Journal of Crohn's and Colitis (2013) 7, 107–112

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Infection-related hospitalizations are associated with increased mortality in patients with inflammatory bowel diseases

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Received 23 January 2012; received in revised form 21 February 2012; accepted 22 February 2012

KEYWORDS
Infections;
Immunosuppression;
Crohn's disease;
Ulcerative colitis

Abstract

Introduction: Serious infections are an important side effect of immunosuppressive therapy used to treat Crohn's disease (CD) and ulcerative colitis (UC). There have been no nationally representative studies examining the spectrum of infection related hospitalizations in patients with IBD.
Methods: Our study consisted of all adult CD and UC related hospitalizations from the Nationwide Inpatient Sample 2007, a national hospitalization database in the United States. We then identified all infection-related hospitalizations through codes for either the specific infections or disease processes (sepsis, pneumonia, etc.). Predictors of infections as well as the excess morbidity associated with infections were determined using multivariate regression models.
Results: There were an estimated 67,221 hospitalizations related to infections in IBD patients, comprising 27.5% of all IBD hospitalizations. On multivariate analysis, infections were independently associated with age, co-morbidity, malnutrition, TPN, and bowel surgery. Infection-related hospitalizations had a four-fold greater mortality (OR 4.4, 95% CI 3.7–5.2). However, this varied by type of infection with the strongest effect seen for sepsis (OR 15.3, 95% CI 12.4–18.6), pneumonia (OR 3.6, 95% CI 2.9–4.5) and *C. difficile* (OR 3.2, 95% CI 2.6–4.0), and weaker effects for urinary infections (OR 1.4, 95%CI 1.1–1.7). Infections were also associated with an estimated 2.3 days excess hospital stay (95% CI 2.2–2.5) and $12,482 in hospitalization charges.
Conclusion: Infections account for significant morbidity and mortality in patients with IBD and disproportionately impact older IBD patients with greater co-morbidity. Pneumonia, sepsis and *C difficile* infection are associated with the greatest excess mortality risk.

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doi:10.1016/j.crohns.2012.02.015

1. Introduction

Inflammatory bowel diseases (IBD; Crohn's disease (CD), ulcerative colitis (UC)) are chronic inflammatory diseases of the intestine characterized by a relapsing-remitting course, frequently requiring hospitalizations.[1] Significant advances in therapy over the past few decades have increased our ability to achieve remission and reduce the need for hospitalizations and surgery. However, systemic immunosuppression which remains the crux of IBD therapeutics, particularly for moderate or severe disease, is accompanied by an increase in risk of potential adverse effects including infections and malignancy.[2–5] Indeed, infectious complications remain one of the most common and serious adverse outcomes in IBD patients. In addition to iatrogenic immunosuppression, IBD patients also have a higher risk of infections by virtue of other disease-associated risk factors including malnutrition, requirement for hospitalizations, or need for high-risk interventions such as parenteral nutrition or surgery.

Recent studies have focused on the prevalence and impact of specific infections.[6–9] In particular, several recent studies have demonstrated the significant adverse effects associated with *Clostridium difficile* (*C difficile*),[6] and other healthcare-associated organisms.[7,8] However, to obtain a truly representative study of the overall burden of all infections in IBD patients, one would need to utilize a multicenter sample with information collected across different hospital types and regions. Studies utilizing such databases have focused on specific infections, while those adopting an approach to provide an overview of all infections have been from single referral centers[9,10] that are susceptible to bias and have limited power to estimate the impact of such infections on relatively uncommon but important outcomes such as mortality.

We performed this study with the following specific aims—(1) to examine the spectrum of infections resulting in hospitalizations in IBD patients from a nationally representative sample in the United States; (2) to examine the risk factors for all infections, as well as specific infections; and (3) to estimate the effect of infections on in-hospital mortality and length of stay, both for all infections, as well as for specific infections.

2. Methods

2.1. Data source and study population

Our study utilized data from the Nationwide Inpatient Sample (NIS) for the year 2007. This is the largest, all-payer hospitalization database in the United States and comprises all hospitalizations from a stratified sample of over 1,000 hospitals from 44 states.[11] This database has been utilized previously in examining the epidemiology of IBD hospitalizations as well as the effect of specific complications.[6,12–14] Each hospitalization in the NIS is coded with one primary discharge diagnosis, up to 14 secondary diagnoses, and up to 15 procedures associated with the hospitalization. Our primary study population consisted of all patients with a primary or secondary discharge diagnosis for infections. Such patients were identified through the presence of the International Classification of Diseases, 9th edition, clinical modification (ICD-9-CM) codes for infections (ICD-9-CM 001.x–0139.x). In addition, we included patients who had infectious complications that were coded based on organ system rather than a specific infectious pathogen. These included hospitalizations associated with pneumonia, urinary tract infection (UTI), abdominal or perirectal abscesses, meningitis or encephalitis, and post-operative infection. The control population consisted of all IBD hospitalizations that were not associated with any of the above codes representing infectious hospitalizations.

