Use of Proton Pump Inhibitors and the Risk of Community-Acquired Pneumonia

A Population-Based Case-Control Study

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Background: Recently, the use of proton pump inhibitors (PPIs) has been associated with an increased risk of pneumonia. We aimed to confirm this association and to identify the risk factors.

Methods: We conducted a population-based case-control study using data from the County of Funen, Denmark. Cases (n = 7642) were defined as all patients with a first-discharge diagnosis of community-acquired pneumonia from a hospital during 2000 through 2004. We also selected 34 176 control subjects, who were frequency matched to the cases by age and sex. Data on the use of PPIs and other drugs, on microbiological samples, on x-ray examination findings, and on comorbid conditions were extracted from local registries. Confounders were controlled by logistic regression.

Results: The adjusted odds ratio (OR) associating current use of PPIs with community-acquired pneumonia was 1.5 (95% confidence interval [CI], 1.3-1.7). No association was found with histamine$_2$-receptor antagonists (OR, 1.10; 95% CI, 0.8-1.3) or with past use of PPIs (OR, 1.2; 95% CI, 0.9-1.6). Recent initiation of treatment with PPIs (0-7 days before index date) showed a particularly strong association with community-acquired pneumonia (OR, 5.0; 95% 2.1-11.7), while the risk decreased with treatment that was started a long time ago (OR, 1.3; 95% CI, 1.2-1.4). Subgroup analyses revealed high ORs for users younger than 40 years (OR, 2.3; 95% CI, 1.3-4.0). No dose-response effect could be demonstrated.

Conclusion: The use of PPIs, especially when recently begun, is associated with an increased risk of community-acquired pneumonia.

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PROTON PUMP INHIBITORS (PPIs) are the mainstay of treatment for acid-related disorders in the upper gastrointestinal tract.[1] They are generally viewed as safe drugs,[2,3] but the development of gastrointestinal neoplasia, malabsorption of nutrients, and increased susceptibility of infections have all been claimed as potential complications of these widely used drugs.[4] The use of PPIs has previously been associated with an increased risk of infections in the lower gastrointestinal tract, mainly due to *Salmonella*, *Campylobacter*, and *Clostridium difficile*.[5-9]

Laheij et al[10] reported on the association between gastric acid–suppressive therapy and the increased risk of community-acquired respiratory infections in a questionnaire study. Afterward, they performed a population-based case-control study and found an increased incidence of community-acquired pneumonia (CAP) among current users of PPIs (odds ratio [OR], 1.8) or histamine$_2$-receptor antagonists (H_2RAs) (OR, 1.6). They also found a dose-response–like relationship; ie, more profound acid suppression resulted in a higher OR. Since the effect was seen with the use of both PPIs and H_2RAs, it was considered to be related to the acid suppression per se.[11] A prospective study performed in pediatric patients showed that the use of gastric acid inhibitors is associated with an increased risk of acute gastroenteritis and CAP in children with gastroesophageal reflux disease.[12]

The aims of this study were to confirm the possible association between PPI use and CAP, to identify risk factors, and to evaluate potential noncausal associations between the use of PPIs and CAP.

METHODS

SETTING

Data were retrieved from 4 different sources: the Patient Registry of the County of Funen, Denmark; the Danish Civil Registry, Copen-

hagen, Denmark; the Odense University Pharmacoepidemiological Database, Odense, Denmark; and the Department of Clinical Microbiology at Odense University Hospital. The Patient Registry of the County of Funen contains data on all discharges from hospitals in the County of Funen (population, 470 000) since 1977. Discharge diagnoses are encoded by physicians, using either the *International Statistical Classification of Diseases, 8th revision (ICD-8)*, from 1977 to 1993 or the *International Statistical Classification of Diseases, 10th revision (ICD-10)*, from 1994 to 2003. Some other clinical data are also accessible, eg, x-ray descriptions. Because medical care in Denmark is furnished almost exclusively by the government, use of these data resources allows true population-based studies.

