Colon Surgery Risk With Corticosteroids Versus Immunomodulators or Biologics in Inflammatory Bowel Disease Patients With *Clostridium difficile* Infection

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Background: Inflammatory bowel disease (IBD) is an independent risk factor for *Clostridium difficile* infection (CDI), and CDI often precipitates IBD exacerbation. Because CDI cannot be distinguished clinically from an IBD exacerbation, management is difficult. We aimed to assess factors associated with adverse outcomes in IBD with CDI, including the role of escalating or de-escalating IBD therapy and CDI treatment.

Methods: Records for patients with IBD and CDI from 2008 to 2013 were abstracted for variables including IBD severity before CDI diagnosis, CDI management, subsequent IBD exacerbation, CDI recurrence, and colon surgery. Colon surgery was defined as resection of any colonic segment within 1 year after CDI diagnosis.

Results: We included 137 IBD patients (median age, 46 years; 55% women): 70 with ulcerative colitis (51%), 63 with Crohn's disease (46%), and 4 with indeterminate colitis (3%). Overall, 70% of CDIs were mild-moderate, 14% were severe, and 15% were severe-complicated. *Clostridium difficile* infection treatment choice did not vary by infection severity ($P = 0.27$). Corticosteroid escalation (odds ratio [OR], 5.94; 95% confidence interval [CI], 2.03–17.44) was a positive predictor of colon surgery within 1 year after CDI; older age (OR, 0.09; 95% CI, 0.01–0.44) was a negative predictor. Modifying the corticosteroid regimen did not affect CDI recurrence or risk of future IBD exacerbation. Adverse outcomes did not differ with CDI antibiotic regimens or biologic or immunomodulator regimen modification.

Conclusions: Corticosteroid escalation for IBD during CDI was associated with higher risk of colon surgery. Type of CDI treatment did not influence IBD outcomes. Prospective studies are needed to further elucidate optimal management in this high-risk population.

Key Words: biologic therapy, *Clostridium difficile*, colectomy, immunomodulator therapy, inflammatory bowel disease

INTRODUCTION

Clostridium difficile, a spore-forming, anaerobic, gram-positive bacillus, is the most common nosocomial infection.[1] Although historically reported mostly in hospitalized patients with previous antibiotic exposure, *C. difficile* infection (CDI) is now prevalent in community settings, with up to one third of infected patients having no history of recent hospitalization or antibiotic use.[2, 3] Patients with inflammatory bowel disease (IBD) are at an increased risk for developing both initial and recurrent CDI[4] regardless of the presence of traditional risk factors such as older age, antibiotic exposure, and hospitalization. In fact, patients with IBD are younger than typical patients with CDI and have a higher proportion of community-acquired CDI than patients without IBD.[5, 6] *Clostridium difficile* infection begins with disruption of normal colonic microbiota, which is often triggered by antibiotic therapy in otherwise healthy individuals.[7]

In IBD, active colitis due to an IBD exacerbation leads to disruption of the gut microbiome, thereby facilitating colonization and active infection by toxigenic *C. difficile* spores even without antibiotic exposure.[8, 9] After an initial infection, the risk of recurrent CDI in patients with IBD is higher (~40%) than among those without IBD (20%–30%) because of persistent microbial dysbiosis attributable to underlying IBD and to treatment of CDI.[10, 11] In addition, an inflammatory response triggered by *C. difficile* toxins on the colonic mucosa can often lead to IBD exacerbation.[12, 13]

The incidence of CDI among patients with IBD and the proportion of total CDI cases occurring in patients with IBD are increasing.[14–17] Unfortunately, IBD complicated

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Abbreviations: 5-ASA, 5-aminosalicylic acid derivative; CDI, *Clostridium difficile* infection; EHR, electronic health record; IBD, inflammatory bowel disease; OR, odds ratio; PCR, polymerase chain reaction.

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by CDI can result in several adverse outcomes that pose a substantial risk of morbidity for patients. Compared with IBD alone, CDI in IBD leads to increased IBD-related hospitalizations, length of stay, and a higher risk of colon surgery.[15, 18, 19] Patients with IBD and CDI have a lesser response to antibiotics and a higher risk of CDI recurrence than those with CDI alone.[15, 16, 18] However, clinical data for the relationship between these adverse outcomes and different management approaches for patients with CDI and IBD are currently limited.

Given this gap, we aimed to further elucidate this complex issue by evaluating 1) the incidence of subsequent CDI, hospitalizations, colon surgery, and future IBD exacerbations in patients with IBD and CDI and 2) whether different treatment options for CDI or IBD were associated with these adverse outcomes.