2.2. Variables and outcomes

Information on demographic data (age, gender, race, primary insurance source, and ZIP code level income) was obtained from the NIS. Co-morbidity was measured using the Elixhauser co-morbidity score, a validated and widely used measure of co-morbidity in hospitalized patients.[15] The Elixhauser score was categorized into four strata based on the presence of 0, 1, 2, and 3 or more co-morbidities. Hospital characteristics that were included in the analysis included hospital teaching status and the region of hospital (Northeast, West, South, and Midwest). Other risk factors that were included in our analysis were chronic steroid use (ICD-9-CM V58.65) and current smoking (ICD-9-CM V15.82). Our study had three primary outcomes—in-hospital mortality, length of stay, and total hospitalization charges.

2.3. Statistical analysis

Continuous variables were summarized using means and standard deviations while categorical variables were expressed as proportions. Appropriate *svy* commands using survey weights provided within the NIS were used to estimate the burden of hospitalizations on a national scale, accounting for the stratified survey sampling method of the NIS. Univariate and multivariate logistic regression were used to identify independent predictors of occurrence of infection-related hospitalizations. Variables were selected for inclusion in the multivariate model based on significance at $p<0.05$ in the univariate analysis. Similar logistic regression analysis was also used to identify the independent effect of infections on in-hospital mortality while linear regression was used to examine its effect on length of stay and hospitalization charges. Analyses were performed for all infections combined together as well as individual infections. All analyses were performed using Stata 11.1 (StataCorp, College Station, TX).

The Partners Institutional Review Board for Massachusetts General Hospital approved the study.

3. Results

There were an estimated 67,221 hospitalizations associated with infections in IBD patients in 2007. Of these, 23,502 hospitalizations had infections listed as the primary diagnosis for hospitalization, accounting for 150,602 days in hospital stay. Table 1 compares the characteristics of patients with infection-associated hospitalizations compared to those without. Patients with infections tended to be older (mean age 54.7 years) than controls (mean age 51.0 years, $p<0.0001$) and have greater co-morbidity. Approximately 41% of patients in the infection group had a score of 3 or more on the

Table 1 Characteristics of hospitalized patients with inflammatory bowel disease, stratified by presence of infections.

Characteristics	Infection (n=67,216)	No infection (n=169,244)	p-Value
Age category	%	%	< 0.0001
19–35 years	19.6	24.5	
36–50 years	23.2	26.2	
51–65 years	25.0	24.0	
66 years and older	32.3	25.3	
Female	59.6	57.2	0.0001
Non-white race	41.8	43.0	0.06
Insurance			<0.0001
Private	39..2	47.5	
Medicare	42.5	33.4	
Medicaid	9.7	8.8	
Self-pay	8.6	10.3	
Elixhauser co-morbidity score			
0	14.3	24.3	
1	21.5	27.7	
2	23.1	21.8	
≥ 3	41.1	26.2	
IBD type			0.0004
Crohn's disease	62.2	64.2	
Ulcerative colitis	37.8	35.8	
Bowel surgery	15.6	10.5	< 0.0001
Malnutrition	8.0	3.2	< 0.0001
Parenteral nutrition	6.6	2.5	< 0.0001
Anemia	25.5	21.4	< 0.0001
Smoking	17.4	20.4	< 0.0001
Chronic steroid use	3.7	3.9	0.26

IBD—inflammatory bowel disease.

Table 2 Multivariate analysis of predictors for infection-related hospitalizations in patients with inflammatory bowel disease.

