The Burden of Vaccine-preventable Diseases in Patients With Inflammatory Bowel Disease

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Background: Patients with inflammatory bowel disease (IBD) are at an increased risk of infections, including vaccine-preventable diseases (VPDs). The aim of this study was to explore the inpatient prevalence of VPD in patients with IBD, as well as inpatient outcomes.

Methods: Retrospective study using the 2013-2017 Nationwide Inpatient Sample databases. All patients 18 years of age or older with *International Classification of Diseases, Ninth and 10th Revisions*, Clinical Modification (ICD-9/10 CM) codes for IBD were included, as well as patients with VPDs as a principal diagnostic code. The primary outcome was the occurrence and odds of VPD in patients with IBD compared with patients with no IBD. Secondary outcomes were inpatient mortality, morbidity, and economic burden compared with patients with IBD and non–vaccine-preventable infections (VPIs). Multivariate regression yielded adjusted odds ratios.

Results: Of 1,622,245 (0.9%) patients with a diagnosis of IBD, 3560 (0.2%) had associated VPDs, while 131,150 patients had non-VPI (8.1%). The most common VPDs were influenza, herpes zoster (HZ), pneumococcal pneumonia, and varicella. Only HZ and varicella had increased odds of occurrence in patients with IBD of all ages. Patients with IBD 65 years of age or older had increased odds of VPD compared with patients under 65 years. Patients with IBD and associated VPD had higher odds of intensive care unit stay, systemic inflammatory response syndrome, and multiorgan failure compared with patients with IBD and non-VPI.

Conclusions: VPDs represent a clinically relevant cause of infectious disease-related hospital admissions in patients with IBD. Patients with IBD are at increased risk for hospitalization due to HZ and varicella. Those hospitalized for VPD have higher morbidity compared with patients with IBD and non-VPI. These findings echo the importance of instituting optimal immunization schedules in patients with IBD, particularly in patients 65 years or older.

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Advances in the treatment of inflammatory bowel disease (IBD) include monoclonal antibodies, such as tumor necrosis factor (TNF) alpha inhibitors, anti-integrin agents, interleukin-12/23 inhibitors, and novel small molecules Janus Kinase inhibitors such as tofacitinib.[1,2] These agents achieve higher rates of clinical remission and mucosal healing than conventional therapies.[3] However, some of these agents also increase the risk of viral, bacterial, and fungal infections, including some vaccine-preventable diseases (VPDs).[4–7] In recent years, the importance of preventive care has been recognized in patients with IBD, including strong support for appropriate immunization which is now included as part of the health maintenance guidelines for patients with IBD.[3,8]

Patients with IBD are at increased risk for many of these VPD, such as influenza, invasive pneumococcal disease (IPD), and herpes zoster (HZ) when compared with the general population.[4,9–12] The increased risk of IPD and HZ is present before initiation of immunosuppressive medications suggesting that the risk may be related to underlying altered immune function.[9,12] Furthermore, immunosuppressive regimens such as anti-TNF therapy and corticosteroids are independently associated with an increased risk for IPD and HZ. Preventing HZ is particularly important with the introduction of Janus Kinase inhibitors, such as tofacitinib, which confer a higher risk of HZ than conventional agents.[13] Preventive care guidelines for patients with IBD recommend appropriate immunization to reduce the burden of VPD.[3] When possible, vaccines should be administered before starting immunosuppression since certain immunosuppressive regimens such as anti-TNF therapy may blunt the vaccine response.[14–16]

Many of these VPD can result in serious infections, defined as those requiring hospitalization, which are associated with significant morbidity in patients with IBD. A recent study reported the annual VPD incidence of 2.2% (1 in 45) for those on combination therapy (anti-TNF therapy and an immunomodulator) with the risk amplified to 5.1% (1 in 20) in those aged 65 years and older. above age 65 years.[7] In addition, these infections lead to significant morbidity and have a mortality rate at 3 months of 3.9%.[7] Pneumococcal pneumonia is a common infection in those under age 65 years accounting for 9% of all serious VPD infections.[10,17,18]

Previous studies have explored the incidence of hospitalization for VPD of patients with IBD using large

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administrative dataset analyses. However, although these studies examined VPD inpatient prevalence, morbidity, mortality, and resource utilization, the examined conditions included all cases of VPD and did not account for VPD as the primary reason for admission. Our objective was to better understand the burden of VPD in patients with IBD, as in previous studies, HZ and viral hepatitis B were reported to represent over 65% of VPD in patients with IBD.[17] Therefore, the aim of this study was to evaluate the inpatient prevalence, mortality, morbidity, and economic burden of VPD as a primary reason for hospitalization in patients with associated IBD.