METHODS

Patient Selection

The Mayo Clinic Institutional Review Board approved the study protocol to review electronic health records (EHRs) of patients who had provided research authorization on June 2, 2015. Patients with IBD diagnosed and treated for CDI from January 1, 2008, through December 31, 2013, were identified by codes from the International Classification of Diseases, Ninth Revision and confirmed by manual review. The first CDI within this interval was used as the infection episode of focus, referred to as the CDI of interest. The criteria for CDI were defined as ≥3 loose or watery stools per day for ≥2 days and at least 1 positive polymerase chain reaction (PCR)–based stool test, detecting the regulatory gene responsible for production of *C. difficile* toxins A and B at the time of symptoms. Patients were excluded from the study if they 1) did not have a confirmed IBD diagnosis before the CDI of interest; 2) lacked a documented positive PCR stool test for CDI; 3) were primarily treated for CDI at a site other than Mayo Clinic, Rochester, Minnesota, or their CDI treatment duration was not sufficiently documented; 4) were younger than 18 years at the time of CDI diagnosis; 5) were lost to follow-up before 1 year after the CDI; 6) underwent total colectomy before CDI diagnosis; or 7) had documented non-CDI infections along with the CDI of interest.

Design and Outcomes

By using a retrospective cohort design, we aimed to evaluate outcomes of CDI in patients with IBD to identify factors associated with adverse outcomes such as future CDI episodes, CDI-related hospitalizations, IBD exacerbation, and colon surgery.

Demographic and Clinical Variables

All demographic and clinical variables were obtained from the EHRs of patients who met the inclusion criteria. Demographic variables collected included sex, race, ethnicity, smoking history (eg, current, past, or never), and age at diagnosis of the CDI of interest. IBD-related clinical factors included IBD subtype; age of IBD onset; number of IBD-related exacerbations, hospitalizations, and corticosteroid prescriptions ≤1 year before diagnosis of the CDI of interest; medical management of IBD at CDI diagnosis and during CDI treatment; IBD-related surgery after CDI; and date of last documented follow-up with a provider regarding IBD status and symptoms.

CDI-related clinical factors included severity of the CDI of interest, mode of acquisition, and treatment; number of previous and subsequent CDI episodes ≤1 year before and after the CDI of interest; number of subsequent CDI-related hospitalizations ≤1 year after the CDI of interest; and whether or not a patient received fecal microbiota transplantation after the CDI of interest.

Variable Definitions

Age of IBD onset

Age of IBD onset was calculated from the date corresponding to the earliest record of endoscopic or radiologic findings consistent with IBD—or both—or the earliest documented date a patient sought medical care for symptoms suggestive of IBD and used to best determine the length of time a patient had IBD.

IBD exacerbation

An IBD exacerbation before or after the CDI was defined as 1) an acute increase in symptoms of diarrhea, rectal bleeding, or abdominal pain not otherwise attributed to a non-IBD process (eg, irritable bowel syndrome, hemorrhoids); 2) persistence of symptoms despite medical or surgical management; 3) evidence of active colitis on colonoscopy; 4) new onset of extra-intestinal manifestations of IBD; or 5) other complications directly resulting from the inflammatory or mechanical processes of IBD, such as fistula, abscess, bowel obstruction, or perforation. We excluded any presentations that met the criteria but were associated with a positive CDI stool test.

IBD-related hospitalization

An IBD-related hospitalization was defined as any hospitalization directly related to an IBD exacerbation or surgical management of IBD or both.

IBD-related corticosteroid escalation

IBD-related corticosteroid administration was defined as any administration or escalation of intravenous or oral corticosteroids equivalent to 40 mg of prednisone or more to treat intestinal or extraintestinal manifestations of a patient's IBD.

Medical management of IBD at CDI diagnosis

All IBD medications being taken by a patient when the CDI of interest was diagnosed were considered as medical management.

Medical management of IBD during CDI treatment

Medical management of IBD during CDI treatment was defined as any modification to medical management of IBD (eg, continuation, escalation, de-escalation, addition, or discontinuation of medication) during treatment of the CDI of interest. Any temporary courses of IBD medications given during the CDI treatment period were also considered medication additions. Therapy escalation of a given IBD medication was defined as the addition or dose-escalation of that drug. Therapy de-escalation of a given IBD medication was defined as discontinuation or de-escalation of a drug dose. Modifications to IBD medications were considered to have occurred during treatment of the CDI of interest if changes occurred ≤10 days of CDI diagnosis date or during the antibiotic course if a patient was taking CDI therapy >10 days after diagnosis.

Colon surgery after CDI

Colon surgery after CDI was considered as any surgical colonic resection for medically refractory IBD or CDI—or both—or associated complications within 1 year after management of the CDI of interest, most commonly full or partial colectomy. For multistage colectomy procedures, the date of the initial operation was used. Procedures to manage complications of prior operations were not included.

