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Increased Risk of Pneumonia among Patients with Inflammatory Bowel Disease

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Abstract

Background & Aims—Patients with inflammatory bowel disease (IBD) may be at increased risk for infectious complications. We aimed to determine the risk of pneumonia in IBD and how biologic and immunosuppressive medications affect this risk.

Methods—We performed a retrospective cohort and a nested case-control study using administrative data from IMS Health Inc, LifeLink™ Health Plan Claims Database. In the cohort, IBD patients were matched to 4 individuals without IBD. Pneumonia risk was evaluated by incidence rate ratio (IRR) and by adjusted Cox proportional hazards models. In the nested case-control analysis, 4856 IBD patients with pneumonia were matched to up to 4 IBD patients without pneumonia by incidence density sampling. Conditional logistic regression was used to determine associations between medications and pneumonia.

Results—The cohort included 50,932 patients with Crohn's disease (CD), 56,403 patients with ulcerative colitis (UC), and 1,269 with unspecified IBD; matched to 434,416 individuals without IBD. The IBD cohort had an increased pneumonia risk when compared to non-IBD (IRR 1.82, 95% CI 1.75-1.88). In adjusted Cox analysis, pneumonia risk remained increased for the IBD vs. non-IBD cohort (HR 1.54, 95% CI 1.49-1.60), with increased risk in both CD (HR 1.71, 95% CI 1.62-1.80) and UC (HR 1.41, 95% CI 1.34-1.48). In the nested case-control analysis, use of biologic medications (OR 1.28, 95% CI 1.08-1.52), corticosteroids (OR 3.62, 95% CI 3.30-3.98) and proton pump inhibitor (PPI) (OR 1.14, 95% CI 1.03-1.25) in the preceding 120 days were significantly associated with pneumonia.

Conclusions—Patients with IBD are at increased risk for pneumonia. Use of corticosteroids particularly increases pneumonia risk.

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Introduction

Patients with inflammatory bowel disease (IBD), particularly those treated with immunosuppression, are at increased risk for infectious complications. In fact, infectious complications are among the most common causes of death in patients with IBD.¹ In the United States (US), community acquired pneumonia (CAP) is the leading infectious cause of death.² The most common etiologic agent of CAP in the US is pneumococcal pneumonia. In 2004, there were an estimated 866,000 cases of pneumococcal pneumonia in the US with estimated costs of 2.5 billion dollars.³

Little is known about the risk of pneumonia in IBD patients. In a recent study of death certificates, respiratory illness was identified as a common causes of mortality in IBD patients¹ and bacterial pneumonia has been one of the most frequently reported complications in IBD clinical studies.⁴ In the rheumatoid arthritis (RA) population, pneumonia has been shown to be a major cause of morbidity and mortality.^{5, 6} In these patients, prednisone use has been associated with an increased risk of pneumonia hospitalization.⁵ The anti-tumor necrosis factor-alpha (anti-TNF) agents have been associated with an increased overall risk of infection in some,^{7, 8} but not all⁹ studies. Anti-TNF agents have not been found to increase the risk of hospitalization for pneumonia in RA.⁵

To further evaluate these associations in the IBD population, we aimed to determine the risk of pneumonia in patients with IBD as compared to a non-IBD cohort. We also aimed to determine whether specific immunosuppressive medications increase the risk of pneumonia in patients with IBD.

Methods

We analyzed the procedural and outpatient pharmaceutical insurance claims contained in the LifeLink™ Health Plan Claims Database (IMS Health Inc, Norwalk, CT) for the period January 1, 1997 through December 31, 2009. This longitudinal, patient-level database has been used in previous epidemiologic studies of IBD.^{10, 11} The source database contains enrollment information on over 60 million persons from over 98 health plans across the U.S. The included health care plans capture a geographically diverse sample from across the United States. Only health plans that submit data for all members are included in the database, ensuring complete data capture and representative samples. Prior studies have reported the IMS Health database to be representative of the national commercially insured population on a variety of demographic measures, including geographic region, age, gender, and health plan type.¹²

Study Design

We performed a retrospective cohort study to determine the overall risk of pneumonia in IBD patients compared with a non-IBD cohort and a nested case-control study to determine the independent effects of medication use (immunosuppressive, anti-TNF therapy and corticosteroids) on pneumonia risk among patients with IBD. A similar design has

previously been used by our group¹⁰ and also by Gupta et al¹³ to evaluate the incidence of disorders in patients with IBD and the effects of various medications.