Characteristic	Odds ratio	95% Confidence interval
Age category		
19–35 years	Reference	
36–50 years	1.00	0.94–1.07
51–65 years	1.08	1.01–1.16
66 years and older	1.20	1.11–1.30
Gender		
Male	Reference	
Female	1.07	1.01–1.12
Race		
White	Reference	
Non-white	0.99	0.94–1.04
Elixhauser co-morbidity score		
0	Reference	
1	1.27	1.18–1.36
2	1.68	1.56–1.80
≥ 3	2.31	2.14–2.50
Bowel surgery		
No	Reference	
Yes	1.78	1.67–1.90
Chronic steroid use		
No	Reference	
Yes	0.97	0.87–1.09
Smoking		
No	Reference	
Yes	0.81	0.77–0.86
IBD type		
Ulcerative colitis	Reference	
Crohn's disease	0.96	0.91–1.00
Emergent admission		
No	Reference	
Yes	1.41	1.34–1.49
Nutritional status		
None	Reference	
Malnutrition	1.83	1.65–2.03
Parenteral nutrition	2.27	2.02–2.56

IBD—inflammatory bowel disease.

Elixhauser co-morbidity index compared to 26% of controls. A greater proportion of patients in the infection group had malnutrition, required parenteral nutrition, or underwent bowel surgery compared to controls (Table 1). The most common primary listed diagnosis in those without an infection was CD (24%) or UC (15%). In those with a non-CD/UC first listed diagnosis, the most common diagnoses were intestinal obstruction, coronary artery disease, and acute pancreatitis.

3.1. Risk factors for infection-related hospitalizations

Table 2 presents the multivariate analysis of the demographic and clinical risk factors for infection related hospitalizations in IBD patients. Age>66 years (multivariate odds radio (OR) 1.20, 95% confidence interval (CI) 1.11–1.30) and Elixhauser index of 3 or more (OR 2.31, 95% CI 2.14–2.50) were independently associated with infections. Nutritional status was also strongly associated with infections. Compared to controls without malnutrition, malnourished patients had a nearly two-fold elevated risk for infections (OR 1.83, 95% CI 1.65–2.03) while those on total parenteral nutrition (TPN) experienced a greater risk with an OR of 2.27 (95% CI 2.02–2.56). Bowel surgery, emergent admission, and female gender also conveyed elevated risk of infections. Similar estimates were arrived at when restricting the analysis to those with a primary diagnosis of infection alone (data not shown).

The effect of risk factors associated with overall infection varied when we performed subgroup analysis by specific infection type. Age>65 years was strongly associated with hospitalization for pneumonia (OR 4.01, 95% CI 3.33–4.82), sepsis (OR 2.30, 95% CI 1.90–2.79), urinary tract infection (OR 1.94, 95% CI 1.74–2.17) and *C difficile* (OR 1.42, 95% CI 1.17–1.73) but was associated with a lower risk for intra-abdominal abscesses, viral infection (herpes, cytomegalovirus, Epstein–Barr virus), systemic fungal, and enteric infections (Fig. 1). Similar associations were seen for co-morbidity. However, other risk factors, in particular nutritional status, displayed more consistent positive association with 'any infection' as well as each of the specific infections.

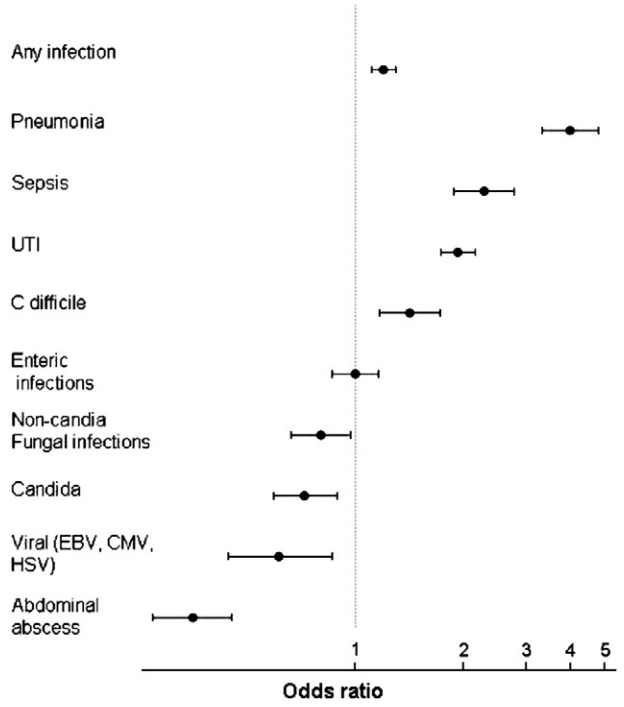

Figure 1 Older age (≥ 65 years) as a risk factor for all infection and specific infections. * All odds ratios are for age>65 - years compared to age 19–35 years. *C. difficile*–*Clostridium difficile*; UTI–urinary tract infection; CMV–cytomegalovirus; EBV–Epstein–Barr virus, HSV–Herpes simplex virus.