Previous CDI episode

A previous CDI episode was defined by either a positive PCR stool test, a stated positive stool test in an EHR note, or empiric treatment for a CDI with appropriate antibiotics and initial symptomatic response in the absence of results for a positive stool test. We included episodes responsive to empiric therapy to minimize the number of false-negative infections preceding and after the CDI of interest, given that the proportion of other bacterial colitides in this context is low. Using our institutional data, Hanada et al[20] performed a large retrospective study in a similar patient population investigating the presence of non-CDI bacterial infections in patients with an IBD flare and found that non-CDI bacterial infections comprised fewer than 3% of the stool samples tested.

Classification of CDI of interest

Classification of CDI of interest was defined as community-acquired if symptom onset occurred without a patient history of hospitalization or meeting the CDI case definition ≤48 hours of a hospital admission or >12 weeks after hospital discharge. Health care facility–associated CDI was defined as infection with symptom onset >48 hours after a hospital admission and ≤4 weeks after their discharge from the hospital. Infections for which onset of symptoms occurred from 4 to 12 weeks after hospital discharge were classified as indeterminate.[21]

Severity of CDI of interest

Severity of the CDI of interest was defined by a white blood cell count ≥15,000 cells/μL or serum creatinine ≥1.5 times baseline creatinine.[21] Severe-complicated CDI was defined by hypotension or shock, sepsis, ileus, megacolon, or bowel perforation not clearly attributed to another process.[21] Patients who were admitted to the intensive care unit or underwent bowel resection to manage IBD at the time of active CDI or both were also classified as having severe-complicated infection.[21] *Clostridium difficile* infection that did not meet any of the previously stated criteria was classified as mild-moderate infection. Laboratory findings used to determine CDI severity, anemia, or hypoalbuminemia were based on the most extreme values documented within 1 week of CDI diagnosis.

Subsequent CDI episode

Subsequent CDI episode was defined by a stated or documented positive repeat stool test with ≥3 loose or watery stools per day for ≥2 days or initiation of empiric antibiotic therapy for clinical features consistent with CDI, each after completion of initial antibiotic therapy for the CDI of interest with symptom resolution. Subsequent CDI episodes occurring ≤56 days from the diagnosis of the CDI of interest were considered as recurrent infection.

Statistical Analyses

Statistical analyses were performed using JMP software, version 13.0 (SAS Institute Inc, Cary, NC). Descriptive statistics were used for demographic and other clinical variables. Differences in normally distributed continuous variables were calculated using *t* tests. Categorical variables were compared using χ^2 analysis, Fisher exact test for small cell counts, one-way analysis of variance, or multiple regression analysis correcting for age and CDI severity. A P value of <0.05 was considered statistically significant.

RESULTS

Patient Demographic Variables and Clinical History

Overall, 137 patients with IBD were included in the study. Patients' demographic variables are summarized in Table 1. There were 70 patients with ulcerative colitis (51%), 63 with Crohn's disease (46%), and 4 with indeterminate colitis (3%). The median (range) duration of IBD before CDI was 7 (0–66) years. Two thirds of patients had ≥1 IBD exacerbation in the year preceding the CDI of interest. Most patients did not have a documented history of CDI in the institutional EHR before the CDI of interest. The proportion of patients without prior CDI history was 66% for those with ulcerative colitis, 76% for those with Crohn's disease,

and 75% for those with indeterminate colitis. Eight of the 23 patients (35%) with a history of CDI within 1 year of the CDI of interest had infection <56 days from the CDI diagnosis (6% of all study patients). One of 25 (4%) cases of CDI ≤1 year before the CDI of interest was treated empirically. Additional IBD and CDI characteristics and histories are summarized in Table 2.

TABLE 1. Patient Demographic and Disease Information (N = 137)

Variable	Median (IQR) or No. (%)
Age, y	
Median (range)	46 (19–88)
Sex	
Men	62 (45)
Women	75 (55)
Tobacco use	
Never	75 (55)
Past	50 (36)
Current	12 (9)
IBD subtype	
Ulcerative colitis	70 (51)
Crohn's disease	63 (46)
Indeterminate colitis	4 (3)
Duration of IBD, y	
Median (range)	7 (0–66)
Mean (SD)	11.5 (12.3)

Clinical Presentation and Treatment of CDI of Interest

The mode of acquisition and treatment of all CDIs, stratified by severity, are summarized in (Supplementary Table S1). Approximately 40% of CDIs of each severity were treated with metronidazole. Treatment with both vancomycin and metronidazole was the second most commonly used regimen for severe or severe-complicated CDI.