Cohort Study

Patient selection—All patients aged <64 years with at least 12 months of continuous health plan enrollment were eligible for inclusion in this analysis. We chose 64 as the upper age limit to avoid the possibility of missing data resulting from Medicare dual eligibility (which begins at age 65). Individuals were also required to have ongoing pharmacy coverage with their health plan in order to fully capture medication exposures. We identified cases of Crohn's disease (CD) and ulcerative colitis (UC) using a previously reported administrative definition expanded to include updated medications recently approved for IBD indications.¹⁴ The precise definition included patients with at least 3 health care contacts, on different days, associated with an International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9) diagnosis code for CD (555.xx) or UC (556.xx), or patients with at least 1 claim for CD or UC and at least 1 pharmacy claim for any of the following medications: mesalamine, olsalazine, balsalazide, sulfasalazine, 6-mercaptopurine, azathioprine, methotrexate, infliximab, adalimumab, certolizumab pegol, natalizumab and enteral budesonide. For patients who had claims for both CD and UC, disease assignment was made according to the majority of the last 9 claims or the majority of total claims if there were fewer than 9. We matched each IBD patient to 4 non-IBD subjects by age, gender, calendar time and U.S. census region. Region of the country was defined by standard regional definitions from the United States Census Bureau. We ensured that each non-IBD subject was enrolled during the same calendar time as the IBD subject in order to account for the seasonality of pneumonia outcomes. All individuals with any ICD-9 code for human immunodeficiency virus (HIV) (042-044.9) were excluded related to differences in susceptibility to infections.

Cohort lead time and follow-up—Each cohort member was required to have a minimum of 6 months of health plan enrollment prior to cohort entry. This “screening period” was used to assess potential confounders of interest. Additionally, anyone with a pneumonia claim in the last month of this “screening period” was excluded, as this was considered to represent a prevalent pneumonia. Each member of cohort was followed until the first diagnosis of pneumonia, or, if none, until censoring at the earlier of one of two events: discontinuation of primary or pharmacy insurance coverage, or age > 64.

Assessment of outcome (pneumonia)—Pneumonia was defined as 1) any 1 ICD-9 code for bacterial pneumonia (481, 482.xx-483.xx, 485, 486) combined with a prescription for a systemic antibiotic or 2) any hospital confinement code accompanied by one of the above ICD-9 codes for bacterial pneumonia. For the first definition, the antibiotic prescription had to be filled in the time period of 1 week prior to 1 week after the pneumonia ICD-9 code. Antibiotic prescriptions for any of the following classes (any day supply) were included in the definition: macrolide class (erythromycin, clarithromycin, azithromycin), penicillin class (amoxicillin, ampicillin, oxacillin, penicillin, dicloxacillin, nafcillin, oxacillin, amoxicillin/clavulanate), 3rd or 4th generation fluoroquinolone class (levofloxacin, moxifloxacin, gatifloxacin, gemifloxacin), 3rd or 4th generation cephalosporin class

(cefдинир, цефксиме, цефотаксиме, цефподоксиме, цефтибутен, цефтизоксиме, цефтриаксон, цефоперазон, цефтазидиме, цефепиме) or tetracycline class (tetracycline, minocycline, doxycycline). Of note, ciprofloxacin (a second generation fluoroquinolone) was not included as part of the pneumonia outcome, as this antibiotic is not a “respiratory fluoroquinolone”¹⁵ and is often used for an indication of IBD independent of infection. A similar definition for outpatient pneumonia consisting of medication dispensing and ICD-9 codes has been used in prior studies of community acquired pneumonia using administrative data.¹⁶ A more sensitive secondary definition of pneumonia consisting only of any one of the above ICD-9 codes for bacterial pneumonia was then investigated.

Assessment of exposures—All exposure assessment occurred during the 6 month “screening period” prior to cohort entry. Health care utilization was estimated in a continuous fashion by the total of days with at least one health care contact over the time period. Utilization has been measured in this fashion in prior pharmacoepidemiology studies.¹⁷ Comorbidities were assessed using the Quan update¹⁸ of the validated Deyo comorbidity index for administrative data.¹⁹ Medication use, including immunosuppressive and biologic medications, was assessed in the exposure period in an any/none fashion. Additionally, as proton pump inhibitor (PPI) use can be associated with IBD and also with pneumonia, any PPI use was also extracted during the exposure period.