The Odense University Pharmacoepidemiological Database has been described elsewhere.[13] In brief, it has a complete list of all reimbursed prescriptions in the county since 1992. Each prescription record contains a unique patient identifier, age and sex of the patient, date of dispensing, name of the pharmacy, a prescriber code, and a full account of the dispensed product. Substances are classified according to their anatomic-therapeutic-chemical (ATC) code, and quantities are expressed by the defined daily dose according to the World Health Organization (2005 version). Drugs not recorded in the database include over-the-counter drugs (eg, laxatives, high-dose aspirin, acetaminophen, and antihistamines) and a few prescription drugs that are not reimbursed, mainly tranquilizers and oral contraceptives. Also, H_2RAs and ibuprofen (200 mg/d) were available without prescription.

Finally, we retrieved the results of blood cultures, sputum cultures, and polymerase chain reaction tests obtained from cases during the period from 1 day before admission (to account for specimens obtained by general practitioners) to 4 days after admission (to account for weekends). The data were provided by the Department of Clinical Microbiology at Odense University Hospital, which at the time of the study period serviced the County of Funen. The microbiological data were used to calculate stratum-specific ORs according to the microbiological findings. We were particularly interested in the association between PPIs and pathogens that are most likely transmitted through air, droplets, or exposure to upper respiratory secretions (airborne pathogens). The Danish Civil Registry was used to identify the source population, to extract controls, and to ensure that all subjects were residents of County of Funen for at least 6 months before their index date. Linkage across these sources was carried out by the use of a 10-digit code, a unique and permanent identifier of each Danish citizen.[14]

CASES

Cases of all ages were defined by the first admission with a CAP to a hospital in the County of Funen within the period of 2000 through 2004. Cases were assigned an index date equivalent to the first registered date of a CAP diagnosis. The *ICD-10* codes used were J13 to J18, including all subcategories. In total, we identified 8950 such admissions. All chest x-ray descriptions from the first 2 days of admission were manually reviewed and coded. We did not ascertain x-ray descriptions after the first 2 days of admission, as we could not assume that a given infiltrate was acquired outside the hospital.

Our primary end point was defined as any admission with a discharge diagnosis of CAP. We also tested the sensitivity of our analyses toward misclassification by subanalyses using more strict criteria for the end point, ie, including only cases with a positive result on x-ray film, culture, or polymerase chain reaction test.

CONTROLS

Control subjects were randomly extracted from the County of Funen population and frequency matched by age (in 10-year bands) and sex to the cases with a 4:1 ratio. Each control was assigned a random index date during the period from January 1, 2000, to December 31, 2004. Control subjects whose random date fell outside their eligibility period were excluded. Therefore, the subjects' probability of eventually being selected as controls was proportional to their time spent as being eligible. We allowed that cases could also be extracted as control subjects (n = 767) before they became cases.[15] Consequently, the generated ORs are unbiased estimates of the incidence rate ratios.

EXCLUSION CRITERIA

We excluded subjects, 887 cases and 1395 controls, with a diagnosis of malignancy apart from nonmelanoma skin cancer established between 5 years before and 6 months after the index date to avoid misclassifying malignant infiltrates as pneumonias. Finally, we excluded 421 cases who were discharged from a hospital department within the past 7 days before the index date to avoid including cases with hospital-acquired infections. We also excluded 178 controls who were discharged within 7 days before their index date, as they were not eligible as cases. After these exclusions, the final case-control ratio deviated slightly from 1.0:4.0 to 1.0:4.4.

EXPOSURE DEFINITION

Exposure status of the cases and the control subjects was determined from prescription data extracted from the Odense University Pharmacoepidemiological Database. Subjects were considered exposed to PPIs if they had redeemed a prescription for a PPI (ATC code A02BC) during the past 90 days before the index date (current use). Subjects who had redeemed a prescription for a PPI more than 90 days before the index date were classified as past users. The choice of a 90-day exposure window was based on analyses of PPI prescription renewal patterns, using among other techniques the waiting-time technique.[16] Very few subjects redeemed prescriptions regularly at more than 3-month intervals, and the majority of users had irregular patterns, suggesting use as needed. Unless otherwise specified, other drug exposures were classified as current use if the last prescription occurred less than 90 days before the index date.