METHODS

Study Design and Data Source

All data included in this study were obtained from the National Inpatient Sample (NIS) spanning from January 1, 2013, to December 31, 2017, the largest publically available inpatient dataset in the US. This dataset contains data of over 7 million hospital discharges and is a 20% stratified sample from >4000 nonfederal acute care hospitals across up to 48 states of the US. The entity that maintains the dataset is the Healthcare Cost and Utilization Project (HCUP), Agency for Healthcare Research and Quality, which is a branch of the US Department of Health and Human Services. The HCUP provides discharge weights that enable the dataset to be representative of 95% of hospital discharges nationwide. The dataset includes one "principal diagnosis," which is the primary discharge diagnosis, as well as up to 39 other secondary diagnoses. Up to 25 procedural diagnostic codes are also included for each hospital discharge. In addition to basic demographic and hospital factors, the dataset specifically provides the total length of hospital stay (LOS) and total hospitalization charges, among other outcome measures. Hospital characteristics that are contained in the dataset include hospital region according to the US census regions specified by the HCUP, teaching status, hospital bed size, and hospital urban versus rural location.

Study Population

This study included all hospitalizations within the NIS datasets for 2013-2017 with an *International Classification of Diseases, Ninth and 10th Revisions*, Clinical Modification (ICD-9/10 CM) who were 18 years of age or older. Patients were identified as having IBD if they had any associated diagnostic code for IBD (555.xx, 556.xx, K50.xxx, and K51.xxx). Patients with associated ICD-9/10 principal diagnostic codes for diseases identified as acute vaccine-preventable diseases (hereafter referred to as VPD) were also identified within the database.[17,19] Only hospitalizations with a principal diagnosis for VPD were selected to isolate only the patients that were admitted to the hospital due to the VPD. No patients were excluded. Patients without IBD were identified as those who did not have an associated diagnostic ICD-CM code for IBD.

Four groups of patients with IBD were created using respective ICD-CM codes: (1) patients with no infection, (2) patients with associated VPD, (3) patients with associated non–vaccine-preventable infectious disease excluding *Clostridioides difficile* (see Supplementary Table 1 for respective codes, Supplemental Digital Content 1, http://links.lww.com/JCG/A812), and (4) patients with *Clostridioides difficile* infection (CDI). For purpose of analysis, the comparator group was the group of patients with IBD admitted for a non–vaccine-preventable infectious (VPIs) disease. All diagnostic codes are included in Supplementary Table 1 (Supplemental Digital Content 1, http://links.lww.com/JCG/A812).

Variable Definition

The selected VPD included HZ (053.xx, B02.xx), varicella (052.x, B01.xx), meningococcus (036.x, A39.xx), influenza (48.7x, J09.xx, J10.xx, J11.xx), and pneumococcal pneumonia (481, J13). Viral hepatitis type B (HBV) was not included in the analysis as, due to coding aspects, it was not found to be a principal diagnosis (eg, a principal diagnosis for patients with HBV could be hepatic encephalopathy in the setting of decompensated end-stage liver disease). Patient general characteristics included demographics such as age, sex, race, median income in patient's zip code, and insurance status. The examined hospital characteristics were hospital region, teaching status, hospital bed size, and hospital urban versus rural location. Each patient's vital status at the conclusion of hospital stay, total days of hospitalization, and total hospitalization charges were also abstracted from the database. To account for patient comorbidities, the Deyo adaptation of the Charlson Comorbidity Index (CCI) was used, which is a validated tool for large database analysis.[20]

The primary aim was to determine the inpatient prevalence of VPD as the primary reason for admission in patients with any associated diagnosis of IBD compared with patients with no associated IBD.