Evaluation of an Alternate Cohort—In order to cross-validate the outcome of pneumonia within our dataset, we also investigated the risk of pneumonia in a separate cohort of individuals with diabetes mellitus as compared to a non-diabetic cohort, using the same methodology as that used in the IBD cohort. Diabetes was chosen as a reference population due to the known increased risk of pneumonia²⁰ and death from pneumonia in this population.²¹ Diabetes was defined using any 2 separate ICD-9 codes for diabetes (250-250.7).

Statistical analysis: We used descriptive statistics to summarize characteristics of patients with and without IBD. Continuous variables are reported as mean \pm standard deviation or median and interquartile range (IQR), and categorical variables are reported as percentages. We then calculated incidence rates of pneumonia (per 100,000 person-years) and used incidence rate ratios (IRRs) and 95% confidence intervals (CIs) to compare the incidence of pneumonia in IBD and non-IBD patients. We also performed subsequent analyses, stratifying by region of the country (defined by United States census groups), age (in decades), and disease type (UC vs CD). To control for confounding, we assessed for possible violation of the proportional hazards assumption via log-log plots. As the assumption was not violated, we used Cox proportional hazards models to calculate hazard ratios (HRs) and 95% CIs for the risk of pneumonia in the IBD cohort as compared to the non-IBD cohort, controlling for health care utilization and comorbidities. Analyses were repeated stratified by CD versus UC and within the alternate diabetes cohort.

Nested Case-Control Study

We next conducted a case-control study evaluating the association between corticosteroids, immunosuppressive or biologic anti-TNF medication use and pneumonia. This study was nested within the previously defined cohort of patients with IBD.

Selection of cases and controls—Cases were those IBD patients who were diagnosed with pneumonia, and controls were those IBD patients without pneumonia. Each case patient was matched on gender, age, geographic region, disease type (CD or UC), and duration of follow-up to 4 IBD patients who did not have pneumonia using incidence density sampling. In this sampling technique, a case patient can also be a control patient, provided that the case patient has not yet been diagnosed with pneumonia (has not yet become a case) at the time he or she is selected as a control. Once a case is diagnosed with pneumonia, he or she is no longer eligible to become a control, or a case again. A total of 756 patients were included as both cases and controls. Each control was assigned an index date identical to the matched case's date of pneumonia, in order to account for seasonality.

Assessment of outcome (pneumonia)—The outcome was outpatient or inpatient pneumonia, as defined within the cohort study by ICD-9 codes, antibiotic prescriptions and hospital confinement codes.

Assessment of exposures

Medication Use: The primary medications evaluated included azathioprine and 6-mercaptopurine (thiopurine class), methotrexate, tacrolimus and cyclosporine (calcineurin class), mycophenolate mofetil, infliximab, adalimumab, and certolizumab pegol (biologic anti-TNF class) and systemic corticosteroids. PPI use was also assessed, as this could be associated with both exposure and outcome. Medication exposures were analyzed with respect to the amount of time preceding the diagnosis of pneumonia in cases or the corresponding index date in controls. All exposures were defined as at least 1 outpatient pharmacy claim occurring during the 120 days prior to pneumonia diagnosis.

Potential confounders: Data on utilization and comorbidities were also included as exposure variables in the case-control study. These variables were assessed during the 6 month exposure period prior to pneumonia diagnosis. Utilization was defined in a continuous fashion as total number of days with at least one health care contact. Comorbidities were assessed through the Quan update¹⁸ of the validated Deyo comorbidity index¹⁹ for administrative claims data.

Statistical analysis: Characteristics of cases and controls were described using descriptive statistics. We then used conditional logistic regression to calculate odds ratios (ORs) and 95% CIs for each medication exposure related to the outcome of pneumonia. We constructed a full model by using all potential confounders and eliminated these confounders via a backwards elimination strategy by using a change in estimate approach (threshold of <10% change). Analyses were performed for patients with IBD and also stratified by UC and CD diagnosis.

