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Comprehensive National Inpatient Sample data reveals low but rising *Pneumocystis jiroveci* pneumonia risk in inflammatory bowel disease patients

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Abstract

Background There are only limited data to guide the management of infectious risk for *Pneumocystis jiroveci* pneumonia (PCP) in patients with inflammatory bowel disease (IBD). We evaluated the frequency of admissions for PCP among patients with IBD, as well as the temporal trend in PCP admission rates and the contribution of non-IBD risk factors to the development of infection.

Methods The National Inpatient Sample from 2016-2017 was queried for all admissions involving both PCP and either Crohn's disease or ulcerative colitis. Inpatient outcomes associated with PCP and additive risk factors for development of PCP within the IBD patient population were assessed using multivariate regression. Linear regression was performed on data from 2002-2017 to measure infectious trends over time.

Results There were an estimated 225 admissions involving PCP among patients with IBD from 2016-2017 nationwide, representing 0.035% of total admissions. IBD patients with PCP faced a 4.67-fold higher adjusted odds of inpatient mortality (95% confidence interval 1.72-12.66), while 49% of patients with IBD who developed PCP had an unrelated risk factor. The most common factors were HIV and congenital immunodeficiency, both of which were associated with PCP in adjusted regression. The infectious incidence of PCP increased by 141% from 2002 to 2017 (P=0.003).

Conclusions National admissions data indicate that significant PCP is rare in IBD patients. Routine PCP prophylaxis is probably not necessary, although further study of high-risk subgroups of patients is required. The rising incidence of PCP indicates a need for continued surveillance.

Keywords Crohn's disease, ulcerative colitis, epidemiology

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Introduction

Pneumocystis jiroveci pneumonia (PCP) is an opportunistic infection associated with impaired cell-mediated immunity. Initially an HIV-defining illness, it is increasingly associated with non-HIV immunocompromised populations [1]. Non-HIV patients have been found to have a more rapid and aggressive clinical course, with higher rates of respiratory failure and mortality [2]. There are multiple reports of PCP in patients with inflammatory bowel disease (IBD) [3-5], as in other rheumatologic and hematologic conditions treated with immunomodulatory therapies. Current data and recommendations guide the use of antimicrobial prophylaxis in many immunosuppressed populations, but standardization for the management of IBD is lacking. Different professional societies offer varying recommendations, or no recommendations at all, with respect to which combinations of therapies warrant prophylaxis against PCP [6,7]. As a result, clinical practice patterns vary widely by provider and

institution, with one study reporting prophylaxis rates as low as 11%, with even lower use outside of academic medical centers [8]. Furthermore, much of this practice is based on assumptions from other diseases that may not apply to patients with IBD.

The lack of data on the risk of PCP in the IBD population limits the formulation of comprehensive national guidelines regarding the need for prophylaxis. To date, no study has looked at the scope of morbidity and mortality of PCP among patients with IBD on a national level. We therefore sought to explore the frequency of admissions for PCP among the IBD patient population using a National Inpatient Sample (NIS) dataset. Given the clinical experience and prior literature suggesting that such infections occur infrequently, we hypothesized there would be very low rates of hospitalization for PCP among patients with IBD. Furthermore, we hypothesized that the incidence of PCP admissions among patients with IBD has not significantly risen in the past 2 decades, given the gradual shift from steroids to more modern immunomodulator therapies with lower risk. We additionally sought to explore risk factors in patients with IBD for development of PCP to better define which, if any, cohort warrants prophylaxis.

Materials and methods

This study utilized data and research tools provided by the NIS from 2016 and 2017, produced by the Healthcare Cost and Utilization Project and sponsored by the Agency for Healthcare Research and Quality [9-11]. This database is an all-payer stratified sample of 20% of admissions in the United States, weighted to represent the entire country and drawn from 97% of the population. Information includes primary and secondary diagnoses, demographic and hospital characteristics, primary/secondary payer information, and illness severity measures [12]. Per institutional policy, Institutional Review Board approval was not required in view of the anonymized nature of the data.