DATA ANALYSIS

The crude and adjusted ORs with 95% confidence intervals (CIs) of exposure for CAP cases compared with control subjects were estimated using unconditional logistic regression. We were particularly interested in current and past users of PPIs, comorbid illnesses as effect modifiers, the array of relevant microorganisms, dose-response and duration-response effects, protopathic bias, or bias by concurrent antibiotic use. Potential confounders included were age; sex; current use of inhaled bronchodilators, corticosteroids, or anticholinergic agents; use of systemic corticosteroids; use of antipsychotic agents or nonsteroidal anti-inflammatory drugs; previous diagnosis of CAP at least 1 month before the index date; previous diagnosis of chronic obstructive pulmonary disease or peptic ulcer; and any history of alcohol-related disorder, disulfiram use, diabetes mellitus, renal failure, hepatic cirrhosis, ischemic heart disease, heart failure, stroke, or psychiatric disorder (*ICD* and ATC codes not shown). All of these variables were either risk factors in univariate analyses of CAP or were found to modify the OR for the association between PPIs and CAP by at least 5% if included in a multivariate model. We could not include recent antibiotic use in the multivariate models, however, as it could

Table 1. Characteristics of Cases With Community-Acquired Pneumonia and Control Subjects*

Variable	Cases (n = 7642)	Controls (n = 34 176)
Age, mean ± SD, y	55.5 ± 31.2	56.5 ± 29.5
<40	2123 (27.8)	9016 (26.4)
40-60	990 (13.0)	4448 (13.0)
≥60	4529 (59.2)	20 712 (60.6)
Men	4035 (52.8)	18 293 (53.5)
Infiltrate	3942 (51.5)	NA
Current drug use		
PPIs	817 (10.7)	1584 (4.6)
H_2RAs	161 (2.1)	512 (1.5)
Bronchodilators	1125 (14.7)	1026 (3.0)
Inhaled corticosteroids	857 (11.2)	910 (2.6)
Systemic corticosteroids	814 (10.6)	921 (2.7)
NSAIDs	855 (11.2)	2717 (7.9)
Anticholinergic agents	387 (5.0)	282 (0.8)
Immunomodulating drugs	20 (0.2)	36 (0.1)
Antipsychotic agents	485 (6.3)	833 (2.4)
Antibiotics	3726 (48.7)	4021 (11.7)
Disulfiram	20 (0.2)	26 (0.0)
History of		
Community-acquired pneumonia	1190 (15.5)	1412 (4.1)
Chronic obstructive lung disease	1442 (18.8)	918 (2.7)
Peptic ulcer	555 (7.2)	1114 (3.2)
Diabetes mellitus	609 (7.9)	1116 (3.2)
Renal failure	150 (1.9)	114 (0.3)
Hepatic cirrhosis	57 (0.75)	68 (0.2)
Ischemic heart disease	1183 (15.4)	2325 (6.8)
Heart failure	1105 (14.4)	1504 (4.4)
Stroke	840 (11.0)	1659 (4.8)
Alcohol-related diagnosis or drug use	316 (4.1)	430 (1.2)
Psychiatric disorder	553 (7.2)	904 (2.6)

Abbreviations: H_2RAs, histamine$_2$-receptor antagonists; NA, not applicable; NSAIDs, nonsteroidal anti-inflammatory drugs; PPIs, proton pump inhibitors.
*Data other than age are expressed as number (percentage).

be in the causal pathway between PPI use and CAP. Instead, we restricted some analysis to persons who had not used antibiotics.

Stratified analyses were conducted by age, season, dose of PPI, and recency of PPI use. The dose-response relationship was evaluated by using the cumulative amount of PPIs redeemed during the past 90 days as a crude marker of dose. Cutoff points were less than 50 DDD, 50 to 100 DDD, and greater than 100 DDD. In the analyses of recency of PPI use, we stratified according to when the first-ever PPI prescription was issued for the exposed subjects. Cutoff points were 7, 14, 28, 56, and 84 days before the index date. We also analyzed for recent past use of PPIs (last prescription 90-180 days before index date) and old past use (last prescription >180 days before index date). Finally, we performed subgroup analyses for fatal pneumonia (defined by the subject's death within 30 days after admission), for x-ray–positive and –negative pneumonia, for pneumococcal pneumonia, and for pneumonia with a test that was positive for an airborne pathogen.