Results

The cohort study population included 108,604 patients with IBD. Of these, 50,932 had CD, 56,403 had UC and 1,269 had IBD with unknown type. There were a total of 434,416 individuals in the non-IBD comparison cohort. The median length of follow up within this cohort was 24 months (IQR 12-42) with a range from 1-138 months after the 6 month “screening” period. Length of follow-up was similar for CD (34 months, IQR 19-51) and UC populations (36 months, IQR 21-54), while significantly less in the non-IBD comparison cohort (21 months, IQR 10-38). Characteristics of the patients with IBD as compared to the non-IBD cohort are shown in table 1. There was increased health care utilization, immunosuppressive medication use and PPI use among the IBD cohort as compared to the matched non-IBD cohort, as expected. These same factors were increased in those with CD as compared to those with UC. Among the IBD cohort, there were also slightly higher rates of liver disease and COPD as compared to the non-IBD cohort.

For patients with IBD, the overall annual incidence of pneumonia was 138/10,000, compared to 76/10,000 in the non-IBD cohort (IRR 1.82 95% CI 1.75-1.88) (figure 1). The risk was somewhat greater for CD as compared to non-IBD (IRR 2.05 95% CI 1.94-2.15) than for UC as compared to non-IBD (IRR 1.62 95% CI 1.54-1.71). The incidence of pneumonia was then evaluated in strata of age, with the highest incidence in the 60+ age strata (226/10,000). On adjusted Cox analysis, controlling for comorbidities, health care utilization, and PPI use, the relative risk remained elevated in the overall IBD population (HR 1.54, 95% CI 1.49-1.60). Compared to non-IBD controls, the risk was greater for CD (HR 1.71, 95% CI 1.62-1.80) than for UC (HR 1.41, 95% CI 1.34-1.48). Analyses were also performed using the alternate definition of pneumonia (any 1 ICD-9 code). The effect size estimate remained similar with this alternate definition, with an IRR of 1.83, 95% CI 1.78-1.89 for pneumonia risk in the IBD cohort as compared to the non-IBD cohort.

In the alternate diabetes cohort, the risk of pneumonia in diabetics as compared to non-diabetics was elevated to a similar extent (IRR 2.26, 95% CI 2.17-2.35). The overall incidence of pneumonia among diabetics was 178/10,000 as compared to 79/10,000 in the non-diabetic cohort. In adjusted analyses, adjusting for health care utilization and comorbidities, the risk estimate remained similar (HR 1.84, 95% CI 1.76-1.93).

In the nested case control study, 4856 IBD patients with pneumonia were matched to 18928 IBD patients without pneumonia. The characteristics of the populations are shown in table 2. Patients with pneumonia had significantly more comorbidities, particularly COPD. Those with pneumonia also had significantly higher health care utilization and immunosuppressive medication use. PPI use was also associated with pneumonia. In the adjusted analyses, corticosteroid use (OR 3.62, 95% CI 3.30-3.98), biologic use (OR 1.28, 95% CI 1.08-1.52) and PPI use (OR 1.14, 95% CI 1.03-1.25) were independently associated with pneumonia in the overall IBD population. Interestingly, calcineurin inhibitor use was associated with lower risk. Similar risk estimates were seen when stratified by CD or UC. Crude and adjusted analyses are shown in table 3 for specific medication use in the overall population, and by IBD subtype.

Discussion

In this large cohort of commercially insured Americans, we have demonstrated an increased risk of pneumonia in patients with IBD as compared to the general population, with an adjusted effect estimate of HR 1.54, 95% CI 1.49-1.60. Additionally, we found a particularly increased risk of pneumonia among patients on corticosteroids (OR OR 3.62, 95% CI 3.30-3.98), a mild to moderate increased risk in patients on anti-TNF agents (OR 1.28, 95% CI 1.08-1.52), and no increased risk associated with other classes of IBD medications.

Streptococcus pneumoniae is the most common cause of community acquired pneumonia (CAP), accounting for about 36% of cases of CAP in the general population. Vaccination against invasive pneumococcal disease is currently available in the US for both children and adults. Pneumococcal vaccine is recommended in IBD immunization guidelines.²² Therefore, studying pneumonia is important in IBD, as 1) pneumonia is associated with substantial costs, morbidity and mortality and 2) complications from pneumonia may be preventable through vaccination.

