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Associations between Community Acquired Pneumonia and Proton Pump Inhibitors in the Laryngeal/Voice Disordered Population

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Abstract

Objectives: To examine the relationship between community acquired pneumonia (CAP) and proton pump inhibitor (PPI) treatment in laryngeal/voice disordered patients.

Study Design: Retrospective cohort analysis.

Setting: Large, national administrative U.S. claims database.

Subjects and Methods: Patients 18 years of age with outpatient treatment for a laryngeal/voice disorder per ICD-9-CM codes from January 1, 2010 to December 31, 2014 with 12 months continuous enrollment prior to the index date (first laryngeal/voice disorder diagnosis), no pre-index diagnosis of CAP, and had prescription claims captured from 1 year pre-index to end of follow-up were included. Patient demographics, comorbid conditions, index laryngeal diagnosis, number of unique pre-index patient encounters, and CAP diagnoses during 3 year post-index date were collected. Two models, a time-dependent Cox regression model and a propensity score based approach with marginal structural model, were each separately performed in patients with and without pre-index date PPI prescriptions.

Results: 392,355 unique patients met inclusion criteria. 188,128 (47.9%) patients had a PPI prescription. The 3 year absolute risk for CAP was 4.0% and 5.3% in patients without and with pre-index PPI use, respectively. The CAP occurrence for a person who already received a PPI is 30% to 50% higher than for a person who has not yet had a PPI but may receive one later for patients without and with pre-index date PPI use, respectively.

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Conclusions: Patients without and with pre-index date PPI use experienced roughly 30% to 50% increased likelihood of CAP, respectively, compared to patients who had not had PPI prescriptions.

Keywords

laryngeal disorders; voice disorders; larynx; dysphonia; voice; proton pump inhibitor; adverse event; pneumonia

Introduction:

Medications, especially proton pump inhibitors (PPIs), have a prominent role in the management of patients with laryngeal/voice disorders. Half of all patients presenting to general medical providers (GMPs) and otolaryngologists for voice-related complaints undergo medication trials, of which PPIs are common.^{1, 2} Furthermore, the frequent use of PPIs is associated with significant health care costs, accounting for 10% of the direct costs in the evaluation and management of patients with laryngeal/voice disorders.³ Yet, when caring for patients with laryngeal/voice disorders, practice patterns of GMPs and otolaryngologists suggest uncertainty surrounding the indications for PPI use, with the subsequent potential for inappropriate use.^{4–8} Thus, the frequent use of PPIs in the treatment of voice disorders has important public health implications for patients and society.

Beyond cost concerns, there is growing interest in and awareness of the potential adverse effects of PPIs. In a systematic review of systematic reviews, community acquired pneumonia (CAP) was one of the three most commonly reported adverse events along with bone fractures and enteric infections.⁹ Alterations in the bacterial microbiome from acid suppression has been proposed as a possible mechanism of increased CAP risk with PPI use.^{10–12} In particular, CAP may have substantial impact at the population level and also brings additional morbidity, mortality, and associated health care costs.^{9, 13}

Despite the frequency of PPI use, there are no data concerning the relationship between PPIs and CAP at the population level in a cohort of laryngeal/voice disordered patients. Understanding this association among this patient population is an important consideration for patients and providers when deciding about PPI treatment. The MarketScan[®] database, a large, national administrative U.S. claims database, has been a useful means for exploring adverse events in diverse patient populations during real-world care.^{14, 15} The purpose of this study is to assess the association between PPI treatment and CAP in a laryngeal/voice disordered patient cohort.

Methods:

This study was approved by the Duke University Medical Center Institutional Review Board. The MarketScan[®] Commercial Claims and Encounters and MarketScan[®] Medicare Supplemental and Coordination of Benefits dataset, a large, national administrative U.S. claims database, was retrospectively analyzed for January 1, 2010 to December 31, 2014. Health care claims are representative of typical clinical care.¹⁶ The MarketScan[®] databases (Truven Health Analytics and IBM Watson Health, Ann Arbor, MI) encompass the average

annual health care claims, including pharmacy claims, of roughly 59 million individual employees < 65 years of age, Medicare beneficiaries ≥ 65 years of age, and their dependents integrated from all care providers and linked to health care utilization at the patient level.

