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Microbial evaluation of proton pump inhibitors and the risk of pneumonia

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Abstract

Background: Recent initiation of proton pump inhibitor (PPI) treatment may increase the risk of community-acquired pneumonia (CAP), hypothetically by allowing colonization of the oropharynx by gastrointestinal bacteria. Aim of this study was to assess the causal pathway by considering microbial etiology of pneumonia and indications for initiation of PPI treatment.

Methods: This was a population-based case-control study with 430 cases with pneumonia and 1720 matched controls. An elaborate diagnostic protocol was used to identify the causative microorganism of pneumonia. For patients recently starting PPI treatment, indications for treatment were assessed.

Results: Recent initiation of PPI treatment (<30 days) was associated with an increased risk of CAP (adjusted OR 3.1, 95% CI 1.4 – 7.1). Oropharyngeal bacteria were evenly distributed among current, past and non-users of PPIs (p=0.41). Only in 5 patients (1.2%) with pneumonia (2 current users and 3 non users), gastrointestinal bacteria were identified. Excluding patients who possibly were prescribed PPI treatment for early symptoms of pneumonia (protopathic bias) did not alter the study findings.

Conclusions: This study reaffirmed that use of PPIs is associated with an increased risk of CAP, especially when treatment is started recently. Neither protopathic bias nor shifts in microbial etiology seem to explain the association.

Keywords: case-control study, community-acquired pneumonia, proton pump inhibitors

Abbreviations

ACE: angiotensin converting enzyme

CAP: community-acquired pneumonia

CHF: congestive heart failure

COPD: chronic obstructive pulmonary disease

DDD: defined daily doses

DM: diabetes mellitus

GERD: gastroesophageal reflux disease

ICU: intensive care unit

NSAID: nonsteroidal anti-inflammatory drug

PPI: proton pump inhibitor

PSI: pneumonia severity index

Introduction

Recent evidence has suggested that gastric acid-suppressive medication might increase the risk of community acquired pneumonia (CAP). Results have been conflicting, however, and a meta-analysis failed to draw a definite conclusion due to significant heterogeneity.(1-10) Some researchers are skeptical about the reported association, because causality seemed improbable and results are suspected to be biased.(11-13) Given the widespread use of these medications and the severity of pneumonia, further research remains warranted. So far, most studies used medical record databases to examine the use of proton pump inhibitors (PPIs) in relation to the incidence of CAP. The shortcomings of this approach are inherent to retrospective epidemiologic research on administrative databases. Misclassification of cases might have occurred because clinical information (such as radiographic data) was not always available. Confounding by indication and protopathic bias (when a treatment for the first symptoms of a disease appears to cause the disease) could not be ruled out because most databases did not include information on the indication for PPI treatment. Furthermore, there were no conclusive data on the causative organisms of CAP included in these analyses. Such data would provide more insights into often suggested, but not demonstrated, causal mechanisms, namely overgrowth and microaspiration of gastrointestinal bacteria.

The present study tries to overcome the methodological limitations addressed above by including a well defined cohort of hospitalized CAP patients with elaborate clinical and microbial information and matching them to a population-based control group.

The aim of the present study was to examine the association between use of PPIs and CAP, by including microbial etiology and clinical characteristics of patients with pneumonia who recently started PPI treatment in the analyses.

Methods

Study design

This was a population-based matched case-control study where cases were defined as patients with CAP admitted to the St. Antonius Hospital in Nieuwegein or at the Gelderse Vallei Hospital in Ede, both of which are teaching hospitals (880 and 500 beds, respectively) in the Netherlands. Population-controls were drawn from the PHARMO record linkage system database. The PHARMO institute is an independent scientific research organization studying drug use and outcomes. Records include detailed information on patient demographics, drug use and hospital admissions, and approximately 3 million community-dwelling inhabitants of 48 geo-demographic areas in The Netherlands are included.(14;15)