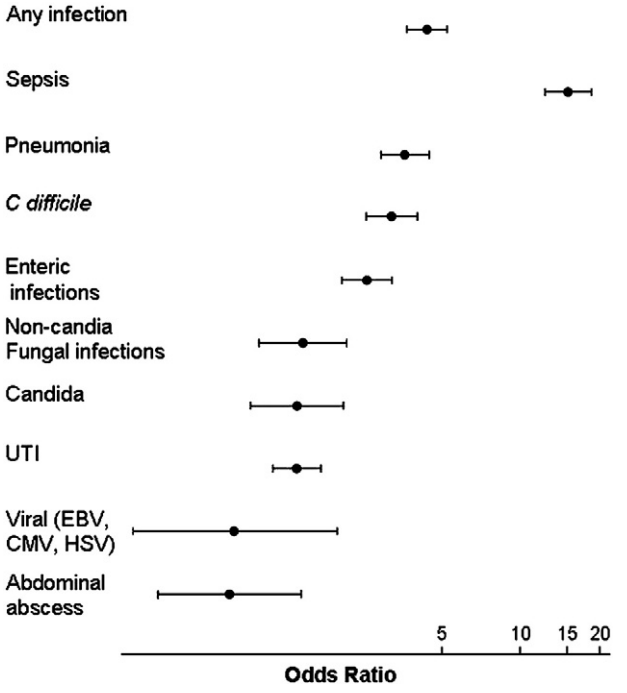

Figure 2 Effect of any infection and specific infections on in-hospital mortality in patients with inflammatory bowel disease. *C. difficile*–*clostridium difficile*; UTI–urinary tract infection; CMV–cytomegalovirus; EBV–Ebstein–Barr virus, HSV–Herpes simplex virus.

3.2. Outcomes of infection-related hospitalizations

Patients with infection-related hospitalizations had significantly greater mortality than those without (3.2% vs. 0.5%, multivariate OR 4.8, 95% CI 3.67–5.23). They also had longer hospitalizations (+2.3 days, 95% CI 2.15–2.45) and higher hospitalizations charges (+$12,482, 95% CI $11,172–13,792). This excess mortality risk varied by age-group and type of infection. The highest excess mortality was associated with sepsis (OR 15.18, 95% CI 12.39–16.61), pneumonia (OR 3.61, 95% CI 2.92–4.47) and *C difficile* infections (OR 3.23, 95% CI 2.55–4.03) (Fig. 2). More modest effects were seen for enteric infections (OR 2.58, 95% CI 2.06–3.22) and UTI (OR 1.39, 95% CI 1.13–1.72) while infections such as abdominal abscesses, candida, post-operative infections, and viral infections did not confer any excess mortality (Fig. 2).

The outcomes of infection-related hospitalizations did not differ significantly by age group with statistically similar effects for all infections or specific infections seen in both younger and older patients. We performed a sensitivity analysis by restricting our analysis to those with a primary listed diagnosis of the specific infections and arrived at similar estimates.

4. Discussion

Advances in therapy have increased our ability to achieve remission and reduce the need for surgery and hospitalizations in CD and UC. However, infections remain a significant side effect of systemic immunosuppressive therapy with approximately 5–10% of patients developing serious infections.[2,5,10] To our knowledge, there have been no prior published studies examining the spectrum of infection-associated hospitalizations in an IBD cohort using a nationally representative sample. Using such a national hospitalization database from the United States, we demonstrate that (1) infection associated hospitalizations are associated with a significantly increased morbidity and mortality in IBD patients; (2) older age, greater co-morbidity, and nutritional status including requirement for parenteral nutrition are strong risk factors for such infections, and (3) there is significant heterogeneity in the risk factors and impact of specific infections.

Several recent studies have highlighted the individual impact of specific infections in patients with IBD. Most attention has been focused on *C. difficile* infection which has been demonstrated in numerous cohorts to be associated with excess mortality, need for colectomy, and prolonged hospitalization.[6,13,16] In addition, other studies have highlighted the impact of healthcare-associated infections such as methicillin-resistant staphylococcus aureus[8] and vancomycin-resistant enterocci.[7] Our study findings extend the findings of these individual studies by demonstrating that a substantial excess mortality and morbidity is associated with any infection-related hospitalization in IBD patients, suggesting the need for comprehensive approach to reducing the incidence of such infections. We identified some risk factors that were common to all infections, in particular nutritional status. Both the presence of malnutrition, and requirement for TPN were independent risk factors for all infections. In addition, they also

independently increased the risk of specific infections. Thus, IBD patients with compromised nutritional status due to protracted or severe disease activity must be considered high-risk for the development of infectious complications on immunosuppressive therapy. It is important to adopt measures to improve nutritional status as well as to decrease infection risk in such patients in conjunction with their ongoing systemic immunosuppression. A second risk factor that increased risk for many, but not all infections, was older age. We had previously demonstrated a significant increase in mortality risk in older patients with IBD who are hospitalized.[17] Thus, escalation of systemic immunosuppression must be performed with caution in this cohort owing to higher risk of infectious complications. This is especially important in the presence of other risk factors such as compromised nutritional status.