Patients were included for analysis if (a) they had a diagnosis of at least one *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) code for a laryngeal/voice disorder (Table 1) per outpatient encounter regardless of provider type, (b) had 12 months continuous enrollment prior to the index date which was defined as the first laryngeal/voice disorder diagnosis, (c) were ≥ 18 years of age at index date, (d) no diagnosis of CAP (Table 1) in the 12 months pre-index date period, and (e) had prescription claims completely captured by MarketScan® databases from 1 year pre-index to end of follow-up. Patients were followed for the occurrence of CAP until the end of continuous enrollment or the end of 3-year follow-up. Because patients with a brainstem stroke may have a disordered voice from nucleus ambiguus involvement, 438.10 and 438.19 (late effects of cerebrovascular disease, speech and language deficit unspecified) were included.

Age, gender, index date laryngeal diagnosis, geographic region (divided in to four census regions: northeast, north central, south, and west), urban versus rural status (based on residence in a metropolitan statistical area (MSA)), and employment status (retired, employed, dependent, disabled) were collected. Comorbid disease was determined during the 12-month pre-index date period across outpatient and inpatient settings by creating a set of binary indicator variables using the categories and enhanced ICD-9-CM coding from the Elixhauser index.¹⁷ Number of visits was determined by counting the unique outpatient and inpatient encounters during the 12-month pre-index period, which can be serve as a proxy for general health.¹⁷ The presence of CAP was occurrence of ICD-9-CM codes for CAP (Table 1) during the 3-year post-index date period. The primary outcome is the time from index date to CAP, and patients were censored at disenrollment or at the end of 3-year follow-up.

The primary exposure of this study is the prescription of PPI. The generic identification numbers according to the MarketScan® database dictionary were used to identify PPIs. The number of PPI prescriptions and the timing of PPI prescriptions relative to the index date were determined. Prescription of PPI after index date was included in the analysis as a time-varying covariate, and the time of the first prescription after index date was used. We made the assumption that once PPI was initiated, exposure was not discontinued until the end of 3-year follow-up or censoring. Separate analyses were conducted for patients with and without PPI prescriptions within 1-year pre-index date period.

Summary statistics were calculated. To examine the relationship between PPI and the risk of CAP, a time-dependent Cox regression model with PPI treatment as a time-varying covariate was performed. This model adjusted for age, gender, region, MSA, employment status, index laryngeal/voice diagnoses, GER, number of pre-index encounters, and 29 comorbid conditions. In addition, to evaluate the effect of PPI treatment on CAP and account for treatment selection bias for time-dependent treatments, a propensity score based approach with marginal structural model (MSM) was applied. MSM uses the inverse probability of treatment weighting (IPTW) and inverse probability of censoring weighting (IPCW)

approach to create a synthesis sample in which treatment selection is independent of patients' baseline characteristics and no censoring occurs. For each 60 day time interval, we modeled the probability of receiving a PPI given the patients' covariates using a logistic regression, and only patients not previously on PPI were included in the model. The predicted probability of receiving PPI at each time point was then used to construct the IPTW weights. Similarly, we modeled the probability of not censoring based on patients' covariates at each time interval using patients who were still in the study (uncensored) and used the predicted probability to construct IPCW weights. Additional models were fit to estimate the probability of PPI or not censoring without any covariates for each time point, and the predicted probabilities were used to stabilize the IPTW/IPCW weights. The final weights were then computed by cumulatively multiplying the stabilized IPTW and IPCW weights at each time interval. The hazard ratios for PPI use and covariates were estimated by fitting a weighted pooled logistic regression model that included baseline covariates, time-dependent PPI use, and a smooth function of time (restricted cubic splines with 5 knots placed at Harrell's locations). To examine the robustness of correct CAP diagnosis, sensitivity analyses were conducted by treating patients with only one CAP diagnosis as not experiencing CAP. MarketScan® database management and statistical analysis were performed with SAS 9.4 (SAS Institute Inc., Cary, NC, USA). A two-sided significance level of 0.05 was used for all statistical tests.