Our primary outcome of interest was hospitalization for PCP, as defined as an ICD-10 code of B59.0 listed in any position among the hospitalization problems (including as a secondary problem). We subsequently compared the frequency of PCP admissions among adult patients with IBD to the general inpatient population. Admissions among patients with IBD were defined as those with either Crohn's disease (ICD-10: K50.0-K50.9) or ulcerative colitis (ICD-10: K51.0-K51.9) included in any position on the hospitalization problem list for the admission. Patients classified as having "indeterminate colitis" by ICD-10 K52.3 were not included in order to maintain the specificity of our study population for patients with a confirmed diagnosis of IBD. Given the infrequency of PCP, patients with Crohn's disease and ulcerative colitis were evaluated together in our primary analysis.

The demographic and hospital characteristics and inpatient outcomes of mortality, length of stay, and total charges for patients admitted for PCP were compared with the overall IBD inpatient population using a chi-square test (discrete variables) or bivariate linear regression (continuous variables). To adjust for probable differences in the underlying comorbidity burdens between these 2 groups, an Elixhauser Comorbidity Index was calculated for each patient on the basis of 29 medical comorbidities known to be associated with an increased risk of mortality, as outlined in Supplementary Table 1. This is a validated index, specific to the NIS, that has superior predictive ability compared to the Charlson comorbidity index [13-15]. We then conducted a survey-adjusted analysis on inpatient mortality and length-of-stay, using multivariate logistic and linear regression, respectively. All analyses were survey-adjusted according to the guidelines of the Healthcare Cost and Utilization Project. Missing data was <1% and therefore admissions missing a predictive factor were excluded from the analyses.

To assess the contribution of risk factors independent from underlying IBD in the development of PCP, the prevalence of well-established infectious risk factors was evaluated and compared between all IBD inpatients and those who developed PCP. A full list of the risk factors used is given in Supplementary Table 1. They include: HIV; lymphoma; leukemia; congenital immunodeficiencies; solid organ transplantation; post-transplant lymphoproliferative disorders; connective tissue disorders; and stem cell transplantation. The relative prevalence of chronic steroid use among those with PCP and those without was compared using chi-square testing; constraints of the NIS dataset prevented evaluation of other specific IBD therapies. Survey-adjusted multivariate logistic regression, controlled for age and comorbidity status, was performed to explore the relationship between the most significant known PCP risk factors—including HIV, congenital immunodeficiency, receipt of a solid organ transplant, and chronic steroids—and the development of infection.

Finally, in order to assess the change in hospitalization rates for PCP over time with the introduction of multiple new biologic medications, NIS datasets from 2002-2017 [16] were queried for all admissions involving PCP and either Crohn's disease or ulcerative colitis. Linear regression was performed, evaluating for any trend in PCP rates among patients with IBD during this time period; for comparison, this analysis was repeated amongst the general inpatient population.

Results

In total, there were an estimated 641,265 all-cause admissions involving patients with IBD nationwide from 2016-2017. Of these admissions, only 235 involved management of PCP, representing 0.035% of the total admissions in this cohort during this time period.

Comparisons between the baseline characteristics of IBD patients admitted with PCP and those of the overall IBD population are provided in Table 1. In general, those admitted with PCP were older (58.9 vs. 53.3, P=0.007), more likely to be male (55.6% vs. 43.7%, P=0.117), and had higher comorbidity burdens than those admitted for other reasons (Elixhauser score 17.3 vs. 5.6, P<0.001), all of which is consistent with previously described PCP risk factors.

Table 1 Summary of patient and hospital characteristics for IBD admissions stratified by pneumocystis pneumonia status