In this large cohort of commercially insured Americans, we have demonstrated an increased risk of pneumonia in patients with IBD as compared to the general population, with an adjusted effect estimate of HR 1.54, 95% CI 1.49-1.60. Additionally, we found a particularly increased risk of pneumonia among patients on corticosteroids, a mild to moderate increased risk in patients on anti-TNF agents (OR 1.28, 95% CI 1.08-1.52), and no increased risk associated with other classes of IBD medications. These findings are particularly noteworthy, considering that pneumonia is 1) associated with substantial costs, morbidity and mortality, and 2) often preventable, given that vaccination against *Streptococcus pneumoniae*, the most common cause of community acquired pneumonia (CAP) accounting for about 36% of cases of CAP, is currently available for both children and adults.

To our knowledge, this is the first epidemiological study of the incidence and medication-specific risk factors for pneumonia in patients with IBD. However, these findings are of similar direction and magnitude to prior studies in the RA population. Wolfe et al demonstrated an increased risk for pneumonia hospitalization (HR 1.7, 95% CI 1.5-2.0) for patients with RA on corticosteroids, including a dose related increase in risk.⁵ Coyne et al found the overall annual incidence of lower respiratory tract infection (LRTI) in patients with RA was 2.3% with a mortality rate of 22.5%. Corticosteroids were also associated with an increased risk of hospital admission with LRTI in this study.⁶ The anti-TNF agents have been associated with increased risk of hospitalization for infection in patients with RA,⁸ while other disease modifying agents (DMARDs) such as methotrexate were not. Other studies have not found an increased risk of serious hospitalized infection associated with the anti-TNF class, although there may be a relative increased risk with infliximab in the RA population.⁹

We also investigated the age-specific risks of pneumonia in patients with IBD, and found the highest relative risks in the younger (< 30 years) group, with the highest absolute risk in the elderly (61-64). This is not dissimilar to the general population and the previously described studies of RA,^{5, 6} where elderly individuals are at the highest risk for pneumonia. In the IBD

population, the greatest absolute differences in mortality rates for IBD as compared to the general population also occur in the elderly.²³ As in the general population, we also found that comorbidities, including COPD, were additional risk factors for pneumonia in the IBD population.

Our study has also confirmed two known associations, which help to substantiate the validity of our novel IBD-related findings. First, the relative risk of pneumonia in IBD, particularly for those with CD (HR 1.71, 95% CI 1.62-1.80), was on par with the relative risk in a separate diabetes population (HR 1.84, 95% CI 1.76-1.93). Other studies have found diabetes to be associated with an increased risk of pneumonia (HR 1.92, 95% CI 1.84-1.99)²⁰ and death from pneumonia (HR 1.67, 95% CI 1.45-1.92).²¹ Additionally, recent data show an increased risk of pneumonia associated with PPI use. The mechanism behind this increased risk is hypothesized to be overgrowth of bacteria due to acid suppression in the stomach, which may increase the risk of micro-aspiration of bacteria, and therefore pneumonia.²⁴ We found an increased risk of pneumonia associated with PPI use in our IBD population (unadjusted OR 2.21, 95% CI 2.04-2.39, adjusted OR 1.14, 95% CI 1.03-1.25). Such findings are consistent with a recently published meta-analysis of pneumonia risk with PPI use (OR 1.36, 95% CI 1.12-1.65).²⁴

There are notable strengths to this study of pneumonia in IBD. We were able to include a large sample size. We also had great geographic diversity, with patients from all regions of the US. By drawing from a large number of health plans of varying size, type, and location, we believe these results to be broadly generalizable to the commercially insured US population. We obtained complete data on all billed outpatient prescriptions in order to completely capture medication exposures; rather than relying on patient recall. We were also able to account for health care utilization, as we had access to all health care contacts within the database. By studying an alternate cohort of patients with diabetes, who are known to have an increased risk of pneumonia, we were able to substantiate our outcome in a separate reference population. We were also able to account for other pharmacologic exposures, such as PPIs, that have been associated with pneumonia and may be more common among individuals with IBD. Finally, we were able to account for comorbidities through a validated comorbidity index for administrative data.^{18, 19} This is particularly important, as comorbidities are known to be associated with pneumonia risk.