Results:

A yearly mean of 59,400,337 unique patients were enrolled in the MarketScan® databases during January 1, 2010 to December 31, 2014 with 745,955 (1.3%) unique patients having an initial laryngeal/voice disorder. Cohort selection process is shown in Figure 1 resulting in 392,355 unique laryngeal/voice disordered patients.

Patient demographics are displayed in Table 2. 188,128 (47.9%) of laryngeal/voice disordered patients had a PPI prescription. Of the 188,128 patients who ever had PPI, 55% had a PPI prior to index date with median 3 prescriptions (Interquartile range (IQR) 1 – 5), 40.8% had a PPI on index date or within 2 weeks after the index date, and 77.8% had a PPI from 2 weeks after index date to end of follow-up with median 4 prescriptions (IQR 2–7). PPI was usually prescribed for 30 days (median day supply is 30 days (IQR 30 to 90 days)). Laryngeal/voice disordered patients who had a PPI prior to index date were older (median age 57 vs. 51), more retired (25.6% vs. 18%), lower proportion of acute laryngitis on index date (6.4% vs. 10.4%), higher proportion of benign laryngeal/vocal fold pathology (23.2% vs. 20.0%) and chronic laryngitis (15.2% vs. 13.3%) on index date, higher proportion of GER (58.6% vs. 21.2%), and more visits before index date (median 19 vs. 11). Patients with pre-index date PPI use were sicker compared to patients without pre-index date PPI use with a higher proportion of congestive heart failure (4.5% vs. 2.7%), cardiac arrhythmia (12.7% vs. 8.2%), valvular disease (7.6% vs. 4.8%), peripheral vascular disease (6.3% vs. 4.0%), hypertension uncomplicated (44.7% vs. 30%), chronic pulmonary disease (26.5% vs. 16.9%), diabetes complicated (16.3% vs. 10.8%), hypothyroidism (19.2% vs. 14.8%), rheumatoid arthritis (7.0% vs. 3.8%), obesity (8.5% vs. 5.8%), fluid/electrolyte disorder (7.4% vs. 4.3%), depression (16.3% vs. 11.6%), among other comorbidities.

Overall, 16,945 (4.3%) cases of CAP, based on at least one CAP diagnosis, were identified over the 3 year post-index date period. The 3 year absolute risk of CAP, based on at least one CAP diagnosis was, 5.3% (5,523/103,423) in the pre-index date PPI group and 4.0% (11,422/288,932) in those without pre-index PPI use. Given the differences in patient characteristics and comorbidities, our models examining the relationship between PPI use and CAP were performed on each group separately. The association between PPI use on CAP, based on at least one CAP diagnosis, using both a time-dependent Cox model and MSM model adjusting for confounders are displayed in Table 3. At any given time, the likelihood of CAP for a person who already received a PPI is 30–50% higher than for a person who has not yet had a PPI but may receive one later, among patients without and with pre-index date PPI use, respectively. The hazard ratios (HRs) from the MSM model were slightly different than the time-dependent adjusted Cox model but both showed negative association of PPI use on CAP, and this observation persisted when requiring 2 separate CAP diagnoses to denote a CAP event (Table 3).

Discussion:

PPIs have a prominent place in the treatment of patients with laryngeal/voice disorders. This is concordant with our finding that approximately half of our patient cohort had a PPI prescription as part of their treatment. This high rate of PPI use is consistent with prior survey studies and real-world evaluations of practice patterns among GMPs and otolaryngologists.^{2, 4, 6, 19, 20} The pervasiveness of PPI treatment however may expose laryngeal/voice disordered patients to adverse effects. In a recent survey of internist members of the American College of Physicians, 98% reported having some concern about adverse effects of PPIs with 63% altering the dose, 52% switching to H2 blockers, and 44% discontinuing the PPI.²¹ Moreover, patients are becoming more knowledgeable about their health care and may also have concerns about PPI treatment.²²