Characteristics	Pneumocystis pneumonia n=225		Non-pneumocystis pneumonia n=641,030	
	%	95%CI	%	95%CI
% of overall admissions	0.035	-	99.7	-
Inpatient mortality	15.6	4.8-26.2	1.5	1.4-1.6
Patient characteristics				
Female	44.4	29.9-59.0	56.3	55.9-56.6
Age, years (mean [SD])	58.9	54.8-63.0	53.3	53.1-53.5
Race				
White	77.8	65.5-90.0	75.6	74.8-76.5
Black	11.1	1.9-20.3	10.9	10.5-11.3
Hispanic	6.7	0.0-14.0	5.8	5.4-6.1
Other	-	-	3.7	3.5-4.2
Unknown	4.4	0.0-10.5	3.9	3.1-4.7
Payer				
Medicare	53.3	38.1-68.5	41.7	41.2-42.1
Medicaid	8.9	0.5-17.2	15.1	14.7-15.4
Private	37.8	22.9-52.6	36.7	36.2-37.3
Self-pay	-	-	3.5	3.3-3.6
Elixhauser mortality index	17.3	14.2-20.4	5.6	5.5-5.6
Gastrointestinal surgery	6.7	0.00-14.0	10.7	10.2-11.2
Gastrointestinal admission	37.8	23.8-51.8	72.7	72.4-73.0
Hospital characteristics				
Size (# beds)				
Small	22.2	10.0-34.5	18.5	17.7-19.2
Medium	33.3	18.9-47.8	28.1	27.2-28.9
Large	44.4	29.4-59.5	53.4	52.3-54.6
Teaching status				
Rural	-	-	7.4	7.0-7.8
Urban non-teaching	6.7	0.00-14.0	22.5	21.8-23.2
Urban teaching	93.3	86.0-100.0	70.1	69.2-70.9
Region				
Northeast	37.8	22.8-52.8	21.7	20.6-22.7
Midwest	17.8	6.6-29.0	24.7	23.6-25.8
South	28.9	15.5-42.3	36.5	35.4-37.5
West	15.6	4.9-26.2	17.2	16.4-18.0
Hospital type				
Non-federal government-owned	6.7	0.00-14.0	10.1	9.5-10.8
Private non-profit	91.1	82.8-99.5	78.5	77.7-79.3
Private investor owned	2.2	0.00-6.5	11.3	10.9-11.9

IBD, inflammatory bowel disease; CI, confidence interval; SD, standard deviation

Patients with both IBD and PCP faced a higher unadjusted inpatient mortality rate (15.6% vs. 1.5%, P=0.015) compared to patients with IBD admitted for alternative reasons. This was confirmed on multivariate analysis of the IBD population, which demonstrated that PCP was associated with a 4.67-fold increase in the odds (95% confidence interval [CI] 1.72-12.66; P=0.003) of inpatient mortality, after controlling for comorbidity burden, hospital characteristics, patient age and inpatient surgery (Table 2). Among patients without IBD, those with PCP had 5.29 times higher odds of inpatient mortality (95%CI 4.76-5.85; P<0.001) compared to those admitted for alternative diagnoses.

Length of stay among patients admitted with both IBD and PCP was a mean of 16.8 days, compared to 5.3 days among those IBD admissions unrelated to PCP (P<0.001). After adjustment in multivariate linear regression, the magnitude of this difference was only slightly reduced to 9.47 days (95%CI 4.97-13.96; P<0.001).

Notably, 48.9% (95%CI 34.9-62.9) of patients with IBD hospitalized for PCP were found to have an additional identifiable risk factor not directly related to their underlying IBD (Table 3). Most commonly, 20% of PCP patients had underlying HIV, compared to 0.5% of the non-PCP IBD cohort (P<0.001). Furthermore, almost one third had an underlying congenital immunodeficiency, including hypogammaglobulinemia, severe combined immunodeficiency, or common variable immunodeficiency (Table 3).

Patients with PCP and IBD were more often exposed to chronic steroids (15.6%, 95%CI 4.9-26.2) compared to non-PCP IBD patients (6.4%, 95%CI 6.1-6.6; P=0.10). When adjusted in

multivariate regression, patients with IBD admitted for PCP had 3.4 times higher odds of chronic steroid use than the overall IBD inpatient population (95%CI 1.5-7.9; Table 4). Interestingly, chronic steroid use represented a less significant exposure among those with PCP than both positive HIV status (odds ratio [OR] 55.6, 95%CI 26.3-117.8; P<0.001) and congenital immunodeficiency (OR 7.3, 95%CI 3.6-14.6; P<0.001) (Table 4).