Secondary outcomes were evaluated on patients with IBD and were stratified for the 4 selected groups of patients. The group of interest was that of patients with IBD and associated VPD. Evaluated outcomes included inpatient mortality rates, inpatient morbidity [measured the presence of shock, acute kidney injury, systemic inflammatory response syndrome (SIRS), adult respiratory distress syndrome, multiorgan failure, or need for intensive care unit (ICU) stay], LOS, total hospital costs and hospitalization charges. In addition, to estimate the influence of the presence of IBD in patients with VPD, secondary outcomes were also obtained for patients with VPD, stratified by the presence or absence of IBD.

Statistical Analysis

Discharge-level weights published by the HCUP were used to estimate the number of patients with IBD and VPD. The Fisher exact test was used to compare proportions, and analysis of variance was utilized to compare means. A multivariate logistic regression model was used to control for confounders. Preliminarily, a univariate logistic regression model using all variables considered to be associated with the outcome of interest was conducted. Variables that were significantly associated with the outcomes on univariate analysis using a generous *P*-value of 0.1 were included in the multivariate model.

The variables included in the multivariate model were age, sex, race, CCI, insurance status, median income in patient's zip code, hospital region, hospital urban/rural location, and hospital bed size (see Supplementary Table 2 for specifications on hospital bed size, Supplemental Digital Content 2, http://links.lww.com/JCG/A813). All statistical analyses were conducted by a team member with formal biostatistical background (P.T.K.) using STATA, Version 14 (StataCorp LP, College Station, TX).

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RESULTS

A total of 1,622,245 hospitalizations with IBD were identified, out of which 3560 (0.2%) had an associated VPD as a principal diagnosis, which was less than those admitted with a principal diagnosis of CDI 105,453 (6.5%). In comparison, out of 176,578,181 patient discharges with no IBD, 506,150 (0.3%) were associated with a principal diagnosis of VPD. Of the patients with IBD, the mean age was 51.2 years for patients without associated infection, while it was 58.6 years in patients with non-VPI, 57.1 years in patients with VPD, and 51.4 years in patients with associated CDI, in comparison to 48.9 years in patients without IBD ($P < 0.01$) (Table 1).

When comparing the patient and hospital characteristics, patients with IBD and VPD were significantly older in age compared with the other groups (Table 1). All groups were primarily comprised of female white patients, and although there were statistically significant differences, these were not clinically relevant. The group of patients with VPD and non-VPI were composed of a greater proportion of patients with higher CCI compared with patients with no infection or CDI alone. Regarding hospital characteristics, the Southern region of the US contributed with the greatest proportion of patients from all the geographical regions. Patients across all groups were primarily seen at urban teaching hospitals with large hospital bed sizes. There were statistically significant differences in these parameters among groups, although they were speculated not to be clinically relevant. Patient and hospital characteristics in all groups are presented in Table 1.

For the primary outcome, the most common VPD in patients with IBD was influenza (69.5%), followed by HZ (16.9%) and pneumococcal pneumonia (10.5%). When comparing the number of VPD cases per 100,000 admissions between patients with and without IBD, only HZ and varicella were more common in patients with IBD compared with patients without IBD (Table 2).

The mean age (SD) of patients hospitalized with VPD was 58.6 years (20.7), which was not statistically significantly different from 59.1 years (27.4) in patients without IBD ($P = 0.10$). Patients hospitalized for VPD with IBD had lower associated CCI scores compared with patients without IBD ($P < 0.01$). Of the patients with IBD, 22.3% had a score of 3 or more, 14.0% a score of 2, 26% a score of 1, and 37.6% a score of 0. In comparison, 24.7% of patients without IBD had a CCI score of 3 or more, 16.6% a score of 2, 26.8% a score of 1, and 32% a score of 0.

Although overall patients with IBD did not have greater odds of having VPD be the reason for admission compared with patients without IBD, the subgroup of patients with IBD aged 65 years or older had greater odds of VPD hospitalization compared with 65 years or older without IBD [adjusted odds ratio (aOR): 1.33, $P = 0.04$]. Patients with IBD displayed greater odds of HZ (aOR: 1.29, $P < 0.01$) and varicella (aOR: 2.26, $P < 0.01$) compared with patients without IBD, but decreased odds of influenza (aOR: 0.69, $P < 0.01$) and pneumococcal pneumonia (aOR: 0.71, $P < 0.01$). The odds of VPD in patients with and without IBD are presented in Table 3.