The reference for all analyses was person-time unexposed to PPI, except for the analysis of recent and old past use, for which the reference was never-use of PPI. When analyzing for the effects of current H_2RA use, we excluded current users of PPIs. The project was approved by the Danish Data Protection Agency. An ethics committee approval was not required.

RESULTS

We identified 7642 cases (52.8% men) who met our criteria. Of these, 5709 underwent radiography during the first 2 days of admission, and 3942 (51.6% of all cases) of the x-ray films showed an infiltrate. In all, 776 cases (10.0%) had a diagnosis code of pneumococcal pneumonia; 692 (9.0%) died within the first 30 days after the index date. The characteristics of cases and controls are presented in **Table 1**. As expected, cases were generally more burdened by chronic diseases than were controls.

Among the 7642 cases and 34 176 controls, 817 (10.7%) and 1584 (4.6%) were current users of PPIs. The adjusted OR associating current use of PPIs with CAP was 1.5 (95% CI, 1.3-1.7). No definite association was found with H_2RAs (OR, 1.1; 95% CI, 0.8-1.3), nor was there any association with recent past or old past use of PPIs or H_2RAs (**Table 2**). A dose-response relationship could not be found in current (OR, 1.4, 1.6, and 1.4) or cumulative (OR, 1.7, 2.1, and 1.3) dose for the 3 levels (Table 2). The attributable proportion, ie, the fraction of CAP that was caused by PPIs, was 4%.[15]

Table 3 shows the crude and adjusted stratum-specific ORs for various subgroups of patients. The analysis revealed little variation. All groups showed ORs above unity, although not all had sample size to show statistical significance. Subgroups with an OR above average were users younger than 40 years (OR, 2.3; 95% CI, 1.3-4.0) and patients with a diagnosis of cirrhosis (OR, 4.6; 95% CI, 1.3-17.2). Among the subjects with no previous hospital contacts before their index date, we found an OR of 1.8 (95% CI, 1.0-3.2), and for subjects who had not received antibiotics during the 90 days preceding the index date, the OR was 1.6 (95% CI, 1.4-1.8).

Table 4 lists the crude and the adjusted ORs for subgroups of end points. The entire control group was used for reference for all analysis. Adjusted ORs varied between 1.1 and 1.8, with the latter representing fatal pneumonias. Our adjusted ORs for any airborne pathogen and no airborne pathogen demonstrated were estimated at 1.1 (95% CI, 0.8-1.4) and 1.5 (95% CI, 1.4-1.7), respectively.

Finally, we analyzed the temporal relationship between the start of PPI use and CAP risk (**Figure**). We found a steep temporal relationship with the highest OR for PPI treatments started 0 to 7 days before index date (OR, 5.0; 95% CI, 2.1-11.7). The OR decreased for PPI treatment started earlier; eg, it decreased to 1.3 (95% CI, 1.2-1.4) for PPI treatment started more than 84 days before the index date (Figure).

COMMENT

In our large case-control study, current use of PPIs was moderately associated with the risk of CAP (OR, 1.5; 95% CI, 1.3-1.7). The association was similar across most strata as well as within subgroups of end points. The increase in risk was most pronounced in new users of PPIs. However, neither a dose-response relationship nor a cumulative effect was found. Only current users of PPIs were at increased risk. We could not confirm an increased risk of CAP among H_2RAs users.

Table 2. Association Between Exposure to Proton Pump Inhibitors (PPIs) or Histamine$_2$-Receptor Antagonists (H_2RAs) and Community-Acquired Pneumonia (CAP)