Table 2 Predictors of mortality and length of stay among IBD inpatients

Outcome	OR (95%CI)	P-value
PCP	4.67 (1.72-12.66)	0.003
Adjustment factors		
Alimentary surgery	1.43 (1.23-1.67)	<0.001
Elixhauser mortality index (per 1 pt. change)	1.10 (1.10-1.10)	<0.001
Age	1.04 (1.03-1.04)	<0.001
Hospital type, rural (vs academic)	0.90 (0.75-1.08)	0.932
Hospital type, urban (vs academic)	0.80 (0.71-0.91)	0.018

IBD, inflammatory bowel disease; OR, odds ratio; CI, confidence interval; PCP, Pneumocystis jiroveci pneumonia

Table 3 Summary of concurrent infectious risk factors present among inflammatory bowel disease admissions stratified by PCP status

Risk factors	PCP n=225		No PCP n=641,030	
	%	95% confidence interval	%	95% confidence interval
Presence of at least one risk factor below	64.4	51.1-77.8	11.4	11.1-11.7
HIV	20.0	8.2-31.8	0.5	0.5-0.5
CNS malignancy	0.00	-	0.2	0.1-0.2
Lymphoma	6.6	0.0-14.0	0.8	0.7-0.8
Leukemia	6.7	0.0-14.0	0.8	0.7-0.9
Multiple myeloma	0.0	-	0.2	0.2-0.3
PTLD	0.0	-	0.0	-
Congenital immunodeficiency*	28.9	16.2-41.5	2.6	2.5-2.7
Solid organ transplantation	4.4	0.0-10.3	1.0	0.9-1.1
Connective tissue disorder	0.0	-	0.0	-
Hematopoietic stem cell transplantation	2.2	0.0-6.5	0.1	0.1-0.2
Chronic steroids	15.6	4.9-26.2	6.4	6.1-6.6
HTLV	0.00	-	0.00	-

*Includes hypogammaglobulinemias, severe combined immunodeficiency, common variable immunodeficiency, and other congenital innate immune deficiencies

PCP, Pneumocystis jiroveci pneumonia; HIV, human immunodeficiency virus; CNS, central nervous system; PTLD, post-transplant lymphoproliferative disorder; HTLV, human T-lymphotropic virus

Overall, there was a 141% increase in the rate of annual PCP admissions among the IBD population from 2002-2017, increasing from 58 cases in 2002 to 140 cases in 2017. In bivariate linear regression, the hospitalization rate for PCP among patients with IBD increased by a mean of 5.02 admissions per year (P=0.003) (Fig. 1). Comparatively, the national trend during that time period revealed a 47% decrease in annual PCP admissions from 2002 to 2017 among the overall inpatient population. This translated into an average decrease of 635.7 admissions per year during that time period (P<0.001) (Fig. 2).

Discussion

Overall, national admissions data illustrate that PCP is associated with high mortality rates and longer lengths of stay among patients with IBD, as seen in other non-HIV patients. Incidence among IBD patients is rising, in contrast to the overall case burden, but it remains very rare, with only 225 admissions nationwide over a 2-year time span. Of all patients admitted with PCP and IBD, 49% had an additional risk factor contributing to their risk of developing the opportunistic infection. Given that there are currently an estimated 3 million individuals in the United States with IBD [17], these low case numbers suggest that serious PCP represents a very uncommon phenomenon among patients with IBD.

Our study is consistent with prior reports that found very low rates of PCP within cohorts of IBD patients; however, these studies were often confined to single centers or were retrospective case-control studies [18-21]. Long *et al* (2013) utilized a commercial dataset and found an greater but, overall, very low incidence of PCP among IBD patients (10.6/100,000) [18]. The relatively higher rates of infection reported in their study compared to ours may be partially explained by their inclusion of patients treated in the outpatient setting, while we only evaluated those who required inpatient-