For secondary outcomes, the crude all-cause inpatient mortality rate was 0.8% in patients with IBD and VPD, 1.1% in patients with non-VPI, and 1.5% in patients with CDI ($P < 0.01$). On multivariate analysis, adjusted mortality

TABLE 1. Patient and Hospital Characteristics in Patients With IBD Hospitalized With No Infection, VPD, Non-VPI, and CDI

Patients With IBD	No Infection (N = 1,517,965)	VPD (N = 3560)	Non-VPI (N = 131,150)	CDI (N = 105,435)	*P*
Age [mean (SD)]	51.2 (20.1)	58.6 (20.8)	57.1 (19.8)	51.4 (21.7)	< 0.01
Female gender (%)	55.9	55.1	61.3	60.7	< 0.01
Race (%)					
White	78.7	82.9	83.1	76.9	< 0.01
African American	11.3	8.8	8.4	11.0	
Hispanic	6.1	4.4	5.1	8.2	
Asian	1.2	1.4	0.9	1.1	
Other	2.7	2.5	2.5	2.8	
Median income in zip code (%)					
$1-$37,999	24.4	19.1	24.7	24.1	0.15
$38,000-$47,999	25.4	26.5	25.6	24.9	
$48,000-$63,999	25.5	28.0	25.2	26.1	
> $64,000	24.7	26.4	24.5	24.9	
Charlson Comorbidity Index (%)					
0	53.4	37.6	42.1	57.5	< 0.01
1	19.0	26.0	22.6	19.4	
2	11.1	14.1	16.6	9.8	
≥ 3	16.5	22.3	20.7	13.3	
Hospital region (%)					
Northeast	21.7	24.7	22.2	21.8	< 0.01
Midwest	25.0	28.5	25.3	23.1	
South	36.2	30.1	37.1	37.9	
West	17.1	16.7	15.4	17.2	
Urban location (%)	92.4	88.9	89.1	93.5	< 0.01
Teaching hospital (%)	67.4	62.5	59.6	66.7	< 0.01
Bed size (%)					
Small	16.8	18.0	18.8	16.7	< 0.01
Medium	27.8	30.2	29.0	29.1	
Large	55.4	51.8	52.2	54.2	

CDI indicates *Clostridioides difficile* infection; IBD, inflammatory bowel disease; VPD, vaccine-preventable disease; VPI, vaccine-preventable infection.

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TABLE 2. Number of Admissions for VPD (and Admissions/100,000) in Patients With IBD Compared With Patients Without IBD

	n (%)		
Total VPD Cases (and Cases/100,000 Admissions)	**No IBD (N = 176,578,181)**	**IBD (N = 1,622,245)**	***P***
Any VPD	506,161 (286.6)	3560 (219.5)	< 0.01
Influenza	390,308 (221)	2475 (152.6)	< 0.01
Herpes zoster	47,888 (27.1)	600 (37)	< 0.01
Pneumococcal pneumonia	61,502 (34.8)	375 (23.1)	< 0.01
Varicella	4715 (2.7)	90 (5.6)	< 0.01
Meningococcus	1748 (1.0)	20 (1.2)	0.66

IBD indicates inflammatory bowel disease; VPD, vaccine-preventable disease.

odds ratios were obtained using the non-VPI group as a comparator. There were no statistically significant differences in adjusted odds of inpatient mortality in patients with IBD and VPD compared with patients with IBD and non-VPI (aOR: 0.71, $P = 0.42$). However, patients with CDI had increased adjusted mortality odds compared with patients with non-VPI (aOR: 1.61, 95% CI: 1.14-2.10, $P < 0.01$).

In evaluating the extent of the impact that VPD have on inpatients with IBD, the outcome measures on patients with VPD were compared with the non-VPI patient group. Patients with IBD and associated VPD had increased odds of ICU stay (aOR: 2.44, $P < 0.01$), SIRS (aOR: 2.16, $P = 0.02$), and multiorgan failure (aOR: 1.19, $P = 0.05$) compared with patients with IBD and non-VPI (Table 4). However, no differences in odds of morbidity or mortality were identified when comparing patients with IBD to patients without IBD who were hospitalized for VPD. (Table 4).