For all CDI cases, the median (range) length of treatment was 13 days with oral metronidazole,[7–15] 3 days with intravenous metronidazole,[2–5] and 14 days with oral vancomycin.[10–20] The median duration of treatment for patients receiving both metronidazole and vancomycin was 15 days.[11–24] A significantly greater proportion of individuals with anemia (hemoglobin <9 mg/dL) at the time of CDI had severe (22%) and severe-complicated (37%) infections than those who were not anemic (14% and 12%, respectively) ($P = 0.003$). Similarly, a significantly greater proportion of patients with hypoalbuminemia (<3 g/dL) at the time of CDI had severe (25%) and severe-complicated (38%) infections than those without hypoalbuminemia (14% and 14%, respectively) ($P = 0.01$). Patients with severe or severe-complicated infections were more likely to have corticosteroid medications escalated during CDI treatment ($P = 0.008$) and immunomodulators de-escalated ($P = 0.004$).

Clostridium difficile infection treatment choice did not significantly influence the occurrence of adverse events, including CDI recurrence ($P = 0.92$), CDI-related hospitalization ($P = 0.15$), IBD exacerbation ($P = 0.54$), or colon surgery ($P = 0.33$) ≤1 year after CDI (Tables 3A and 3B). A similar lack of correlation with CDI treatment was shown when severe and severe-complicated infections were analyzed separately

TABLE 2. IBD-Related and CDI-Related Characteristics*

Characteristics	UC (n = 70)	CD (n = 63)	IC (n = 4)
IBD activity before CDI			
Any colon surgery	1 (1)	15 (24)	0 (0)
Any small bowel resection	0 (0)	6 (10)	0 (0)
≥1 IBD-related hospitalization within 1 year	19 (27)	34 (54)	1 (25)
≥1 IBD exacerbation within 1 year	49 (70)	41 (65)	1 (25)
≥1 corticosteroid regimen within 1 year	42 (60)	35 (56)	1 (25)
IBD medication at time of CDI			
Corticosteroid	37 (53)	28 (44)	3 (75)
5-aminosalicylic acid derivative	46 (66)	8 (13)	1 (25)
Immunomodulator	14 (20)	20 (32)	0 (0)
Biologic	10 (14)	16 (25)	0 (0)
Tacrolimus	11 (16)	3 (5)	2 (50)
History of CDI			
No prior CDI	46 (66)	48 (76)	3 (75)
≥1 prior CDI within 1 year	16 (23)	7 (11)	0 (0)

Abbreviations: CD, Crohn's disease; IC, indeterminate colitis; UC, ulcerative colitis.
*Data are presented as No. (%).

TABLE 3A. Distribution of CDI Severity and 1-Year Adverse Outcomes by CDI Treatment for Patients with Crohn's Disease (n = 63)*

	No Treatment	Vanco	Metro	Both	Both+Rifa	N	*P* Value†
CDI severity							
Moderate	1 (2)	11 (24)	20 (44)	13 (29)	0 (0)	45	.40
Severe	0 (0)	1 (13)	3 (38)	4 (50)	0 (0)	8	
Severe-complicated	0 (0)	0 (0)	4 (40)	6 (60)	0 (0)	10	
Subsequent CDI						63	.54
No	1 (2)	7 (11)	21 (33)	15 (24)	0 (0)		
Yes	0 (0)	5 (8)	6 (10)	8 (13)	0 (0)		
Recurrent CDI						63	.63
No	1 (2)	11 (17)	24 (38)	18 (29)	0 (0)		
Yes	0 (0)	1 (2)	3 (5)	5 (8)	0 (0)		
CDI-related hospitalization						63	.20
No	1 (2)	10 (16)	24 (38)	23 (37)	0 (0)		
Yes	0 (0)	2 (3)	3 (5)	0 (0)	0 (0)		
IBD exacerbation						63	.38
No	1 (2)	7 (11)	12 (19)	8 (13)	0 (0)		
Yes	0 (0)	5 (8)	15 (24)	15 (24)	0 (0)		
Colon Surgery						63	.11
No	1 (2)	8 (13)	23 (37)	13 (21)	0 (0)		
Yes	0 (0)	4 (6)	4 (6)	10 (16)	0 (0)		

Abbreviations: both, vancomycin plus metronidazole; both+rifa, vancomycin plus metronidazole plus rifaximin; metro, metronidazole only; vanco, vancomycin only.
*Data are presented as No. (%).
†Fisher exact test.

from mild-moderate infections. No significant association was observed between CDI severity and antibiotic treatment regimen ($P = 0.27$) (Tables 3A and 3B).

Concurrent IBD Management

Corticosteroids, 5-aminosalicylic acid (5-ASA) derivatives, and immunomodulators (eg, methotrexate, azathioprine, or 6-mercaptopurine) were the most common active medications prescribed for IBD at the time the CDI of interest was diagnosed (Table 2).

Modifications to IBD Management During CDI

Patients taking immunomodulators or tacrolimus at CDI diagnosis most often had their medication continued at the same dose. The 5-ASA derivatives and biologic agents were the most commonly de-escalated or discontinued medications, whereas corticosteroids were the most commonly added or escalated medications (Supplementary Table S2).