There are also several limitations to this study of administrative claims data. There is the possibility of misclassification of exposure and outcome related to the lack of clinical detail. We did use an IBD exposure definition previously used by our group^{10, 11} that requires multiple health contacts and/or IBD related prescriptions. A similar, but even less specific, administrative case definition has been validated by Herrinton et al. The Herrinton definition was found to have a sensitivity exceeding 90% and a PPV exceeding 80% for overall IBD.²⁵ We used an outcome definition of pneumonia that required both ICD-9 code and antibiotic dispensing. A similar definition of ICD-9 codes with antibiotic dispensing has been used in prior studies of pneumonia,¹⁶ although this definition has not been validated. We required both components (ICD-9 and medication dispensing), as prior validation studies of ICD-9 codes alone have been found to be imprecise.²⁶ Any measurement bias in this definition would be non-differential by IBD or non-IBD status and would therefore bias our estimate

towards the null value. We also performed a sensitivity analysis around the outcome definition by investigating a more sensitive definition consisting of any 1 ICD-9 code. The effect estimate for pneumonia risk with this definition did not change. Further support for the validity of the administrative definition used in this study is that the incidence of pneumonia in both the IBD and comparison cohorts was highest in the oldest age strata. Another limitation to this study is that the elderly (>age 65) and uninsured were not represented in our population. The lack of older persons in our study population does not affect the validity of the relative risks (IRRs, HRs, ORs) we presented in the context of the under 65 population. Finally, we were unable to account for certain exposures that may be related to the outcome, particularly smoking status. We were able to control for chronic obstructive pulmonary disease (COPD), which has been used as a proxy for smoking status in other studies using administrative data.

In conclusion, we believe that the increased risk of pneumonia in patients with IBD, particularly those treated with corticosteroids, should be viewed as a call to action. Pneumococcal vaccination is safe, effective, widely available, and known to prevent complications of pneumococcal pneumonia. Unfortunately, current vaccination efforts in the IBD population are lagging. In one tertiary care setting, only 9% of patients with IBD reported pneumococcal vaccination.²⁷ As response to vaccination can be impaired with immunosuppression,²⁸ the optimal time to vaccinate individuals with IBD is likely at diagnosis. Knowing risk factors for pneumonia in the IBD population, such as age and comorbidities, may increase awareness and promote prevention and/or early treatment. Additionally, awareness of the medication-specific risk factors: corticosteroids, anti-TNF agents and PPIs, may provide for timely intervention and ultimately improve outcomes.

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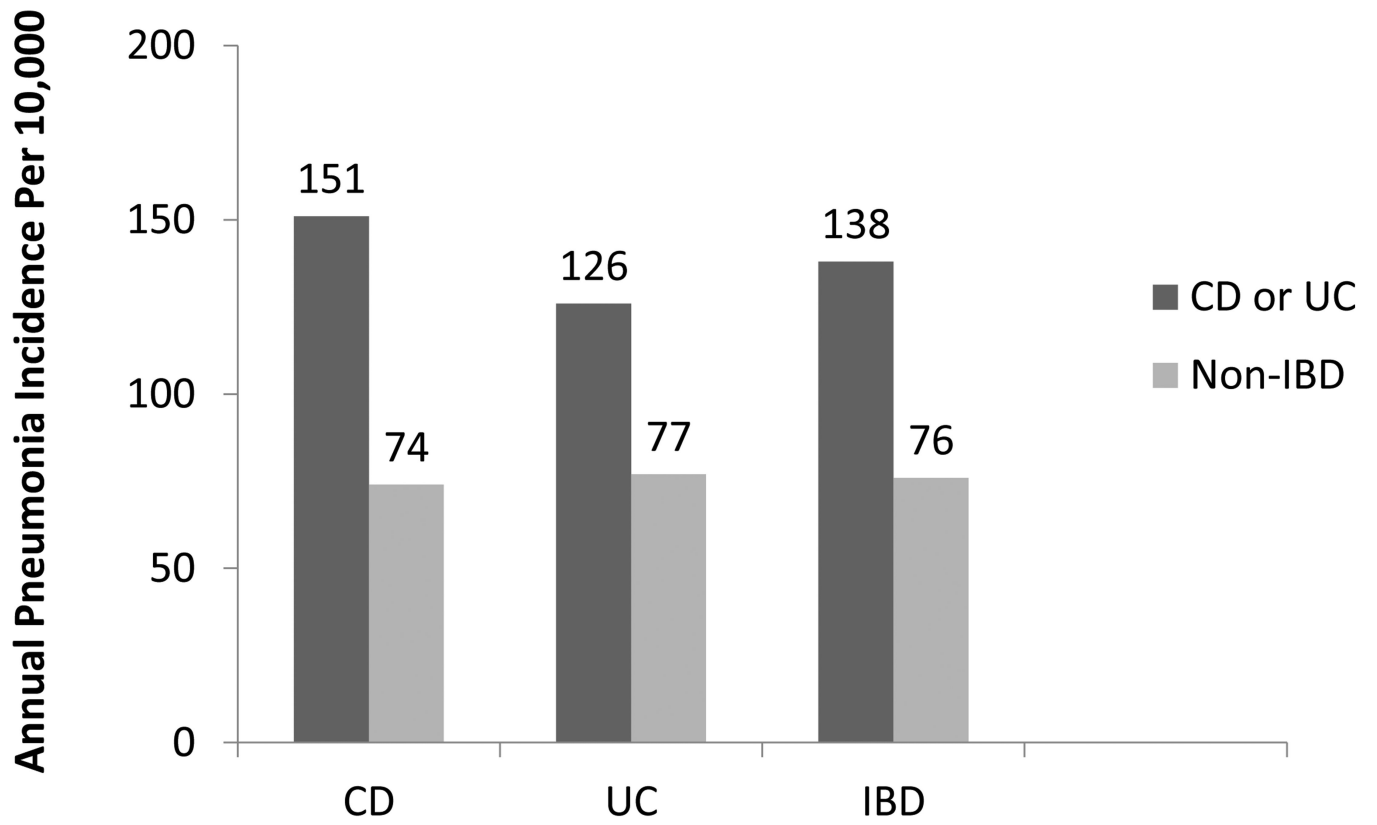