Cases

Cases were patients with confirmed pneumonia who participated in two clinical trials.(16;17) Consecutive patients were included on the emergency department between October 2004 and August 2006 and between November 2007 and February 2010. Pneumonia was defined as a new infiltrate on a chest radiograph plus at least two of the following criteria: cough; sputum production; temperature > 38°C or < 35.5°C; auscultatory findings consistent with pneumonia, leukocytosis, or leukopenia (> 10 G/L, < 4 G/L, or > 10% rods in leukocyte differentiation); and C-reactive protein > 3 times the upper limit of normal. Patients who were immune compromised (hematological malignancies and immunosuppressive therapy, including the use of > 20 mg prednisone equivalent per day for more than 3 days) were excluded. The study was approved by the local Medical Ethics Committee and all patients gave their written informed consent. On the day of hospital admission, the pneumonia

severity index (PSI) was calculated.(18) Need for intensive care unit (ICU) admittance and in-hospital mortality were assessed.

Controls

Control subjects were obtained from the PHARMO database and individually matched by year of birth, sex and index date to the cases in a 4:1 ratio. The index date was the date of the CAP diagnosis of the corresponding case. Controls with a hospitalization for CAP during the research period (i.e. in the six months before index date, identified by the International Classification of Diseases, 9th edition (ICD-9-CM) were excluded.

Pathogen identification

The diagnostic tools used to identify the causative microorganism of CAP have been described before.(16) In short, at least two sets of separate blood and sputum samples from each patient were cultured. Sputum was analyzed by in-house developed polymerase chain reaction for atypical pathogens (*Mycoplasma pneumoniae*, *Legionella pneumophila*, *Coxiella burnetii* and *Chlamydophila pneumoniae and psittaci*). Urine was sampled for antigen testing on *Streptococcus pneumoniae* and *Legionella pneumophila* serogroup 1. In addition, serum samples taken on the day of hospital admission and day 10 were analyzed in pairs for detection of a fourfold rise of antibodies to respiratory viruses, *Coxiella burnetii*, *Mycoplasma pneumoniae*, and *Chlamydophila psittaci* by complement fixation assay. In addition, antibodies against pneumococcal polysaccharides of 14 different serotypes were measured using the Luminex xMAP® Pneumococcal Immunity Panel.(19) Pharyngeal samples were taken for viral culture. Pathogens were classified in two different ways. First, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, *Haemophilus parainfluenzae*

and other streptococci were considered as oropharyngeal bacteria. Second, pathogens considered as gastrointestinal were *Escherichia coli* and *Klebsiella pneumoniae*.

Exposure definition

Community pharmacies were approached in order to identify all dispensed prescription drugs for cases issued in the six months before CAP diagnosis. For controls, drug dispensing records were retrieved from the PHARMO database. Exposure definition was identical for cases and controls. PPIs were not over-the-counter available in the Netherlands during the study period. We identified all prescriptions for omeprazole, pantoprazole, lansoprazole, rabeprazole and esomeprazole for both cases and controls. Current use of PPI was defined as a dispensed prescription that lasted beyond 30 days before the index date or started after 30 days before the index date. Past use of PPI was defined as one or more dispensed prescriptions in the 6 months before index date, that did not last beyond 30 days before index date. Non use was defined as no dispensed prescriptions during the 6 months period. These categories were mutually exclusive for each category. A subdivision of the group of current users was made according to the date of the first prescription. Recent initiation was defined as a first prescription < 30 days before index date; chronic use was defined as a first prescription ≥ 30 days before index date. Defined daily doses (DDDs) were calculated based on strength and prescribed dosing regimen of the most recent prescription prior to the index date to express the prescribed daily dose within current users.(20) For all patients who started PPI treatment within 15 days prior to the index date, the indications for starting treatment were assessed through telephonic interview with the patient and or the prescribing physician.

Potential confounders

Current use of statins, ACE- inhibitors and angiotensin II receptor antagonists was defined analogous to current PPI use. These drugs have been reported to influence the risk of CAP.(8) Exposure to the following medications was used as a proxy (indicator for disease) for comorbid illness predisposing for CAP and was defined as 2 or more prescriptions in the 6 months before index date. We evaluated use of NSAIDs, antidiabetics (as a proxy for diabetes mellitus (DM)), opiates, antiplatelet therapy, inhalation medication (as a proxy for chronic obstructive pulmonary disease (COPD) or asthma) and digoxine plus diuretics (as a proxy for congestive heart failure (CHF)). Besides this, inhaled corticosteroids and anticholinergics were also evaluated as separate potential confounders.(21;22) Prescriptions for oral corticosteroids during the month before index date and for antibiotics during the 6 months before index date were also assessed.