Clinical Outcomes up to 12 Months After CDI

Colon surgery

A total of 41 of 137 patients (18 with Crohn's disease, 22 with ulcerative colitis, and 1 with indeterminate colitis) underwent colon surgery ≤1 year after the CDI of interest. For both patients with Crohn's disease and those with ulcerative colitis, colon surgery was more common in individuals who had corticosteroid escalation than in those for whom corticosteroids were continued at the same dose or those who did not receive corticosteroids (Fisher exact test adjusted, $P < 0.02$) (Tables 4A and 4B).

Among all patients, corticosteroid escalation was further predictive of all-cause colon surgery within 1 year compared with no corticosteroid treatment on multiple linear regression analysis including age and CDI severity (odds ratio [OR], 5.94; 95% CI, 2.03–17.44) (Table 5). There was no significant difference in the rate of colon surgery with variations to immunomodulator therapy, biologic therapy, or antibiotic selection for CDI. In a separate analysis that was adjusted for immunomodulator de-escalation, corticosteroid escalation continued to be independently associated with increased incidence of colon surgery.

The median (range) age of patients undergoing colon surgery within 1 year was significantly lower than that of those who did not undergo colon surgery (41 [30–52] vs 50 [34–64], $P = 0.006$). On multiple regression analysis adjusting for CDI severity, younger age was predictive of colon surgery within 1 year ($P = 0.015$). Specifically, age >65 was associated with a decreased risk of colon surgery (OR, 0.09; 95% CI, 0.005–0.44).

TABLE 3B. Distribution of CDI Severity and 1-Year Adverse Outcomes by CDI Treatment for Patients with Ulcerative Colitis (n = 70)*

	No Treatment	Vanco	Metro	Both	Both+Rifa	N	*P* Value†
CDI severity							
Moderate	0 (0)	17 (34)	20 (40)	13 (26)	0 (0)	50	.49
Severe	0 (0)	2 (20)	5 (50)	2 (20)	1 (10)	10	
Severe-complicated	0 (0)	2 (20)	5 (50)	3 (30)	0 (0)	10	
Subsequent CDI						70	.97
No	0 (0)	12 (17)	19 (27)	11 (16)	1 (1)		
Yes	0 (0)	9 (13)	11 (16)	7 (10)	0 (0)		
Recurrent CDI						70	.93
No	0 (0)	18 (26)	25 (36)	16 (23)	1 (1)		
Yes	0 (0)	3 (4)	5 (7)	2 (3)	0 (0)		
CDI-related hospitalization						70	.07
No	0 (0)	17 (24)	30 (43)	17 (24)	1 (1)		
Yes	0 (0)	4 (6)	0 (0)	1 (1)	0 (0)		
IBD exacerbation						70	.88
No	0 (0)	10 (14)	17 (24)	10 (14)	1 (1)		
Yes	0 (0)	11 (16)	13 (19)	8 (11)	0 (0)		
Colon Surgery						70	.86
No	0 (0)	13 (19)	21 (30)	13 (19)	1 (1)		
Yes	0 (0)	8 (11)	9 (13)	5 (7)	0 (0)		

Abbreviations: both, vancomycin plus metronidazole; both+rifa, vancomycin plus metronidazole plus rifaximin; CDI, *Clostridium difficile* infection; IBD, inflammatory bowel disease; metro, metronidazole only; vanco, vancomycin only.
*Data are presented as No. (%).
†Fisher exact test.

On univariate analysis, severity of the CDI of interest, presence of anemia, or hypoalbuminemia did not influence the rate of colon surgery.

Previous CDI episodes, subsequent CDI episodes, related hospitalizations, and fecal microbiota transplantation

Of the patients, 46 (34%) had ≥1 subsequent CDI episode, 19 (14%) of which were classified as recurrent infections (Table 5). Ten patients (7%) were hospitalized at least once for an additional CDI. Five patients (11%) were empirically treated for a subsequent CDI episode without record of positive findings from a stool sample. History of CDI within 1 year or all-time history of CDI was not associated with increased incidence in subsequent CDI, recurrent CDI, CDI-related hospitalizations, or all-cause colon surgery in the year after the CDI of interest. No significant differences in the presence of subsequent CDI, recurrent CDI, or CDI-related hospitalizations were shown with variations to any IBD therapy, CDI antibiotic selection, or the presence of anemia or hypoalbuminemia. No significant associations were observed between age and subsequent CDI episodes or related hospitalizations. Four patients (3%) underwent fecal microbiota transplantation within 1 year of the CDI of interest.

IBD exacerbations

At least 1 subsequent IBD exacerbation not associated with CDI occurred in 67 (50%) patients (Tables 3A and 3B). The presence of IBD exacerbations after CDI was not significantly associated with variations to any IBD therapy, CDI antibiotic selection, or the presence of anemia or hypoalbuminemia. The median (range) age of patients with a subsequent IBD exacerbation ≤1 year was significantly lower than that of those without (44 [30–56] vs 49 [35–65] years, $P = 0.045$).