An association between PPI use and increased risk for CAP was observed in our laryngeal/voice disordered cohort. Because we could not precisely determine the reason for PPI prescription due to limitations of the database, we examined the association between CAP and PPI use in two subgroups based on the relationship between PPI claims and the index date. As previously mentioned, differing demographic and comorbidity characteristics in patients with pre-index versus without pre-index date PPI claims necessitated examining the relationship PPIs and CAP in each subgroup separately. From these analyses, we found an absolute risk of CAP, based on at least one CAP diagnosis, of 5.3% and 4.0% in laryngeal/voice disordered patients with and without pre-index PPI use, respectively. We observed a similar association between CAP diagnosis and PPI use in the subgroup of patients with PPI use prior to the index laryngeal/voice diagnosis and in patients without pre-index PPI use (Table 3). Furthermore, two different analytic approaches identified a similar increased association between CAP diagnosis and PPI use.

Various reasons may explain the association between CAP and PPI use. A pooled odds ratio of 1.04 to 1.92 for CAP with PPI use was found in a systematic review of systematic reviews.⁹ However, PPI claims are a proxy measure for actually taking the PPI. Thus, PPI use was treated as a binary time-varying variable with its value changed at the time of first

post-index PPI prescription. Medication adherence including if and when patients discontinued PPIs could not be known which prevented precise estimates of PPI exposure. Our assumption of continuous PPI exposure until follow up or censoring could have overstated the PPI exposure. Furthermore, observational, population-based studies have found higher rates of CAP with PPI use among patients with recent use compared to long-term, current PPI use, which calls in to question a true causal association.^{10, 11, 23} We could not examine issues such as a dose-response relationship between the length of PPI use and higher dosing regimens on CAP occurrence. It also is possible that the association between CAP and PPI is correlative as patients may have been started on PPIs for symptoms such as cough or dysphonia that were mis-attributed to reflux but were actually early signs of CAP.²⁴ Although this potential scenario cannot be evaluated in the current data source, it could indicate possible inappropriate PPI use instead of a causal association between PPIs use and CAP occurrence. Although we attempted to control for comorbid disease and care-seeking behavior, PPIs may also be a marker for sicker individuals who may be at increased risk for CAP irrespective of PPI use. In addition, randomized studies examining pneumonia rates in patients receiving PPIs versus placebo for stress ulcer prophylaxis have not found increased pneumonia rates in PPI use.^{25, 26} Further investigation is needed to evaluate the nature of the association between PPI use and CAP in laryngeal/voice disordered patients.

The association between CAP diagnosis and PPI use in laryngeal/voice disordered may be useful in guiding treatment decisions. For instance, the potential for misdiagnosis and inappropriate PPI treatment exists among GMPs who do not routinely visualize the larynx.^{4, 6} Among laryngeal/voice disordered patients who saw GMPs with associated PPI treatment and subsequently had otolaryngology evaluation, otolaryngologists more frequently diagnosed laryngeal structural abnormalities, neuromuscular impairment, and multiple laryngeal diagnoses.⁷ Likewise, prior investigations focused on otolaryngology care have found a high rate of diagnosis change in laryngeal/voice disordered patients initially treated with PPIs, suggesting that initial PPI treatment may not have been needed.^{27–29} The association between PPI use and CAP occurrence combined with the possible misuse of PPIs should caution GMP and otolaryngology providers when considering PPI treatment. Although beyond the scope of this study, a careful assessment of the possible role of reflux in a patient's presentation, such as considering objective testing, may be necessary to determine the need for PPI.

Given that our study cannot prove *causation* between PPI use and CAP risk and acknowledging that the benefits of PPIs may outweigh their risk in specific patients with strong indications for PPI treatment, the following recommendations may reduce potential CAP in laryngeal/voice disordered patients. (1) Patients already on or who have PPIs initiated should be followed and doses reduced to the minimum effective dose based on symptom improvement.^{25, 30} If patients cannot reduce their PPI dose, objective reflux testing can examine the correlation between reflux events and patient symptoms and may lead to consideration of alternative diagnoses and treatments.²⁴ (2) Discussions about specific PPI weaning protocols with patients should be undertaken to help reduce rebound reflux symptoms when tapering the dose and the resulting persistent dependence on PPIs.³¹ Having shared decisions between patients and providers can lead to more informed decisions regarding PPI treatment.