The sensitivity of the proxies for DM, COPD or asthma and CHF was checked by studying the consistency of the proxy with the corresponding disease as recorded in the medical charts of cases.

Statistical Analysis

Conditional logistic regression analysis was performed to obtain crude odds ratios (OR) in matched cases and controls. Results are presented as numbers (percentages), ORs (95% confidence intervals (CI)) and p-value. We considered factors associated with CAP in the univariate analysis and variables previously found to be associated with CAP and PPI use as potential confounders in the multivariate model. We selected potential confounders for the multivariate model stepwise by direct estimation of the degree of confounding produced by each variable (relative change in OR of CAP associated with current use of PPI). We continued including potential confounders to the multivariate model until further addition of confounders modified the OR less than 5%.

A backward logistic regression analysis including age, sex, comorbidities (CHF, COPD or asthma, DM, and renal failure) and PSI score was used to study the outcome of CAP in relation to use of PPIs. The association between PPI use and causative agents of CAP was studied using Chi-square and Fisher's exact tests where appropriate.

Results

Characteristics of cases and controls

The study population comprised 430 CAP cases and 1720 matched controls. Characteristics of cases and controls are shown in table 1. The mean age of cases and controls was 62 (SD 18) years and 59% were male. Among cases, 32 patients were admitted to the ICU and 24 patients died during hospital stay. Overall, cases were more likely to use medication than controls.

Association between use of PPIs and CAP

Table 2 lists the crude and adjusted ORs for CAP associated with use of PPIs. In the crude analysis, current use of PPIs was associated with an OR for CAP of 1.8 (95% CI 1.4 – 2.4). In the final multivariate model, oral corticosteroids, inhaled corticosteroids, anticholinergics and NSAIDs were included as confounders. The adjusted OR for CAP associated with current PPI use was 1.6 (95% CI 1.2-2.2).

The risk of CAP increased as the starting date of the PPI approached the index date. To ensure that patients identified as new users were not intermittent users, only cases and controls that had not redeemed a prescription for PPIs during the year before index date were included. Patients with a first prescription ≤15 days before index date had an adjusted OR of 3.1 (95% CI 1.1 – 8.8). Patients with a first prescription 16-29 days before index date had an adjusted OR 3.3 (95% CI 0.91 – 11.6). A sensitivity analysis including new users that did receive PPIs during the half-year period of 12 up to 6 months before index date (but did not receive any prescriptions > 6 months before index date until < 30 days before index date), included 1 new user for cases and 6 new users for controls extra. In this analysis, recent initiation of PPI treatment remained significantly associated with an increased risk for CAP (adjusted OR 2.4

(95% CI 1.1 – 5.0)). As shown in table 2, there was a modest dose effect relation for current use of PPIs.

Clinical details of CAP cases recently starting PPI treatment

Table 3 provides clinical background information on the pneumonia patients that recently started PPI treatment. Medical history differed markedly between patients, although cardiovascular disease and COPD were common comorbidities. The indications for PPI treatment were diverse as well. Patient number 7 received a PPI for xyphoid pain, which might have been CAP- and not reflux related. Patient number 9 also experienced possible symptoms of CAP. Half of the patients received a PPI as prophylaxis for gastrointestinal bleeding and ulcera due to NSAIDs. There was no reason to suspect that their pain complaints (e.g. lower back pain) were early symptoms for CAP. The indications for the remaining cases were (bleeding) ulcera, *Helicobacter pylori* infection and dyspepsia.

In order to assess whether protopathic bias could explain the demonstrated increase in risk associated with recent initiation of PPI treatment, we conducted a sensitivity analysis by considering case number 7 and 9 non-exposed. The risk for CAP remained significantly elevated for recent initiation of PPI treatment (adjusted OR 2.5, 95% CI 1.0 – 5.8). If case numbers 1, 7 and 9 were excluded (because prescriptions were issued 2 or less days before CAP diagnosis, which could be too short to produce an acid suppressive effect and subsequent change in commensal flora) the adjusted OR yielded 2.1 (95% CI 0.85 – 5.1).