DISCUSSION

This retrospective study of IBD patients with CDI at a tertiary referral center aimed to identify specific predictors of adverse outcomes, including subsequent CDI episodes, colon surgery, and IBD exacerbation. We analyzed the effect of escalation and de-escalation of IBD medications in the setting of CDI and their influence on the incidence of adverse outcomes. We found that corticosteroid escalation was an independent predictor of colon surgery within 1 year of CDI. No correlation

TABLE 4A. Distribution of 1-Year Adverse Outcomes by IBD Medication Changes for Patients With Crohn's disease (n = 63)*

	Subsequent CDI		Recurrent CDI		IBD Exacerbation		Colon Surgery After CDI	
Medication Change†	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**
Corticosteroids‡,§								
Not given medication	20 (32)	7 (11)	25 (40)	2 (3)	15 (24)	12 (19)	24 (38)	3 (5)
Continued	4 (6)	2 (3)	4 (6)	2 (3)	3 (11)	3 (33)	3 (5)	3 (5)
Added or escalated	19 (30)	8 (13)	23 (37)	4 (6)	9 (14)	18 (29)	15 (24)	12 (19)
Discontinued or de-escalated	1 (2)	2 (3)	2 (3)	1 (2)	1 (2)	2 (3)	3 (5)	0 (0)
Immunomodulators¶								
Not given medication	32 (51)	11 (17)	38 (60)	5 (8)	18 (29)	25 (40)	30 (48)	13 (21)
Continued	9 (14)	6 (10)	13 (21)	2 (3)	6 (10)	9 (14)	12 (19)	3 (5)
Added or escalated	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Discontinued or de-escalated	3 (5)	2 (3)	3 (5)	2 (3)	4 (6)	1 (2)	3 (5)	2 (3)
Biologics‖								
Not given medication	33 (52)	13 (21)	40 (63)	6 (10)	23 (37)	23 (37)	33 (52)	13 (21)
Continued	7 (11)	2 (3)	8 (13)	1 (2)	2 (3)	7 (11)	7 (11)	2 (3)
Added or escalated	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	1 (2)	0 (0)	1 (2)
Discontinued or de-escalated	4 (6)	2 (3)	4 (6)	2 (3)	2 (3)	4 (6)	4 (6)	2 (3)
Unknown	0 (0)	1 (2)	1 (2)	0 (0)	1 (2)	0 (0)	1 (2)	0 (0)

*Data presented as No. (%) of N.
†Medication changes were at the time of infection.
‡Includes oral, rectal, and intravenous preparations.
§Colon surgery was more likely in patients with corticosteroid escalation at the time of CDI than in those who had corticosteroids continued at the same dose or those who were not prescribed corticosteroids ($P < 0.02$, Fisher exact test for colon surgery after CDI).
¶Includes azathioprine, 6-mercaptopurine, and methotrexate.
‖Includes infliximab, adalimumab, certolizumab, vedolizumab, and natalizumab.

was shown between escalation or de-escalation of other IBD medications at the time of CDI and the incidence of adverse events. Younger age was also associated with a higher incidence of colon surgery. Patients with severe or severe-complicated infections were significantly more likely to have corticosteroids escalated and immunomodulators de-escalated during CDI treatment, although CDI severity was not an independent predictor of colon surgery risk.

A CDI or IBD exacerbation with colitis often presents similarly. Therefore, it is recommended that all patients with IBD who have new onset or worsening diarrhea or bloody stools, or a combination of those, undergo CDI testing.[21–23] Patients with CDI and IBD pose a difficult management dilemma, both for CDI therapy and for determining whether to discontinue, continue, or initiate immunomodulators, biologics, or corticosteroids for IBD. A paucity of data exists for guiding management of an IBD exacerbation in patients who develop CDI.[24, 25] A survey of gastroenterologists showed split positions on the issue of adding immunosuppression when treating CDI in IBD, with 46% in favor and 54% choosing to treat with antibiotics alone.[26] Given limited evidence, it is recommended to begin CDI-directed therapy first and to consider initiating corticosteroids or escalating other IBD immunosuppressive medications if antibiotics alone do not elicit a clinical response.[27, 28]

Reports in the literature are inconsistent regarding the effect of immunosuppressive medications on disease-related outcomes of patients with IBD and CDI, with evidence of both harm and benefit. One small observational series noted lower rates of colectomy when corticosteroids were rapidly de-escalated soon after detection of CDI in patients with IBD.[16] Similarly, a European cohort study reported significantly lower colectomy rates and death among IBD patients treated with antibiotics alone for their CDI versus antibiotics plus IBD medications.[25] In that study, treatment with ≥1 IBD medication further increased the risk of adverse events among patients, irrespective of initial disease severity.[25] Conversely, a US study showed no increased risk of colon surgery or death with use of immunomodulators, corticosteroids, or biologic antitumor necrosis factor agents.[24] Rather, laboratory values such as anemia, hypoalbuminemia, and increased creatinine at the time of initial CDI diagnosis were predictive of future surgery and mortality.[24]