One of the key findings of our study was the demonstration of heterogeneity in the risk factors for and outcomes related to specific infections. In particular, we found that the greatest excess mortality risk is associated with sepsis, pneumonia, and *C. difficile*. Fortunately, each of these infections may be amenable to specific risk reduction strategies. In our cohort, 15% of sepsis occurred in patients requiring TPN. While the administrative nature of our database precluded us from concluding about causation, minimizing the need for such indwelling catheters where possible and adoption of appropriate intravenous line management strategies that reduce risk of such catheter-associated infections would reduce the risk of sepsis and adverse consequences associated with it.[18] Similarly, a significant proportion of pneumonia related hospitalizations may be prevented through the administration of pneumococcal and influenza vaccination as recommended by experts and professional societies.[19–21] Recent studies continue to demonstrate that rate of such vaccination among patients with IBD remains low.[20] Efforts at improving such vaccination coverage should, in particular, target older patients who were at the greatest risk of developing pneumonia in our cohort. Recent reviews have highlighted general and specific strategies to reduce the excess morbidity and mortality associated with *C difficile* infection in IBD patients.[22] This includes judicious use of antibiotics, maintaining a high index of suspicion facilitating early diagnosis and institution of appropriate treatment, as well as general institution-wide infection-control measures. Despite a more modest effect on mortality, by virtue of their being the most common type of infection, UTI's are also associated with significant healthcare costs. They occurred mostly in the elderly population suggested need for efforts to minimize risk factors such as indwelling urinary catheters, particularly in individuals with other risk factors including age, co-morbidity and compromised nutritional status.[23]

There are a few implications to our findings. Infection-related hospitalizations are common in patients with IBD and account for a significant healthcare burden with a four-fold increase in mortality associated with such hospitalizations. Efforts at reducing the associated healthcare burden should, in particular, target those infections which are common and are associated with the greatest increase in adverse outcome, including pneumonia, sepsis and *C difficile*. Infection-specific interventions such as pneumococcal and influenza vaccination and measures to prevent catheter-associated infections would confer significant benefits in reducing the healthcare burden associated with infections in the IBD population. High risk groups, in particular older patients, those with co-morbidity, and compromised nutritional status, should be targeted for such measures.

There are several limitations to our study that merit acknowledgement. We were unable to examine the effect of specific medications as risk factors. Indeed, immunosuppressive medications, in particular corticosteroids, have been demonstrated as important risk factors for infectious complications, and our adjustment for chronic steroid use is imperfect as it relies on administrative codes. Nevertheless, as the primary aims of our study were to demonstrate (1) the distribution of various infections among those with an infection-related hospitalization, particularly when stratifying by age; and (2) the effect of an infection-related hospitalization on morbidity and mortality, it is unlikely that medication information would confound our results and we believe our findings to be robust. Our definition of infections and risk factors was also reliant on administrative coding which is susceptible to errors. Our analysis was also restricted to the cohort of patients requiring hospitalization and may not be generalizable to the impact of infections in the ambulatory setting. Nevertheless, hospitalizations account for the bulk of morbidity, mortality, and healthcare costs, and are an important cohort for study.

In conclusion, infection-associated hospitalizations are associated with a four-fold increase in mortality in IBD patients. We also demonstrate that the distribution of infections may differ between younger and older IBD patients. Pneumonia, sepsis, and *C difficile* infections are the most-common and associated with the greatest increase in mortality. However, as these infections also lend themselves to specific measures that may reduce their incidence, both general and specific infection prevention measures should be adopted to minimize the healthcare burden associated with such infections, and to improve outcomes in IBD patients.

Conflicts of interest statement

None.

Author contributions

Ananthakrishnan—study concept and design, analysis and interpretation, drafting of the manuscript; McGinley—obtained data for analysis, critical revision and approval of final manuscript.

Source of funding

Ananthakrishnan is supported in part by a grant from the American Gastroenterological Association.

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