Comparing the 4 groups in terms of hospital costs, charges, and LOS, patients with IBD who were admitted for noninfectious reasons had higher resource use as compared with patients with IBD who were admitted for any of the associated infectious conditions (Table 5).

Patients with IBD and VPD represented a total of 15,450 days of hospitalization, incurring in $119,326,100 of total hospitalization charges during the course of the study period. Table 5 displays all crude values for economic burden associated with VPD in patients with IBD and compares these to hospitalizations for no infection, non-VPI, and CDI.

TABLE 3. aOR of Hospitalization for VPDs in Patients With IBD Compared With Patients Without IBD

Odds of Occurrence	aOR	95% CI	*P*
VPD in patients ≥ 65 y old	1.33	1.02-1.74	0.04
Influenza	0.69	0.63-0.76	< 0.01
Herpes zoster	1.29	1.07-1.56	< 0.01
Pneumococcal pneumonia	0.71	0.56-0.89	< 0.01
Varicella	2.26	1.40-3.65	< 0.01
Meningococcus	1.47	0.55-3.94	0.44

aOR indicates adjusted odds ratio; CI, confidence interval; VPD, vaccine-preventable disease.

DISCUSSION

This study found that influenza, HZ, and pneumococcal pneumonia are the most common VPD for which patients with IBD are admitted to the hospital. Of these diseases, only HZ was found to have statistically significantly greater odds of occurrence in patients with IBD when compared with patients without IBD. It could be speculated that a comparatively lower comorbidity index in patients with IBD may partially explain the absence of difference in odds of other VPDs in this patient population compared with patients without IBD. When present, patients with IBD admitted for VPD had associated increased odds of ICU stay, shock, and acute kidney injury compared with patients with IBD and no VPD. Admission for a VPD was less likely than one for CDI, but only VPD are potentially preventable with immunization. Thus, to reduce the morbidity of VPD, patients with IBD will benefit from close adherence to immunization recommendations, particularly those 65 years or older who were more likely to have a VPD in our analysis and in other studies.[21] Patients with IBD admitted for VPD had statistically significantly less additional hospital costs and length of hospitalization compared with patients with IBD and no associated VPD (Table 5). The differences in costs between these 2 groups are speculated to reflect the decreased LOS.

The results of this study are in accordance with other large database studies. A study by Vinsard and colleagues reports that the most common VPD in patients with IBD are HZ (34.9%), viral hepatitis B (31.6%), influenza (22.1%), and pneumococcal pneumonia (9.1%). However, the above-mentioned study included all patients with any diagnostic ICD code for a VPD. In contrast to selecting only patients with principal diagnostic codes of VPD, including all diagnostic codes introduces substantial bias to a study given that the vast majority of patients may not have the acute vaccine preventable illness as the reason for admission. This is seemingly not an issue for VPDs that specifically trigger an acute illness, such as meningococcemia. However, for diseases that may be subclinical or be relatively mild enough (eg hepatitis B), in that they do not directly impact the patient's hospital course, the issue becomes evident. For example, patients with IBD with an associated diagnosis of hepatitis B are very unlikely to be admitted to the hospital for that specific reason. Moreover, (and as mentioned in the limitations), since this dataset does not allow for tracking individual patients, the likelihood of counting a specific patient with IBD and hepatitis B multiple times further introduces bias to the study. In contrast, our study included patients with IBD that had a principal diagnosis of a VPD, meaning that only patients whose primary reason for admission was a VPD were included. Tinsley et al[4] found that patients with IBD are at increased risk of influenza and are more likely to require hospitalization than patients without IBD. Our study found that hospitalization due to influenza was the most common VPD in patients with IBD and occurred less frequently compared with those without IBD. This may be explained by potential higher rates of immunizations for influenza (as well as pneumococcus) in patients with IBD. To reduce the risk of an influenza infection, certain patients with IBD may benefit from an altered immunization schedule. Those on anti-TNF monotherapy and those aged 65 years and older may benefit from the high-dose influenza vaccine, which contains 4 times the antigens of the standard dose influenza vaccine.[22] The high-dose influenza vaccine is more efficacious in preventing