Clinical outcomes

Four of the 12 patients (33%) who recently started PPI treatment (<30 days before admission) were admitted to the ICU, whereas only 7% and 11% of non and current users, respectively, were admitted to the ICU. After adjusting for comorbidities, age, sex and PSI score, recent

initiation of PPI treatment was independently associated with ICU admission ($p<0.01$). Chronic and past use were not associated with ICU admission ($p=0.89$ and $p=0.99$ respectively). None of the patients who recently started PPI treatment died during hospital stay.

Causative pathogens

Among CAP patients, *Streptococcus pneumoniae* was identified in 30% of the cases. In 36% of cases, a causative organism could not be identified. Table 4 shows the microbial etiology for current, past and non users of PPIs.

In the 430 CAP cases, five were caused by defined gastrointestinal bacteria. Three of these (1%) were not receiving PPI treatment, two (2%) were current users of PPIs. Defined oropharyngeal bacteria were identified in 41% of current users, 25% of past users and in 39% of non users (versus non-oropharyngeal and unidentified pathogens, $p=0.41$). The frequency of oropharyngeal pathogens did not differ between patients recently starting PPI treatment and non users (versus non-oropharyngeal and unidentified pathogens, $p=1.00$).

Performance of proxies in cases

The results of the comparison of our proxies with recorded medical diagnoses are shown in figure 1.

Discussion

In this study, the risk of CAP was increased in patients currently using a PPI. We confirmed that the risk was highest shortly after initiation of PPI treatment. Because of this seemingly contradictory timing effect, we further examined the CAP patients who recently started PPI

treatment. It became clear that protopathic bias is not the sole explanation for the observed risk. Study of the causative microorganism of CAP did not show an increase in the frequency of either oropharyngeal or gastrointestinal bacteria in patients using PPIs.

Laheij et al.(7) were the first to report a positive association between current use of PPIs and risk of CAP. Most, but not all subsequent studies confirmed this association and also described a gradual increase in effect size when treatment was started closer to the index date. As maximum acid suppression is reached after 7 days of PPI treatment, this pattern of association is difficult to account for. Prothopathic bias has been put forward as a possible explanation: patients presenting with CAP-related cough might be misdiagnosed as having gastroesophageal reflux disease (GERD) or patients presenting with CAP-related pain might be prescribed an NSAID with a PPI for prophylaxis. Our study is the first to provide detailed information on patients who recently started PPI treatment, for whom the supposed association is most controversial. Only two of these patients received a prescription intended for complaints that might have been linked to early pneumonia, and a sensitivity analysis excluding these cases showed that the observed association remained increased.
Previous reports have suggested that backflow and overgrowth of gastrointestinal bacteria during PPI treatment may result in colonization of the oral space and predispose to pneumonia. Although such a mechanism has been demonstrated in mechanically ventilated patients, it remains speculative in CAP. (23-25) The current study was the first to include elaborate microbial data, acquired using an extensive diagnostic protocol to identify the causative agent of CAP. As in only two (2%) current PPI users CAP was caused by gastrointestinal bacteria, overgrowth and aspiration of gastrointestinal flora seems not the most prominent cause of pneumonia during acid-suppressive treatment. Our alternative hypothesis was that overgrowth of oropharyngeal bacteria during PPI treatment predisposes

patients for developing CAP. Plausibly, clearance of oropharyngeal bacteria is reduced when the pH of aspirated gastric contents is increased and possibly of the oropharyngeal fluid, as the proton pump is also assumed to be present in the larynx.(26-28) However, the frequency of CAP caused by bacteria that typically colonize the oropharynx was not increased in patients using a PPI. Five cases of pneumonia (42%) from the 12 patients recently starting PPI treatment were caused by oropharyngeal bacteria. Thus, also in the group in which the risk of CAP is the highest, overgrowth of either gastrointestinal or oropharyngeal bacteria does not seem to explain the association between use of PPIs and risk of CAP.