TABLE 4B. Distribution of 1-Year Adverse Outcomes by IBD Medication Changes for Patients With Ulcerative Colitis (n = 70)*

	Subsequent CDI		Recurrent CDI		IBD Exacerbation		Colon Surgery After CDI	
Medication Change†	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**
Corticosteroids‡,§								
Not given medication	12 (17)	10 (14)	18 (26)	4 (6)	12 (17)	10 (14)	19 (27)	3 (4)
Continued	13 (19)	8 (11)	19 (27)	2 (3)	10 (14)	11 (16)	16 (23)	5 (7)
Added or escalated	15 (21)	6 (9)	19 (27)	2 (3)	12 (17)	9 (13)	11 (16)	10 (14)
Discontinued or de-escalated	3 (4)	3 (4)	4 (6)	2 (3)	4 (6)	2 (3)	2 (3)	4 (6)
Immunomodulators¶								
Not given medication	33 (47)	23 (33)	47 (67)	9 (13)	30 (43)	26 (37)	38 (54)	18 (26)
Continued	7 (10)	4 (6)	10 (14)	1 (1)	6 (9)	5 (7)	9 (13)	2 (3)
Added or escalated	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Discontinued or de-escalated	3 (4)	0 (0)	3 (4)	0 (0)	2 (3)	1 (1)	1 (1)	2 (3)
Biologics‖								
Not given medication	36 (51)	23 (33)	50 (71)	9 (13)	32 (46)	27 (39)	42 (60)	17 (24)
Continued	4 (6)	2 (3)	5 (7)	1 (1)	1 (1)	5 (7)	5 (7)	1 (1)
Added or escalated	0 (0)	1 (1)	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)
Discontinued or de-escalated	3 (4)	1 (1)	4 (6)	0 (0)	4 (6)	0 (0)	1 (1)	3 (4)

*Data presented as No. (%) of N.
†Medication changes were at the time of infection.
‡Includes oral, rectal, and intravenous preparations.
§Colon surgery was more likely in patients with corticosteroid escalation at the time of CDI than in those who had corticosteroids continued at the same dose or those who were not prescribed corticosteroids ($P < 0.02$, Fisher exact test for colon surgery after CDI).
¶Includes azathioprine, 6-mercaptopurine, and methotrexate.
‖Includes infliximab, adalimumab, certolizumab, vedolizumab, and natalizumab.

TABLE 5. Adjusted Odds Ratio for Colon Surgery Risk of CS Modification Compared With No Treatment at CDI Diagnosis*

CS Treatment	Odds Ratio	*P* Value	95% Confidence Interval
CS continued at same dose	2.89	0.08	0.87–9.65
CS escalation	5.94	0.001	2.03–17.44
CS de-escalation	5.13	0.05	1.03–25.57

Abbreviation: CS, corticosteroid.
*Multivariate analysis adjusted for age and CDI severity.

Our study showed a higher rate of all-cause colon surgery for patients receiving corticosteroid escalation at the time of CDI but not for those with anemia or hypoalbuminemia. Anemia and hypoalbuminemia are known markers of disease severity in both CDI and IBD.[24, 29] It is likely that an association with individual markers was not seen because of the smaller sample size in our study. *Clostridium difficile* infection severity also correlated with worse diarrhea and abdominal pain symptoms, which likely led to the addition of corticosteroids. The association between colon surgery and corticosteroid escalation but not with CDI severity was also likely due to lack of a larger sample size. Furthermore, although anemia and hypoalbuminemia in our study were not associated with increased colon surgery or mortality rates as in prior studies, they were significantly more associated with severe and severe-complicated CDIs than with mild-moderate CDIs.

Non-IBD patients who develop CDI at an older age tend to be at higher risk of complications, including colectomy.[30, 31]

However, our study showed that the incidence of all-cause colon surgery at ≤1 year for IBD patients with CDI decreased with increasing age. One possible explanation for this finding is that older patients are less likely to be deemed appropriate surgical candidates in the setting of multiple comorbidities, that they are in a fragile general state of health, or that there are changing goals of care, or a combination of those factors. We also observed a significantly decreased incidence of subsequent IBD exacerbation ≤1 year of CDI with increasing patient age. This finding supports the suggestion of fewer recurrences and a less severe disease course in elderly patients with IBD, including those with later-onset disease and those with prevalent disease for multiple decades.[32–34]