Certain methodologic issues must be acknowledged. As mortality could only be tracked in the inpatient setting in this database, death was not incorporated as a competing risk. However, those who died were censored when continuous enrollment ended. While we captured comorbidity data during the one-year pre-index date time period, potential comorbid diseases may not have been counted if comorbidity-related patient encounters did not occur during this time. Although laryngeal/voice diagnoses and other confounders may change over time, we considered PPI use as the only time-dependent event and assumed that after the first time PPI was prescribed that the exposure and at risk period for CAP continued until the end of follow up. We were not able to determine how the diagnosis of CAP was made, and thus, present results where CAP diagnosis was based on at least one CAP ICD-9 code and based on at least two CAP ICD-9 codes. Although over the counter PPI use could not be assessed, over the counter PPI dosing is often lower and shorter duration than PPI prescriptions and unlikely to be associated with CAP.^{32, 33} As patients had commercial health insurance or supplemental Medicare, results may not be generalizable to patients without health insurance, the broader Medicare population, or Medicaid patients. While there could still be unmeasured confounders that influenced our results, two different analytic techniques were employed, and similar results were noted. These limitations notwithstanding, our study provides new insights regarding the potential association of CAP associated with PPI use in a broad cohort of laryngeal/voice disordered patients during real-world care.

Conclusions:

PPI use was pervasive in the real-world treatment of a cohort of laryngeal/voice disorders patients with half having PPI treatment. Both the cohort of patients who had PPI initiated before the index laryngeal/voice diagnosis and the patients who had PPI treatment on or after the index date experienced a roughly 3 year absolute risk for CAP of 3–5% and a 30–50% increased likelihood of CAP compared to patients who had not had PPI prescriptions, with analyses adjusted for important sociodemographic and clinical characteristics. Furthermore, the association between CAP diagnosis and PPI use was consistent across the time-dependent Cox and MSM analyses. Further investigation is needed to explore the impact of dosing regimen, rates of other reported adverse events potentially related to PPIs, and which laryngeal/voice disordered patients may be most susceptible for PPI-related adverse events.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Flow chart for cohort identification.

Table 1.

ICD-9-CM code for laryngeal/voice-disorder groupings and community acquired pneumonia.

Category	ICD-9 Codes
Vocal fold paralysis	478.30, 478.32
Bilateral vocal fold paralysis	478.34
Vocal fold paresis	478.31, 478.33
Non-specific dysphonia	784.49, 784.42, 784.40, 784.41
Acute laryngitis	464, 464.01, 464.20, 464.21
Benign laryngeal/vocal fold pathology	478.4, 478.5, 478.6, 478.71, 478.79, 212.1, 748.2
Other larynx/vagus	478.70, 352.3
Chronic laryngitis	476.0, 476.1
Laryngeal cancer	161.0, 161.1, 161.2, 161.3, 161.8, 161.9, 231.0, 235.6
Laryngeal spasm	478.75
Late effect cerebrovascular disease, speech and language deficit, unspecified	438.10, 438.19
Community acquired pneumonia	481, 482, 482.0, 482.1, 482.2, 482.3, 482.30, 482.31, 482.32, 482.39, 482.4, 482.40, 482.41, 482.42, 482.49, 482.8, 482.81, 482.82, 482.83, 482.84, 482.89, 482.9, 483, 483.0, 483.1, 483.8, 484.3, 485, 486, 480, 480.0, 480.1, 480.2, 480.8, 480.9, 487.0, 488.01, 488.11

Table 2.

Patient demographics.