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TABLE 4. Odds Ratio of Morbidity and Mortality Associated With Hospitalizations for Patients With IBD and VPDs Compared With Non-VPIs and Patients With IBD and VPDs Compared With Patients With No IBD and VPDs

	IBD With VPD Compared With IBD With Non-VPI		IBD With VPD Compared With No IBD With VPD	
Morbidity and Mortality Associated With Hospitalizations for Patients With IBD	**aOR (95% CI)**	***P***	**aOR (95% CI)**	***P***
Mortality	0.71 (0.31-1.61)	0.42	0.75 (0.34-1.68)	0.49
Shock	0.70 (0.33-1.50)	0.36	1.26 (0.60-2.66)	0.55
ICU stay	2.44 (1.75-3.39)	< 0.01	0.77 (0.57-1.05)	0.10
AKI	0.84 (0.66-1.08)	0.17	1.12 (0.88-1.42)	0.36
SIRS	2.16 (1.12-4.19)	0.02	0.32 (0.08-1.31)	0.11
ARDS	0.98 (0.24-4.08)	0.98	1.86 (0.99-3.48)	0.052
Multiorgan failure	1.19 (1.01-1.47)	0.05	0.99 (0.83-1.20)	0.97

AKI indicates acute kidney injury; aOR, adjusted odds ratio; ARDS, adult respiratory distress syndrome; CI, confidence interval; IBD, inflammatory bowel disease; ICU, intensive care unit; SIRS, systemic inflammatory response syndrome; VPD, vaccine-preventable disease; VPI, vaccine-preventable infection.

influenza and inducing higher antibodies compared with the standard dose influenza vaccine in healthy adults aged 65 years and older.[22,23] A single-center randomized clinical trial found that high-dose influenza vaccine-induced higher antibodies in patients with IBD on anti-TNF monotherapy compared with the SD.[14]

Our study confirms the well-established association between HZ and IBD.[24] The higher rates and odds of HZ infection in patients with IBD suggests that there is much room for improvement in terms of immunization awareness and regimens in this patient population. Cote-Daigneault et al[25] recently reported the results of a population-based study that found the incidence of HZ to be elevated at 7.54 cases/person-years. Khan et al[26] retrospectively examined 2 nationwide US Veterans datasets, examining both inpatients and outpatients comparing with IBD receiving 5-amino-salicylic acid alone to patients without IBD, and reported that the adjusted hazard ratios for HZ were 1.81 [95% confidence interval (CI), 1.56-2.11] for ulcerative colitis, 1.56 (95% CI, 1.28-1.91) for Crohn's disease, and an overall 1.72 (95% CI, 1.51-1.96) for treated IBD, which highly correlates with our study's finding of aOR: 1.77 (95% CI, 1.45-2.17). Our study adds to the evidence for risk of HZ in patients with IBD by showing a higher odds of hospitalization compared with those without IBD. The recombinant HZ vaccine is a 2 dose series indicated for all immunocompetent adults age 50 years and older.[27] Thus, it is important that gastroenterologists share responsibility with primary care providers in assuring that patients with IBD aged 50 years and older are immunized with the recombinant HZ vaccine series to reduce the morbidity of HZ and assure high uptake since previous studies have shown low HZ immunization rates.[26,28] The recombinant HZ vaccine has been found to be safe and immunogenic in a randomized controlled trial in other immunosuppressed populations.[29] A single-center experience did not find an association with recombinant HZ vaccine administration and an IBD flare.[30] To further reduce the burden of HZ, certain patients younger than age 50 years who are at increased risk for HZ, such as those on tofacitinib, may benefit from early HZ immunization.[13]

This study adds to the existing body of literature in that it also measured the association between VPD and inpatient morbidity which included the need for ICU, shock, and acute kidney injury, as well as the costs, charges, and LOS associated with VPD in patients with IBD compared with patients with IBD alone. Despite that increased odds of ICU stay, SIRS and multiorgan failure were noted in patients with IBD and VPD compared with patients with no IBD and VPD, this did not reflect into greater costs, charges, or length of hospitalization. Instead, this group displayed statistically significantly decreased resource utilization. Presumably, patients with IBD admitted for VPDs received dedicated antimicrobial therapy and improved their clinical status comparatively faster than patients with IBD admitted for exacerbations, who may require longer hospital stays and, hence, incur in greater expenditures. Clearly, variable association does not explain causation. However, it could be speculated that although the associated VPD-related disease severity may not be that much more significant, the threshold for hospital admission may be lower in patients with underlying IBD, as they are considered a higher risk population. Undeniably, the sample size is one of the greatest strengths of this study. However, administrative datasets such as NIS have several limitations that warrant mention to carefully interpret results. The NIS is a database dependent on coding, which exposes it to mis-coding error.