The effect of immunosuppression on CDI development or severity in the presence or absence of underlying IBD also remains largely ill-defined, with nearly all available data from retrospective studies. Previous studies reported a significantly increased risk of CDI development with use of immunomodulators (6-mercaptopurine, azathioprine, or methotrexate),[16] corticosteroids, and antitumor necrosis factor agents.[35] Another study failed to show a clear association between corticosteroid use and subsequent IBD exacerbations in patients with CDI.[36] Studies of other patient populations with CDI have also identified immunosuppressive therapy in general as an independent risk factor for hypovolemia,[37] colon surgery secondary to infection, mortality,[38, 39] and infection relapse.[40] Analyses from the current study showed no effect of corticosteroid or immunomodulator use on CDI recurrence but did show a positive association among increasing CDI severity, corticosteroid escalation, and immunomodulator de-escalation. Given that CDI severity was in part defined by laboratory values taken ≤1 week of CDI, it is not clear whether these treatment modifications led to increased CDI severity or whether the associations reflect a tendency among providers to escalate exacerbation-directed IBD therapy and de-escalate immunosuppressive treatment with more severe CDIs.

Immunomodulator de-escalation for concern of adverse effects did not influence the increased incidence of colon surgery in the corticosteroid escalation cohort on multivariate analysis. One explanation for this finding is that 85% of patients receiving immunomodulators at the time of the CDI diagnosis were taking either azathioprine (74%) or 6-mercaptopurine (12%). The cytostatic metabolite of these 2 drugs, thioguanine nucleotide, has a half-life of up to 13 days.[41] Given that immunomodulators were reinstated within 8 weeks after CDI diagnosis in most cases, the potential adverse effect of immunomodulator discontinuation was considered minimal, as the drug continued to be pharmacologically active in most cases.

The current study has several notable strengths. First, we investigated the influence of a broad range of IBD medications on both CDI- and IBD-related adverse events. We accounted not only for the presence or absence of IBD medications in the setting of CDI development but also for how the medication regimen was adjusted when CDI treatment was initiated, including escalation and de-escalation of medication dosages. Though the retrospective nature of the study makes it impossible to draw causal relationships from its findings, the significant associations between corticosteroid escalation and all-cause colon surgery underscore the importance of initiating CDI-directed therapy first and limiting corticosteroid escalation to refractory cases as outlined by existing recommendations.[27, 28]

Limitations of this study largely stem from its retrospective design. A single PCR-based assay instead of a 2-step algorithm was used for CDI diagnosis, thereby raising the possibility of false-positive results due to misdiagnosis of asymptomatic carriers.[42] However, underlying diarrhea worsened in patients or new onset diarrhea occurred for patients with controlled IBD symptoms, and in this setting, the sensitivity and specificity of PCR assays are high (90% and 96%, respectively [42]). The use of PCR-based assays as diagnostic tests in this context are supported by current guidelines of the Infectious Diseases Society of America.[43] In addition, 6% of study patients had a prior CDI <56 days from the CDI of interest, making their current episode a recurrent infection, which is typically less responsive to treatment than a primary infection.[44] The influence of these patients on results of primary outcomes was assumed to be minimal, given their relatively small percentage of the entire cohort. Further, the retrospective study design limited our ability to accurately determine underlying IBD severity (using validated tools such as the Mayo Score or Crohn's disease Activity Index[45] for each patient and evaluate its influence on adverse outcomes. Additionally, few patients underwent fecal transplants in the year after the CDI of interest, and therefore, the effect of fecal transplantation on adverse outcomes could not be assessed.

Although multiple risk factors exist for CDI and are an important area of study, accounting for all major risk factors for CDI was not the main focus of this article. We focused on the risk factors for IBD outcomes in particular and on covariates associated with these outcomes, and we subsequently analyzed the effect of CDI-IBD management on adverse outcomes. Disease course and response to previous treatment are 2 important IBD-related covariates that were not addressed in this study.

CONCLUSION

In conclusion, through this retrospective cohort study, we aimed to identify predictors of adverse outcomes in patients with IBD who develop CDI. We found that the incidence of colon surgery within 1 year was significantly increased for patients who had corticosteroids added to or escalated in their treatment regimen during infection. Moreover, patients with increasing infection severity were also significantly more likely to have corticosteroids added or dose-escalated but also have their dosage of immunomodulators (eg, 6-mercaptopurine,

azathioprine, and methotrexate) discontinued or de-escalated. There were no significant differences in the rates of colon surgery, CDI recurrence, or IBD exacerbation at 1 year among patients treated with oral vancomycin, metronidazole, or both vancomycin and metronidazole. Prospective studies are needed to determine the optimal timing for initiation or dose-escalation of immunosuppressive therapy in patients with IBD and CDI. However, in the absence of current prospective data, these findings add to the understanding of CDI management in this high-risk population and can help guide patient care and future prospective research in the field.

SUPPLEMENTARY DATA

Supplementary data is available at *Inflammatory Bowel Diseases* online.

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