations. First, we had clinical data only at entry into the cohort, so we were unable to identify changes in medical conditions over time; however, this would likely have occurred equally in both the case and control groups and should not have biased our study results. Second, because we studied only patients hospitalized with pneumonia, our findings may not necessarily be generalized to all subjects at risk of pneumonia. Although this might lead to differences in baseline risk and absolute community-acquired pneumonia rates, there is no reason to believe that the relative risk associated with PPI/H2 therapy should be different. Third, the indication for PPI/H2 use was not available, and using PPI/H2 dispensation records likely overestimates actual PPI/H2 exposure. However, this nondifferential misclassification would have biased our study results to the null. Fourth, we did not have access to over-the-counter medications use, and although PPIs are unavailable over the counter in Canada, potential confounding effects of over-the-counter H2 use cannot be excluded. Fifth, although the use of administrative data may have led to some misclassification of community-acquired pneumonia hospitalizations, we used previously well-validated ICD codes to identify our primary outcome of interest. Finally, we were unable to examine “dose-response” relationships because there were too few H2 users and because we did not have PPI/H2 doses in our databases.

CONCLUSION

Use of acid-suppressing therapy is associated with a substantially increased risk of community-acquired pneumonia in patients highly predisposed to pneumonia. Importantly, our research adds to current knowledge by suggesting that the risk is restricted to “new users” of PPI/H2s—a more than 2-fold relative risk and a 7% absolute risk (“number needed to harm of 14”). Our findings, consistent with previous studies, suggest caution when starting acid-suppressive therapy in patients who have been recently hospitalized for pneumonia.
References