TABLE 5. Crude Hospital Costs, Charges, and Length of Stay in Patients With Inflammatory Bowel Disease Across all Groups

Crude Mean	No Infection (N = 1,517,965)	VPD (N = 3560)	Non-VPI (N = 131,150)	CDI (N = 105,435)	*P*
Hospital costs ($)	13,569	9003	10,367	10,713	< 0.01
Hospitalization charges ($)	52,148	33,851	39,401	42,541	< 0.01
Length of stay (d)	5.5	4.3	5.1	5.9	< 0.01

CDI indicates *Clostridioides difficile* infection; VPD, vaccine-preventable disease; VPI, vaccine-preventable infection.

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The baseline unit of information within this dataset is the "hospital discharge," for which individual patients within the dataset are unable to be tracked. For this reason, readmissions cannot be evaluated. Despite using the CCI to adjust for differences in patient comorbidities, there are comorbidities not included in the CCI and could contribute to other differences, as it only accounts for myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular accident, dementia, chronic obstructive pulmonary disease, connective tissue disease, liver disease, diabetes, kidney disease, malignancy, and acquired immunodeficiency syndrome. Other important limitations associated with the database itself include the inability to determine the precise time of diagnosis of IBD, medication use, laboratory findings, or pathology data. Specifically, it needs to be acknowledged that an unknown proportion of patients may have been on immunosuppressive medications. Although HBV has been reported to have a high prevalence and impact in patients with IBD, this study's design selected patients only with a principal diagnosis (reason for admission) of a VPD. This would significantly under-quantify the true inpatient prevalence of patients with HBV and IBD, as patients with HBV complications are not "admitted due to HBV." A difference in the mean ages of patients in the groups may imply the presence of added comorbidities to the older subset of patients. We attempted to counterbalance this by adjusting for comorbidities using a comorbidity index, and the odds of VPD were separately determined for the subset of patients 65 years of age and older. Ideally, patients who were immunosuppressed at baseline from any condition other than the use of long-term immunosuppressive therapy for IBD should have been excluded from statistical analysis. However, given the limitations inherent to the ICD coding indices, this was not possible. Last, it is important for the reader to observe that association between variables does not necessarily imply causation.

The use of immunosuppressive therapy in patients with IBD continues to grow, primarily in the form of biologics and novel small molecules. The immunosuppressed state generated by these agents has been directly linked to increased infection risk, several which are vaccine-preventable.[8] Melmed and colleagues found that immunization rates were lower than expected in patients with IBD, in part due to misconceptions of whether a gastroenterologist or a primary care physician is responsible for the patient's immunization status.[8,31] Therefore, guidelines such as the American College of Gastroenterology Guideline for Preventive Care in IBD emphasizes that the key to adequately manage health maintenance aspects in patients with IBD is a good communication between gastroenterologists and primary care physicians.[3,8] While immunization rates in patients with IBD have increased, gastroenterologists should take or share responsibility for providing and/or recommending vaccines to further increase vaccine uptake.[32,33]

CONCLUSIONS

VPDs represent an important cause of infectious disease-related admissions in patients with IBD. The findings of this study are in concordance with other studies and echo the importance of strong advocacy for immunizations in patients with IBD, particularly in patients 65 years of age and older. Although HZ was the only VPD that this study found to be more-commonly associated with patients with IBD, VPDs, in general, were associated with greater odds of morbidity but lesser hospital costs and LOS compared with patients with IBD alone. Therefore, this study further highlights the importance of optimal immunization strategies for patients with IBD.[21] Further studies with prospectively collected data are needed to better explore inpatient outcomes of this patient population.

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