Given our findings that revoke microbial or non causal pathways as underlying mechanisms of the association; future research should directed towards other PPI properties or other types of bias. One possible explanation could be the immunomodulatory effects of PPIs. Omeprazole and lansoprazole have been shown to inhibit the expression of adhesion molecules on neutrophils, indicating that PPIs may diminish adequate transmigration of leukocytes to inflammatory sites.(29;30) In a small study of ten healthy volunteers, a single oral dose of omeprazole 40mg decreased reactive oxygen production and neutrophil bactericidal activity.(31) Experimental evidence suggests that omeprazole elevates intralysosomal pH, through inhibition of the neutrophil proton pump, thereby reducing the production of toxic oxidants.(32;33) In the present study we were unable to explore this possible causal pathway.

The major weaknesses of our study are inherent to its observational design. Residual confounding might be present as we did not have information on the indications for the PPI treatment of all patients, nor on medical diagnoses and lifestyle of controls. Instead we used proxies to identify comorbidities (COPD or asthma, CHF and DM). As shown in figure 1, the proxies for COPD or asthma and DM are very reliable. Remarkably, COPD or asthma were

present according to proxy but not recorded in the chart in 34% of all cases with COPD or asthma. As only 15% of cases had COPD or asthma that was not identified by our proxy, it seems that the proxy might even perform better than medical record scoring, as it is unlikely that patients would receive and fill two or more prescriptions for airway medication if disease is not present. In The Netherlands, it is possible that a general practioner treats a patient with mild COPD or asthma. The proxy used for CHF is less consistent with medical record scoring. However, the number of CHF patients identified by physicians is low, therefore the impact of the disease as a possible confounder would remain moderate, also with better performance of proxies.

Regarding lifestyle, as no such information was available of the controls, to evaluate the possibility of confounding we searched for associations between both smoking and alcohol abuse and use of PPI treatment within the pneumonia patients. This analysis showed that cases who smoked were less likely to use PPIs than non-smoking patients (11% vs. 28%) and that there was no difference for excessive alcohol use or none (22% vs. 23%). Considering that these habits are risk factors for pneumonia, this could indicate an underestimation of the true association between PPI use and pneumonia in our study.

Another limitation could be the origin of the controls. Instead of hospital controls we selected population controls. We feel confident that population controls represent better the population from which our cases originated. The PHARMO database hold a very representative sample of the Dutch population and a prior study showed that the patients admitted with pneumonia to the St. Antonius Hospital Nieuwegein resemble patients studied in PHARMO very much.(34) The prevalence of PPI use is comparable for all parts of The Netherlands.(35)

Finally, an issue that can only be addressed in a randomized controlled trial is that of poor adherence. Prescriptions for PPIs do not directly reflect exposure to PPIs and patients who are being prescribed a PPI for prophylaxis of gastrointestinal ulcera, will adhere less to therapy

than patients with active ulcera or dyspepsia. This might be the reason that the risk seems to fade out as PPI therapy turns chronic, because continue use will often reflect prophylactic therapy, whereas short term use will mainly be indicated in active ulcera.

In conclusion, recent initiation of PPI treatment is associated with an almost threefold increase in the risk of CAP. Study of the patients recently prescribed PPI treatment, showed that the association is not likely to be attributable to protopathic bias. Neither gastrointestinal nor oropharyngeal bacteria were more present in patients using a PPI compared to patients not using a PPI. Given these findings, further study on the causal pathway of the increased risk for pneumonia during PPI use should be directed towards other PPI properties.

Author contributions

Drs Meijvis and Ms Cornips performed the data collection and analyses and drafted the manuscript.. Dr. Voorn, Dr.Souverein, Dr. Endeman, Dr. Biesma and Dr. Leufkens participated in conducting the study and helped to draft the manuscript. Dr van de Garde designed and coordinated the study and approved the manuscript.