	No Pre-Index PPI use (N=288932)	Pre-Index PPI use (N=103423)	Total (N=392355)
Age			
Mean(SD)	51.4 (15.8)	56.9 (14.2)	52.9 (15.6)
Median (IQR)	52 (41.0,62.0)	57 (48.0,65.0)	54 (43.0,62.0)
Gender of Patient			
Male	107932 (37.4%)	37569 (36.3%)	145501 (37.1%)
Female	181000 (62.6%)	65854 (63.7%)	246854 (62.9%)
Region			
Northwest	69228 (24.0%)	25830 (25.0%)	95058 (24.2%)
NorthCentral	64396 (22.3%)	21891 (21.2%)	86287 (22.0%)
South	102759 (35.6%)	38013 (36.8%)	140772 (35.9%)
West	48419 (16.8%)	16234 (15.7%)	64653 (16.5%)
Unknown	4130 (1.4%)	1455 (1.4%)	5585 (1.4%)
Urban vs Rural			
Rural	35901 (12.4%)	14409 (13.9%)	50310 (12.8%)
Urban	253031 (87.6%)	89014 (86.1%)	342045 (87.2%)
Employment Status			
Employed	119641 (41.4%)	38730 (37.4%)	158371 (40.4%)
Retired	52108 (18.0%)	26456 (25.6%)	78564 (20.0%)
Disability	629 (0.2%)	397 (0.4%)	1026 (0.3%)
Dependent/Other	116554 (40.3%)	37840 (36.6%)	154394 (39.4%)
Number of encounters from 1 year pre-index date to index date			
Mean (SD)	16.7 (18.1)	25.9 (23.4)	19.1 (20.0)
Median (IQR)	11 (5.0,22.0)	19 (10.0,34.0)	13 (6.0,25.0)
Index Laryngeal/Voice Diagnosis			
vocal fold paralysis	6467 (2.2%)	2315 (2.2%)	8782 (2.2%)
Bilateral vocal fold paralysis	184 (0.1%)	66 (0.1%)	250 (0.1%)
Vocal fold paresis	3392 (1.2%)	1237 (1.2%)	4629 (1.2%)
Non-specific dysphonia	159758 (55.3%)	56413 (54.5%)	216171 (55.1%)
Acute laryngitis	30019 (10.4%)	6622 (6.4%)	36641 (9.3%)
Benign laryngeal/vocal fold pathology	57722 (20.0%)	24022 (23.2%)	81744 (20.8%)
Other larynx/vagus	2765 (1.0%)	1066 (1.0%)	3831 (1.0%)
Chronic laryngitis	38322 (13.3%)	15689 (15.2%)	54011 (13.8%)
Laryngeal cancer	6604 (2.3%)	1946 (1.9%)	8550 (2.2%)
Laryngeal spasm	6400 (2.2%)	2297 (2.2%)	8697 (2.2%)
Late effect cerebrovascular disease, other speech deficits	6180 (2.1%)	1780 (1.7%)	7960 (2.0%)
Gastro-esophageal reflux/esophagitis (GER)	61285 (21.2%)	60559 (58.6%)	121844 (31.1%)

Table 3.

Association between PPI use on Community Acquired Pneumonia (CAP) outcomes from a marginal structural model and a time-dependent Cox model adjusting for confounders*.

		Hazard ratio	95% Confidence Interval
Pre-index date PPI group	Primary Analyses** (3-year CAP absolute risk 5.3%)		
	Time-dependent Cox	1.40	(1.31, 1.50)
	Marginal structural model	1.49	(1.36, 1.64)
	Sensitivity Analyses** (3-year CAP absolute risk 4.3%)		
	Time-dependent Cox	1.47	(1.36, 1.58)
	Marginal structural model	1.51	(1.36, 1.67)
Index/Post-index date PPI group	Primary Analyses** (3-year CAP absolute risk 4.0%)		
	Time-dependent Cox	1.30	(1.25, 1.36)
	Marginal structural model	1.31	(1.24, 1.38)
	Sensitivity Analyses** (3-year CAP absolute risk 3.2%)		
	Time-dependent Cox	1.32	(1.26, 1.39)
	Marginal structural model	1.34	(1.26, 1.42)

* Confounders adjusted for include age, gender, region, urban vs. rural, employment status, index laryngeal/voice diagnoses, GER, number of pre-index visits, and 29 comorbid conditions.

** Primary analyses included one CAP diagnosis as positive for experiencing CAP. Sensitivity analyses were conducted by treating patients with only one CAP diagnosis record as not experiencing CAP (i.e., two CAP diagnoses were required as positive for experiencing CAP).