Table 4 Risk factors for PCP infection among IBD and non-IBD admissions

Risk factors	IBD n=225		Non-IBD n=18,810	
	Odds ratio	95%CI	Odds ratio	95%CI
Elixhauser mortality index (per point)	0.93	0.91-0.95	0.95	0.94-0.95
Age (per year)	0.99	0.98-1.00	1.02	1.02-1.02
Chronic steroids	3.4	1.5-7.9	5.7	4.9-6.7
Solid organ transplantation	1.7	0.4-7.1	3.2	2.4-4.1
Congenital immunodeficiency	7.3	3.6-14.6	2.6	2.3-2.9
HIV	55.6	26.3-117.8	218.9	200.1-239-3

IBD, inflammatory bowel disease; PCP, Pneumocystis jiroveci pneumonia; HIV, human immunodeficiency virus; CI, confidence interval

level care, and by differences due to over-coding. It is important to note that their analysis was regional and was confined to commercially insured patients, excluding higher risk subgroups such as the elderly and the uninsured. Similarly, Kojima *et al* (2020) reported a total of 9 cases in a population of over 4500 ulcerative colitis patients over a 12-year time period [20]; Cotter *et al* reported only 3 cases of PCP in over 16,000 years of IBD patient follow up [21]. Cumulatively, Lawrence *et al* found only 92 reported cases of PCP in the literature before 2017, though our study suggests this represents under-reporting of the total disease burden [3]. Okafor *et al* synthesized existing literature into a cost-effectiveness analysis that found no benefit to PCP prophylaxis in patients with IBD [8].

In spite of finding overall low infection rates in 2016-2017, we report a statistically significant increase in admissions for PCP among patients with IBD over the past 15 years, particularly notable when contextualized within the contemporary trend of decreasing PCP rates nationwide. Furthermore, although the prevalence of IBD within the United States increased by 50% during this time period [17], the corresponding rate of PCP admissions increased by 141%, suggesting that recent evolutions in IBD therapy could have contributed to this rise. Most notably, this period saw the introduction of biologic therapies [22], while there are several reported instances of PCP associated with anti-tumor necrosis factor (TNF) therapies, both within [4,5] and outside of IBD [23]. While this increase could theoretically have been offset by corresponding reductions in other immunomodulating therapies, prior studies have shown relative constancy in the use of other classes of IBD medications, including corticosteroids, as biologics became more prevalent [22]. Furthermore, it has been reported that nearly a fifth of patients started on steroids for IBD will still have a prolonged course [24], and up to 15% will be classified as having either steroid excess or dependence [25]. The use of steroids in conjunction with additional immunosuppressant agents has been empirically reported to increase patients' risk of PCP [18,26-28], as well as having an additive lymphopenic effect [29]. Therefore, it seems possible that the rise of multidrug immunosuppressive therapy regimens, particularly those including corticosteroids, is contributing to an increasing risk of PCP among patients with IBD, as has been previously reported in smaller scale studies [18,28,30].

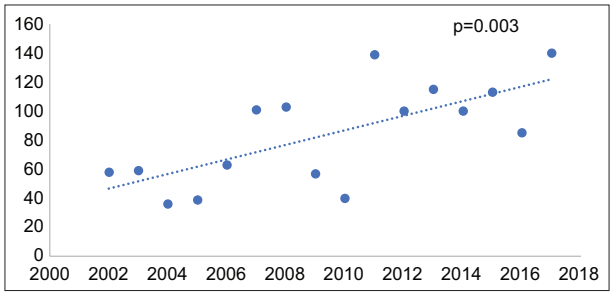

Figure 1 Volume of *Pneumocystis jiroveci* pneumonia (PCP) admissions among inflammatory bowel disease (IBD) patients from 2002-2017. Linear regression evaluating change in annual admission rates for PCP among patients with IBD, showing a statistically significant positive correlation with an average increase of 5.02 admissions annually