All authors had full access to all data in the study and take the responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

Titles and legends of tables and figures

Table 1. Characteristics of Community-Acquired Pneumonia Cases and Controls

NA: not applicable

Table 2. Odds Ratios (ORs) for Community-Acquired Pneumonia Associated With Use of Proton Pump Inhibitors (PPIs)

Data are presented as n (%)

* Adjusted OR: adjusted for use of inhaled corticosteroids, anticolinergics, NSAIDs and oral corticosteroids

† Days from first prescription until index date

‡ DDD Defined Daily Doses, analysis within current users

Table 3. Case Summaries of Pneumonia Patients Who Recently Started Proton Pump Inhibitor (PPI) Treatment

Abbreviations: CAP: community-acquired pneumonia; COPD: chronic obstructive pulmonary disease; CHF: congestive heart failure; DDD: defined daily dose; DM II: diabetes mellitus type II; GERD: gastroesophageal reflux disease; ICU: intensive care unit; O: omeprazole, P: pantoprazole; PPI: proton pump inhibitor; PSI: pneumonia severity index; R: rabeprazole

*This patient received an additional prescription for pantoprazole 40 mg daily 7 days after the omeprazole prescription was issued, 9 days before CAP diagnosis. Based on the prescribed daily dose, the prescription for omeprazole could have lasted until 1 day before CAP diagnosis.

Table 4. Causal Pathogens of Community-Acquired Pneumonia in Non, Past and Current Users of Proton Pump Inhibitors

* Bacteria considered as oropharyngeal were *S. pneumoniae*, *H. influenzae*, *S. aureus*, *H. parainfluenzae* and other streptococci. Use of PPIs was not associated with causation of CAP by oropharyngeal bacteria (tested to non oropharyngeal and unidentified pathogens, p-value=0.41).

† Bacteria considered as gastrointestinal were *E. coli* and *K. pneumoniae.*

Figure 1. Correspondence of Proxies to Medical Chart Information on Comorbidities

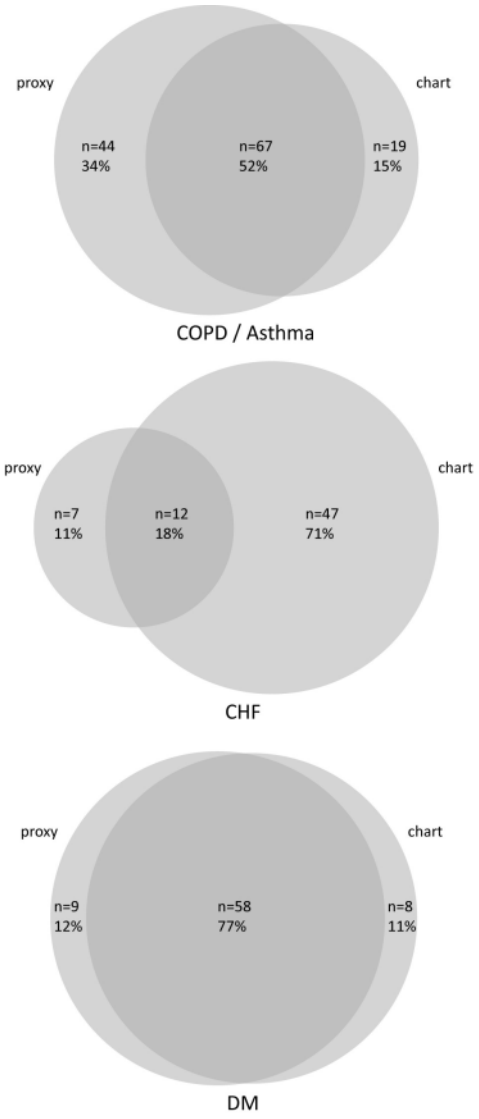
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chart
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34%
n=67
52%
n=19
15%
COPD / Asthma
proxy
chart
n=7
11%
n=12
18%
n=47
71%
CHF
proxy
chart
n=9
12%
n=58
77%
n=8
11%
DM