Exposure	Cases, Exposed/Unexposed	Controls, Exposed/Unexposed*	Crude OR (95% CI)	Adjusted OR (95% CI)†
Current use				
PPIs	817/6825	1584/32 592	2.4 (2.2-2.7)	1.5 (1.3-1.7)
H_2RAs	139/6686	478/32 114	1.4 (1.1-1.7)	1.1 (0.8-1.3)
Recent past use				
PPIs	123/6702	335/32 257	1.7 (1.4-2.1)	1.2 (0.9-1.6)
H_2RAs	26/6660	134/31 980	0.9 (0.6-1.4)	0.7 (0.4-1.1)
Old past use				
PPIs	806/5896	2795/29 462	1.4 (1.3-1.5)	1.0 (0.9-1.1)
H_2RAs	820/5840	2861/29 119	1.4 (1.3-1.5)	1.1 (1.0-1.2)
Cumulative dose of PPIs within past 90 d, DDD				
<50	158/6825	415/32 592	1.8 (1.5-2.1)	1.4 (1.1-1.8)
50-100	307/6825	585/32 592	2.5 (2.1-2.8)	1.6 (1.3-1.8)
>100	352/6825	584/32 592	2.8 (2.5-3.2)	1.4 (1.2-1.7)
Cumulative dose of PPIs ever, DDD				
<50	64/6825	135/32 592	2.2 (1.6-3.0)	1.7 (1.2-2.5)
50-200	170/6825	275/32 592	2.9 (2.4-3.5)	2.1 (1.7-2.7)
>200	583/6825	1174/32 592	2.3 (2.1-2.6)	1.3 (1.2-1.5)

Abbreviations: CI, confidence interval; DDD, defined daily dose; OR, odds ratio.
*Matched by age, sex, and index date.
†Adjusted for age, sex, and a previous discharge diagnosis of CAP, chronic obstructive pulmonary disease, COPD, chronic obstructive pulmonary disease, peptic ulcer, alcohol-related diagnoses, ischemic heart disease, liver cirrhosis, renal failure, diabetes, heart failure, and stroke and for current use of systemic and inhaled corticosteroids, bronchodilators, nonsteroidal anti-inflammatory drugs, anticholinergic agents, and antipsychotic agents.

Table 3. Stratum-Specific Odds Ratios (ORs) for the Association Between Current Use of Proton Pump Inhibitors (PPIs) and Community-Acquired Pneumonia (CAP)

Stratum	Cases, Exposed/Unexposed	Controls, Exposed/Unexposed	Crude OR (95% CI)	Adjusted OR (95% CI)*
Men	423/3612	746/17 547	2.8 (2.4-3.1)	1.7 (1.5-2.0)
Age, y				
<40	30/2094	29/8986	4.1 (2.5-6.9)	2.3 (1.3-4.0)
≥40-60	107/883	127/4321	4.1 (3.2-5.4)	2.0 (1.4-2.8)
≥60	681/3848	1427/19 285	2.4 (2.1-2.6)	1.5 (1.3-1.7)
History of				
CAP	210/980	155/1257	1.7 (1.4-2.2)	1.4 (1.1-1.8)
COPD	242/1200	112/806	1.5 (1.1-1.8)	1.2 (0.9-1.6)
Peptic ulcer	219/336	318/796	1.6 (1.3-2.0)	1.4 (1.1-1.8)
Liver cirrhosis	18/39	6/62	4.8 (1.7-13.1)	4.6 (1.3-17.2)
Ischemic heart disease	267/916	296/2029	2.0 (1.7-2.4)	1.5 (1.2-1.9)
Diabetes mellitus	114/495	110/1006	2.1 (1.6-2.8)	1.7 (1.2-2.4)
Renal failure	51/99	24/90	1.9 (1.1-3.4)	1.8 (0.9-3.4)
Heart failure	204/901	174/1330	1.7 (1.4-2.2)	1.3 (1.0-1.6)
Stroke	162/678	201/1458	1.7 (1.4-2.2)	1.4 (1.1-1.9)
Alcohol-related diagnosis or drug use	62/254	54/376	1.7 (1.1-2.5)	1.2 (0.7-2.0)
Psychiatric disorder	114/439	117/787	1.7 (1.3-2.3)	1.2 (0.9-1.7)
No previous admissions	27/660	100/6701	2.7 (1.7-4.2)	1.8 (1.0-3.2)
No antibiotic use within past 90 d	391/3525	1212/28 943	2.7 (2.4-3.0)	1.6 (1.4-1.8)

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease.
*Adjusted for age, sex, and a previous discharge diagnosis of CAP, COPD, peptic ulcer, alcohol-related diagnoses, ischemic heart disease, liver cirrhosis, renal failure, diabetes, heart failure, and stroke and for current use of systemic and inhaled corticosteroids, bronchodilators, nonsteroidal anti-inflammatory drugs, anticholinergic agents, and antipsychotic agents.