Figure 1.
Incidence of Recorded Pneumonia in IBD and non-IBD Populations

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Table 1
 Characteristics of the Population by Inflammatory Bowel Disease overall, and Crohn's disease or Ulcerative Colitis

Characteristic	Non-IBD Cohort (n=434,416)		IBD Cohort (n=108,604)		Crohn's disease (n=50932)		Ulcerative Colitis (n=56403)	
	n	median (IQR) or %	n	median (IQR) or %	n	median (IQR) or %	n	median (IQR) or %
Age		43 (31-52)		43 (31-52)		41 (29-51)		44 (33-53)
Gender (% female)	238812	55.0	59703	55.0	28723	56.4	30272	53.7
Region of the country								
East	91923	21.2	23069	21.2	10686	21.0	12061	21.4
Midwest	169043	38.9	46232	42.6	22155	43.5	23614	41.9
South	97829	22.5	20350	18.7	9621	18.9	10479	18.6
West	75621	17.4	18953	17.5	8470	16.7	10249	18.2
Medications *								
5ASA **	552	0.1	37609	34.6	15974	31.4	21195	37.6
Thiopurine %	257	0.1	11155	10.3	7558	18.8	3540	6.3
Biologic ^	200	0.1	3013	2.8	2607	5.1	396	0.7
Calcineurin inhibitor &	136	0.0	255	0.2	79	0.2	173	0.3
PPI [†] (any)	20406	4.7	13891	12.8	7427	14.6	6282	11.1
Health Care Utilization [‡]		1 (0-4)		4 (2-9)		5 (2-10)		4 (1-8)
Comorbidities								
Cardiac	2935	0.7	1076	1.0	475	0.9	584	1.0
Diabetes mellitus	16888	3.9	4824	4.4	2055	4.0	2705	4.8
Liver disease	2603	0.6	2112	1.9	982	1.9	1104	2.0
Renal	1181	0.3	845	0.8	399	0.8	440	0.8
COPD	17191	4.0	6654	6.1	3233	6.4	3338	5.9
Total [#] comorbidities		0 (0-0)		0 (0-0)		0 (0-0)		0 (0-0)

Source: IMS Health, LifeLink™ Health Plan Claims Database, From 1997 to 2009

* Defined as any use during screening period, any # of days supply

** Defined as mesalamine, sulfasalazine, balsalazide, olsalazine

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- % Defined as mercaptopurine or azathioprine
- ^ Defined as infliximab, adalimumab or certolizumab pegol
- & Defined as cyclosporine or tacrolimus
- + Any proton pump inhibitor
- π Defined as total number of days (continuous) in screening period with at least 1 billed health care contact
- # Total # of comorbidities from the Devo comorbidity index for administrative data

Table 2

Characteristics of the IBD Population by Pneumonia (matched characteristics include age, IBD type, gender, region)