Table 1. Characteristics of Community-Acquired Pneumonia Cases and Controls

	All patients (n = 2150)	Cases (n = 430)	Controls (n = 1720)	Crude OR (95% CI)
Mean age, years (SD)	62 (18)	62 (18)	62 (18)	NA
Men, n (%)	1270 (59)	254 (59)	1016 (59)	NA
ACE inhibitors, n (%)	343 (16)	80 (19)	263 (15)	1.3 (0.99-1.8)
Angiotensin receptor antagonists, n (%)	210 (9.8)	32 (7.4)	178 (10)	0.69 (0.46-1.0)
Statins, n (%)	478 (22)	102 (24)	376 (22)	1.1 (0.86-1.5)
Antidiabetics, n (%)	255 (12)	67 (16)	188 (11)	1.5 (1.1-2.1)
COPD or asthma drugs*, n (%)	276 (13)	111 (26)	165 (9.6)	3.4 (2.6-4.5)
Inhaled corticosteroids*	234 (11)	86 (20)	148 (8.6)	2.7 (2.0-3.6)
Anticholinergics*	169 (7.9)	69 (16)	100 (5.8)	3.3 (2.4-4.7)
No inhalation steroids or anticholinergics	36 (1.7)	5 (1.2)	31 (1.8)	0.64 (0.25-1.7)
CHF medication, n (%)	50 (2.3)	19 (4.4)	31 (1.8)	2.5 (1.4-4.6)
NSAIDS, n (%)	156 (7.3)	27(6.3)	129 (7.5)	0.82 (0.53-1.3)
Antiplatelet therapy, n (%)	445 (21)	92 (21)	353(21)	1.1 (0.81-1.4)
Antibiotics, n (%)	476 (22)	104 (24)	372 (22)	1.2 (0.97-1.6)
Oral corticosteroids, n (%)	82 (3.8)	44 (10)	38 (2.2)	5.5 (3.4-8.8)
Opiates, n (%)	125 (5.8)	21 (4.9)	104 (6.0)	0.80 (0.49-1.3)

NA not applicable

* Not mutually exclusive categories

Table 2 Odds Ratios (ORs) for Community-Acquired Pneumonia Associated With Use of Proton Pump Inhibitors (PPIs).

Table 2. Odds Ratios (ORs) for Community-Acquired Pneumonia Associated With Use of Proton Pump Inhibitors (PPIs)

				Odds Ratios			
	All	**Cases**	**Controls**	**Crude OR**	**P value**	**Adjusted OR***	**P value**
	(n = 2150)	**(n = 430)**	**(n = 1720)**	**(95% CI)**		**(95% CI)**	
Non user	1690 (79)	307 (71)	1383 (80)	reference		reference	
Past user	90 (4.2)	20 (4.7)	70 (4.1)	1.3 (0.78 – 2.2)	0.308	1.2 (0.72 – 2.1)	0.46
Current user	370 (17)	103 (24)	267 (16)	1.8 (1.4 – 2.4)	<0.01	1.6 (1.2 – 2.2)	<0.01
Start of PPI treatment †							
Recent (< 30 days)	28 (7.6)	12 (12)	16 (6.0)	3.4 (1.6 – 7.3)	<0.01	3.1 (1.4 – 7.1)	<0.01
0 – 15 days	16 (4.3)	7 (6.8)	9 (3.4)	3.5 (1.3 – 9.6)	0.012	3.1 (1.1 – 8.8)	0.04
16 – 29 days	12 (3.2)	5 (4.9)	7 (2.6)	3.3 (1.1 – 10.4)	0.044	3.3 (0.91 – 11.6)	0.07
Chronic (≥ 30 days)	342 (92)	91 (88)	251 (94)	1.7 (1.3 – 2.3)	<0.01	1.5 (1.1 – 2.1)	<0.01
DDD‡							
< 1.5	292 (79)	80 (78)	212 (79)	1.8 (1.3 – 2.4)	<0.01	1.6 (1.2 – 2.2)	<0.01
≥ 1.5	78 (21)	23 (22)	55 (3.2)	2.0 (1.2 – 3.3)	0.01	1.7 (1.0 – 3.0)	0.05

Data are presented as n (%)

Adjusted OR: adjusted for use of inhalation corticosteroids, anticholinergics, NSAIDs and oral corticosteroids

† Days from first prescription until index date

‡ DDD Defined Daily Doses, analysis within current users

Table 3. Case Summaries of Pneumonia Patients Who Recently Started Proton Pump Inhibitor (PPI) Treatment