To our knowledge, the only comparable study is that of Laheij et al.[11] They used a nested case-control design in which all cases (n=475) and controls (n=4690) were recruited among ever-users of PPIs or H_2RAs. An adjusted OR of 1.7 (95% CI, 1.2-2.3) was found for the PPI-CAP association. They also found an association between the use of H_2RAs and CAP (OR, 1.5; 95% CI, 1.1-2.2). The main difference between our study and theirs is that our study comprised a much larger sample, which allowed us to describe risks in subgroups. Also, we did not confine our study to ever-users of PPIs or H_2RAs. Our preliminary analyses of PPI use patterns suggested that,

Table 4. Association Between the Use of Proton Pump Inhibitors (PPIs) and Community-Acquired Pneumonia (CAP), Subgroup Analysis Within Modified End Points*

Subgroup of Cases	Cases, Exposed/Unexposed	Controls, Exposed/Unexposed	Crude OR (95% CI)	Adjusted OR (95% CI)†
x-Ray–positive CAP (n = 3942)	432/3510	1584/32 592	2.5 (2.2-2.8)	1.5 (1.3-1.7)
x-Ray–negative CAP (n = 3700)	385/3315	1584/32 592	2.3 (2.1-2.6)	1.4 (1.2-1.7)
Fatal CAP (n = 692)	129/563	1584/32 592	4.7 (3.8-5.7)	1.8 (1.4-2.3)
Streptococcal CAP (n = 776)	51/725	1584/32 592	1.4 (1.0-1.9)	1.1 (0.8-1.6)
Airborne pathogen demonstrated‡ (n = 1639)	91/1548	1584/32 592	1.2 (0.9-1.5)	1.1 (0.8-1.4)
No airborne pathogen demonstrated‡ (n = 6003)	726/5277	1584/32 592	2.8 (2.5-3.1)	1.5 (1.4-1.7)

Abbreviations: CI, confidence interval; OR, odds ratio.
*The entire control group was used for all analyses.
†Adjusted for age, sex, and a previous discharge diagnosis of CAP, chronic obstructive pulmonary disease, peptic ulcer, alcohol-related diagnoses, ischemic heart disease, liver cirrhosis, renal failure, diabetes, heart failure, and stroke and for concurrent use of systemic and inhaled corticosteroids, bronchodilators, nonsteroidal anti-inflammatory drugs, anticholinergic agents, and antipsychotic agents.
‡The microorganisms considered airborne are *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae*, *Legionella pneumophila*, *Neisseria meningitidis*, respiratory syncytial virus, influenza A and B virus, parainfluenzavirus, *Pneumocystis carinii*, molds, *Chlamydia pneumoniae*, and *Chlamydia psittaci*.

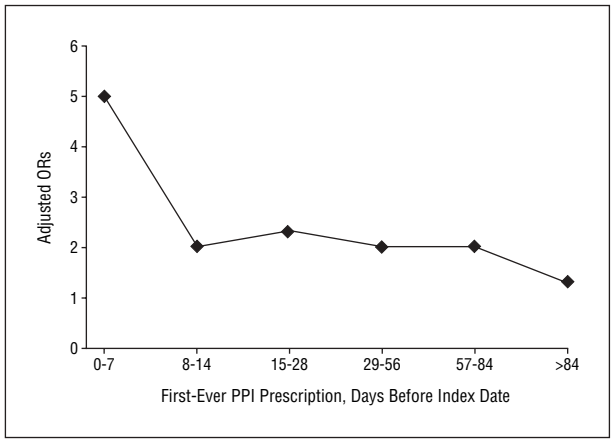

Figure. Association between current use of proton pump inhibitors (PPIs) and community-acquired pneumonia, according to the timing of first PPI prescription. ORs indicates odds ratios.

at least in our setting, PPI use is irregular and probably to a wide extent dependent on an as-needed basis (data not shown). Thus, we would run a substantial risk of misclassifying exposure by including only ever-users.