Characteristics	No Pneumonia (n=18928)		Pneumonia (n=4856)		p value *
	n	% or median (IQR)	n	% or median (IQR)	
Age **	18928	47 (35-55)	4856	47 (35-55)	0.32
Gender (% male)	8087	42.7	2083	42.9	0.83
IBD type					
Crohn's disease	9572	50.6	2453	50.5	0.04
Ulcerative colitis	9276	49.0	2369	48.8	
Unknown	80	0.4	341	0.7	
Utilization ^	18928	5 (1-11)	4856	13 (7-24)	<0.01
Region					
East	3530	18.7	904	18.6	0.99
Midwest	8649	45.7	2229	45.9	
South	2858	15.1	731	15.1	
West	3891	20.6	992	20.4	
Comorbidities					
Cardiac	317	1.7	352	7.3	<0.01
Diabetes mellitus	1219	6.4	596	12.3	<0.01
Liver disease	498	2.6	329	6.8	<0.01
Renal	226	1.2	205	4.2	<0.01
COPD	1423	7.5	1935	31.6	<0.01
Rheumatologic	401	2.1	288	5.9	<0.01
# Comorbidities =	18928	0 (0-0)	4856	1 (0-1)	<0.01
Medications %					
Biologic +	587	3.2	292	6.0	<0.01
Thiopurine &	1617	8.5	593	12.2	<0.01
Calcineurin \$	52	0.3	43	0.9	<0.01
Corticosteroid	1485	7.9	1531	31.5	<0.01
5-ASA	4417	23.3	1314	27.1	<0.01
PPI	2471	13.1	1182	24.3	<0.01

Source: IMS Health, LifeLink™ Health Plan Claims Database, From 1997 to 2009

* p value by Pearson's chi square for categorical variables, Wilcoxon rank sum for continuous variables

** Age at time of pneumonia (case) or index date (control)

^ Defined as total number of days (continuous) with any health care contact over observation period

= Number of comorbidities from Charlson comorbidity index

% Any use over observation period

⁺ Infliximab, adalimumab or certolizumab pegol

[&] Mercaptopurine or azathioprine

^{\$} Cyclosporine or tacrolimus

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Table 3

Crude and Multivariate analyses of medication use and pneumonia in patients with IBD, overall and by CD or UC

Medication	IBD Overall (n=23,784)		Crohns disease (n=12,025)		Ulcerative Colitis (n=11,645)	
	Crude OR, 95% CI	Adjusted OR, 95% CI	Crude OR, 95% CI	Adjusted OR, 95% CI	Crude OR, 95% CI	Adjusted OR, 95% CI
Any use in prior 120 days						
Biologic	2.06 (1.77-2.39)	1.28 (1.08-1.52)	1.91 (1.62-2.26)	1.28 (1.05-1.56)	2.71 (1.96-3.75)	1.26 (0.87-1.82)
Thiopurine	1.51 (1.37-1.67)	1.04 (0.92-1.17)	1.41 (1.25-1.61)	1.02 (0.88-1.18)	1.71 (1.44-2.03)	1.06 (0.87-1.82)
Corticosteroid	5.49 (5.04-5.97)	3.62 (3.30-3.98)	5.35 (4.75-6.01)	3.52 (3.10-4.01)	5.62 (4.97-6.35)	3.74 (3.27-4.29)
Calcineurin	3.19 (2.13-4.79)	0.51 (0.30-0.88)	2.91 (1.57-5.37)	0.59 (0.25-1.38)	3.43 (2.00-5.90)	0.49 (0.24-0.97)
PPI	2.21 (2.04-2.39)	1.14 (1.03-1.25)	2.20 (1.97-2.45)	1.17 (1.03-1.33)	2.19 (1.95-2.47)	1.10 (0.95-1.27)

* ** Biologic defined as infliximab, adalimumab, or certolizumab pegol, thiopurine defined as mercaptopurine or azathioprine

5-ASA defined as mesalamine, olsalazine, balsalazine, sulfasalazine, calcineurin defined as tacrolimus or cyclosporine

***Conditional logistic regression models adjusted for health care utilization, comorbidities, 5-ASA, biologic, thiopurine, corticosteroid, PPI medication use as appropriate

Source: IMS Health, LifeLink™ Health Plan Claims Database, From 1997 to 2009