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Case no	Age	Sex	Medical history	Indication for PPI use	PPI	DDD	Days to CAP	Causative organism	PSI score	Admission to ICU
1	60	f	Resection middle lobe because of recurrent pneumonia caused by bronchiectasis (5 years before CAP), Primary biliary cirrhosis	Gastric protection during NSAID use for artrosis in hands	O	1	2	*H. influenzae*	60	No
2	72	m	Hypertension, COPD (GOLD 1)	Gastric protection during NSAID use for lower back pain	O	1	10	*E. coli*	102	No
3	80	m	Aorta valve replacement after stenosis (6 years before CAP). No further cardial pathology	Gastric protection during NSAID use for lower back pain	O	2	13	Parainfluenzae virus	90	No
4	18	m	-	Gastric discomfort and air regurgitation	O	1	20	*S. pneumoniae*	58	No
5	34	f	Deep venous thrombosis (1 month before CAP)	Gastric protection during NSAID use for painful leg. Previous use of NSAID caused discomfort	O	1	25	unidentified	34	Yes

6	65	f	COPD, transient ischemic attack, breast carcinoma (curative treatment 3 years before CAP)	Gastric protection during use of NSAID, prednisone, aspirin and dipyridamole	P	1	8	*H. influenzae*	105	Yes
7	70	m	Pneumonia, hypertension, hypercholesterolemia	Xyphoid pain radiating to lungs, general practitioner assumed GERD, but it might have been CAP.	O	1	1	unidentified	60	No
8	32	m	-	Gastric protection during NSAID use for painful shoulder	O	1	8	*S. milleri*	57	No
9	41	f	Uterus myomatosis	Stomach ache. Patient reports to always experience stomach ache before fever	P	1	1	*L. pneumophila*	51	No
10	83	f	Aorta valve stenosis, mitralis valve insufficiency, hypertension, COPD, CHF	Stomach ache during *Helicobacter pylori* infection	P	1	29	*S. pneumoniae*	83	No
11	60	f	Alcohol abuse, DM II	Therapy for bleeding duodenal ulcer	O/P *	1	16	unidentified	80	Yes
12	62	m	DM II, hypertension, COPD with emphysema, CHF, pulmonary hypertension	Therapy for peptic ulcer during NSAID use	R	1	22	*S. pneumoniae*	122	Yes

Abbreviations: CAP: community-acquired pneumonia; COPD: chronic obstructive pulmonary disease; CHF: congestive heart failure; DDD: defined daily dose; DM II: diabetes mellitus type II; GERD: gastroesophageal reflux disease; ICU: intensive care unit; O: omeprazole, P: pantoprazole; PPI: proton pump inhibitor; PSI: pneumonia severity index; R: rabeprazole

*This patient received an additional prescription for pantoprazole 40 mg daily 7 days after the omeprazole prescription was issued, 9 days before CAP diagnosis. Based on the prescribed daily dose, the prescription for omeprazole could have lasted until 1 day before CAP diagnosis.

Table 4. Causal Pathogens of Community-Acquired Pneumonia in Non, Past and Current Users of Proton Pump Inhibitors.

Table 4. Causal Pathogens of Community-Acquired Pneumonia in Non, Past and Current Users of Proton Pump Inhibitors

	All (n =430)	**Non users (n=307)**	**Current users (n=103)**	**Past users (n=20)**
Streptococcus pneumoniae	130 (30)	97 (32)	28 (27)	5 (25)
Atypical	69 (16)	54 (18)	7 (6.8)	8 (40)
viral	25 (5.8)	20 (6.5)	5 (4.9)	0 (0)
Gram negative	37 (8.6)	24 (7.8)	13 (13)	0 (0)
Other	15 (3.5)	9 (2.9)	6 (5.8)	0 (0)
Unidentified	154 (36)	103 (34)	44 (43)	7 (35)
Oropharyngeal bacteria identified*	166 (39)	119 (39)	42 (41)	5 (25)
Gastrointestinal bacteria identified†	5 (1.2)	3 (1.0)	2 (1.9)	0 (0)

Data are presented as n (%)

* Bacteria considered as oropharyngeal were *S. pneumoniae*, *H. influenzae*, *S. aureus*, *H. parainfluenzae* and other streptococci. Use of PPIs was not associated with causation of CAP by oropharyngeal bacteria (tested to non oropharyngeal and unidentified pathogens, p-value=0.41).

† Bacteria considered as gastrointestinal were *E. coli* and *K. pneumoniae.*

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