The main strength of our study lies in the use of a true population-based approach, with full coverage of admissions and PPI prescriptions. A unique personal identifier allowed precise linkage between data sources and therefore allowed us to review the results of x-ray investigations manually. Some of our pneumonia cases could be misclassified by the inclusion of cases without verified infiltrate. However, we found the same association between x-ray–positive and –negative cases. Moreover, x-ray–negative pneumonia cases showed the same strong seasonality as did the x-ray–positive ones (data not shown). Any misclassification of case status would most likely be nondifferential, ie, independent on PPI use, and would result in a bias toward the null and thus not alter our conclusions.

Selection bias is unlikely to be influential in this study for several reasons: All our residents were eligible as cases. The PPI-CAP association was not widely known or suspected during the study period. Therefore, it is unlikely that knowledge of a patient's PPI use would affect the decision to refer for admission. We found an even stronger association for fatal cases of pneumonia, which are unlikely to be influenced by referral bias. One limitation of our study could be that we included only hospitalized patients. Moreover, in our data, we cannot account for patient noncompliance with regard to PPI use.

We also need to consider the possibility of a confounded association. Users of PPIs are frailer than others and more often suffer from chronic diseases. The same patients have a high risk of CAP. Indeed, confounding by frailty was demonstrable in our data set by the differences between crude and adjusted ORs. However, the frailty of PPI users cannot entirely explain the association. Young patients and those with no hospital contacts ever showed a stronger association than in the main analysis. Also, our finding of no association with past or recent use and the strong temporal association is not compatible with frailty as the sole cause of the association. Alcoholism and smoking are known risk factors of CAP[17,18] and could be related to the use of PPIs. We did not have data on the smoking status or alcohol consumption of the patients. Instead, we used a diagnosis of chronic obstructive pulmonary disease and an alcohol-related diagnosis as crude markers. The inclusion of these markers in the multivariate models did not change the OR (data not shown). We therefore find it unlikely that there would be strong residual confounding by less excessive smoking or drinking.

Another hypothesis that has been put forward is that gastroesophageal reflux disease itself might explain an excess of CAP among PPI users.[19] Reflux is associated with some airway symptoms, such as cough and uncontrolled asthma, but there is little evidence to support a

strong association between reflux disease and CAP.[20,21] Second, only a minority of PPI users in our setting had verified reflux.[22] Finally, we also found an association among persons who took PPIs for indications other than reflux, eg, peptic ulcer. Therefore, a strong confounding by reflux is unlikely.

A third potential confounder is protopathic bias,[23] which in this case is defined by symptoms such as abdominal pain and vomiting as early manifestations of pneumonia that could have been misinterpreted as reflux disease and treated with PPIs. A protopathic bias would be lead to a strong association with new treatment, but it would not explain why the association seems to fade over several months. Also, abdominal pain and vomiting are atypical presenting symptoms of CAP.[24] A similar bias could arise if the antibiotics that were used to treat the pneumonia before admission caused dyspepsia, which again might have been treated with PPIs. However, we found an even stronger PPI-CAP association among the persons who had not used antibiotics before the index date (Table 3). Furthermore, the steep temporal gradient was even more pronounced after the antibiotic users were excluded (data not shown).

There are now data to support an association between PPIs and *Salmonella* infections, *Clostridium* infections, and CAP with varying pathogens.[5,7,8] The simplest mechanistic interpretation is that the profound inhibition of acid secretion could break a defense barrier—an "acid wall"—for pathogens going "down" (*Salmonell*a or *Clostridium*) or "up" (CAP). This simple, mechanistic model is supported by our finding that the risk of infection with an airborne pathogen is not affected by PPI use.

Undoubtedly, PPIs are of great value for the treatment of peptic ulcers, gastroesophageal reflux disease, or prophylaxis against nonsteroidal anti-inflammatory drug–related ulcer complications in selected patients. However, during the period of 1995 to 2004, there was a 300% increase in PPI use in the County of Funen (www.dkma.dk).[25] Only a small proportion of PPI use can be accounted for by cases of known peptic ulcers, cases of reflux disease, or use of nonsteroidal anti-inflammatory drugs.[20] Our study results and those of others indicate that PPIs should not be prescribed too casually.

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