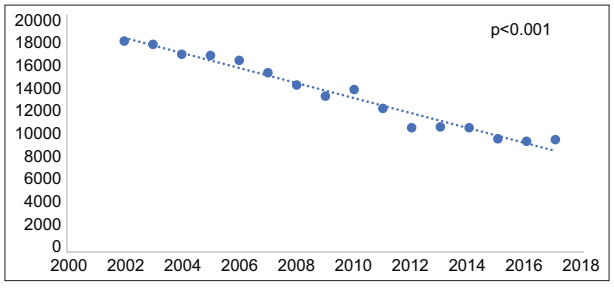

Figure 2 Volume of *Pneumocystis jiroveci* pneumonia (PCP) admissions nationwide from 2002-2017. Linear regression evaluating change in annual admission rates for PCP nationwide, showing a statistically significant negative correlation with an average decrease of 635.7 admissions annually

In spite of this increase in PCP admission rates, the rate of PCP in 2016-1017 does not support an absolute infectious risk of 3.5% [1], recommended for a favorable risk-benefit profile of PCP prophylaxis in non-HIV populations, in any meaningful segment of patients with IBD. We might also expect that this trend will be affected by the recent rise of newer biologics such as vedolizumab [31], ustekinumab, and tofacitinib, which are less frequently associated with PCP than are older anti-TNF therapies [32].

The primary limitation of our study pertains to the data constraints imposed by a national dataset that does not provide more granular clinical information on individual patients. We cannot say definitively the extent to which the low infection rates observed are driven by existing use of prophylaxis, though existing data suggest this remains an uncommon practice [8]. Similarly, we cannot explore the specific immunosuppressive therapies that patients were taking or the duration of their therapy, which would be helpful in tailoring more nuanced prophylaxis recommendations. In addition, we cannot comment on the validity or utility of proposed laboratory monitoring for PCP risk stratification among IBD patients, including T-lymphocyte counts [21], CD4 counts [21], and serum albumin levels [30]. Furthermore, the use of administrative coding poses the risk of diagnostic misclassification, although the use of ICD coding in IBD has been previously validated in a variety of contexts [33-36]. To further minimize this risk, only diagnostic codes specific for IBD were included, resulting in the potential exclusion of patients with undetermined IBD from our study. However, given that undetermined IBD exists on a spectrum between ulcerative colitis and Crohn's disease, without different guidelines for clinical management and immunosuppressive therapy, we anticipate a similar relationship with PCP within this cohort. Overall, we believe these limitations are largely offset by the comprehensive nature of the surveillance data and a focus on clinically more severe infections warranting admissions.

In conclusion, national admissions data indicate that PCP is increasing in frequency among patients with IBD. We postulate that this at least partially due to the rise of multidrug regimens in IBD therapy. However, PCP represents an overall very rare complication of IBD therapy. Almost one half of patients

with PCP have at least one additional risk factor unrelated to their underlying IBD. These data do not support the routine use of PCP prophylaxis in the majority of patients with IBD; however, further study is needed to determine whether there are small subsets of IBD patients with more profound immune compromise who might benefit. Continued population-level surveillance of PCP in patients with IBD is indicated to ensure that the observed rise does not change this calculus.

Summary Box

What is already known:

- Patients with inflammatory bowel disease (IBD) are increasingly exposed to multiple classes of medications reported to increase the risk of *Pneumocystis jiroveci* pneumonia (PCP)
- The national incidence of infection among patients with IBD is unknown

What the new findings are:

- Admission for PCP is rare among patients with IBD and 49% of cases are associated with independent risk factors
- Annual admission rates are rising, in contrast to national trends
- Routine PCP prophylaxis is likely not necessary in the IBD patient population

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Supplementary material

Supplementary Table 1 Elixhauser comorbidity index

Category
Congestive heart failure
Valvular disease
Pulmonary circulation disorders
Peripheral vascular disorders
Hypertension
Paralysis
Other neurologic disorders
Chronic pulmonary disease
Diabetes, uncomplicated
Diabetes, complicated
Hypothyroidism
Renal failure
Liver disease
Peptic ulcer disease
AIDS
Lymphoma
Metastatic cancer
Solid tumor without metastasis
Rheumatoid arthritis/collagen vascular diseases
Coagulopathy
Obesity
Weight loss
Fluid and electrolyte disorders
Blood loss anemia
Deficiency anemias
Alcohol abuse
Drug abuse
Psychoses
Depression