Escalation of Immunosuppressive Therapy for Inflammatory Bowel Disease Is Not Associated With Adverse Outcomes After Infection With *Clostridium difficile*

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Background: *Clostridium difficile* infection (CDI) is common in patients with inflammatory bowel disease (IBD), often leading to diagnostic confusion and delays in IBD therapy escalation. This study sought to assess outcomes after CDI in IBD patients exposed to new or escalated immunosuppressive therapy.

Methods: This multicenter retrospective cohort study included IBD patients with documented CDI at 4 academic medical centers. Data were abstracted from clinical databases at each institution. Outcomes at 30 and 90 days were compared between patients undergoing new or intensified immunosuppressive therapy and those without therapy escalation. Continuous variables were compared using *t* tests, and proportions using chi-square tests. Multivariable logistic regression was used to determine the association of individual variables with severe outcomes (including death, sepsis, and/or colectomy) within 90 days. Secondary outcomes included CDI recurrence, rehospitalization, worsening of IBD, and severe outcomes within 30 days.

Results: A total of 207 adult patients with IBD and CDI were included, of whom 62 underwent escalation to biologic or corticosteroid therapy (median time to escalation, 13 days). Severe outcomes within 90 days occurred in 21 (15.6%) nonescalated and 1 (1.8%) therapy-escalated patients. Serum albumin <2.5 mg/dL, lactate >2.2 mg/dL, intensive care unit admission, hypotension, and comorbid disease were associated with severe outcomes. Likelihood of severe outcomes was decreased in patients undergoing escalation of IBD therapy after CDI (adjusted odds ratio [aOR], 0.12) and increased among patients aged >65 years (aOR, 4.55).

Conclusions: Therapy escalation for IBD within 90 days of CDI was not associated with worse clinical outcomes. Initiation of immunosuppression for active IBD may therefore be appropriate in carefully selected patients after treatment of CDI.

Key Words: inflammatory bowel disease, Crohn's disease, ulcerative colitis, *Clostridium difficile*, immunosuppressive therapy

INTRODUCTION

Clostridium difficile infection (CDI) in patients with inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is frequent and increasing in incidence.[1, 2] *Clostridium difficile* infection is more frequent in patients with UC than CD[3] and is associated with adverse clinical outcomes, including IBD-related surgery and mortality.[4] Infection with the hypervirulent *C. difficile* strain B1/NAP1/027 is increased in patients with IBD as compared with the general population and may account for the observed increase in severe disease and mortality.[5] Additionally, IBD patients are more susceptible to recurrent CDI than the general population; it affects up to 40% of patients after an initial infection.[6] *Clostridium difficile* infection in IBD patients is associated with younger age, less prior antibiotic exposure, less frequent use of proton pump inhibitor medications, and more frequent outpatient acquisition than in the general population.[7, 8] Testing for

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CDI is advised for outpatients and inpatients presenting with signs or symptoms of IBD exacerbation.[9]

The management of CDI in IBD patients is challenging due to overlapping symptoms of both conditions. Determination of causality for increased clinical symptoms is made more complex by difficulties in differentiating between *C. difficile* colonization and active infection with toxigenic organisms.[10] Data regarding the management of immunosuppressive medications after CDI in IBD patients are inconclusive. A retrospective cohort study of 155 IBD patients with CDI found that those patients receiving immunomodulatory therapy in addition to antibiotics had an increase in adverse outcomes as compared with patients on antibiotic therapy alone.[11] Corticosteroid use within 2 weeks of CDI diagnosis among hospitalized patients has also been associated with a 2-fold increase in mortality.[12]

A single-center study in 60 hospitalized patients with IBD and CDI found that patients receiving corticosteroids before admission who did not continue steroid therapy while receiving antibiotic therapy for CDI were less likely to achieve 6-month steroid-free remission, although those receiving intravenous corticosteroids and antibiotics during this time had a longer length of hospital stay and a trend toward increased colectomy at 12 months.[14] In contrast, a study of 294 hospitalized IBD patients with CDI did not find an association between the use of tumor necrosis factor (TNF) antagonists, immune modulators, or corticosteroids and severe CDI.[13]

Given these contradictory data, appropriate management of IBD with immunosuppression after CDI remains uncertain. This is reflected in the 2013 American College of Gastroenterology Guideline on CDI, which suggests that initiation or dose escalation of corticosteroids or anti-TNF-α therapy "probably should be avoided" for 72 hours after initiating antibiotic therapy for CDI, a conditional recommendation based on low-quality evidence.[9]

Although in theory the initiation or intensification of immunosuppressive medications after CDI may place patients at risk for infectious complications, delays in treatment of IBD and subsequent active inflammatory disease also place patients at risk for adverse clinical outcomes and disease progression. This multicenter retrospective study sought to assess 90-day outcomes in IBD patients undergoing initiation or dose escalation of immunosuppressive therapies after CDI after the initiation of appropriate antibiotic therapy for *C. difficile*.

METHODS

Subjects and Variables

Patients with an established diagnosis of IBD (CD, UC, or indeterminate colitis) with at least 1 positive assay for *Clostridium difficile* by any testing method were identified using patient databases and/or electronic medical record search using ICD-9 and ICD-10 codes, with confirmation by manual chart review, in accordance with the protocols approved by the institutional review board at each site. Participating centers included Montefiore Medical Center (Bronx, NY, USA), New York Presbyterian Hospital–Columbia University Medical Center (New York, NY, USA), New York University Langone Medical Center (New York, NY, USA), Northwell Health Lenox Hill Hospital (New York, NY, USA), and Northwell Health North Shore University Hospital/Long Island Jewish Medical Center (Manhasset, NY, USA). Patient demographic, laboratory, medication, and clinical outcomes were abstracted for analysis. Assays for *C. difficile* varied by institution. The majority of institutions utilized testing with enzyme immunoassay (EIA) for glutamate dehydrogenase (GDH), followed by reflex to toxin testing and/or polymerase chain reaction (PCR) for toxin if this was positive, although some centers performed PCR testing only (NYU, NSUH outpatients). Recurrence of CDI was defined as a new discrete episode of infection after resolution of a prior infection using clinical documentation from patient chart review.

Outcomes

The primary outcome was the occurrence of severe outcomes, which was defined as death, colectomy, and/or sepsis within 90 days of the most recent positive *C. difficile* assay. Secondary outcomes of interest included CDI recurrence, rehospitalization among patients diagnosed with CDI in the inpatient setting, worsening of IBD after CDI as determined by physician assessment and/or endoscopic or radiographic findings, and 30-day occurrence of severe outcomes. The time from CDI diagnosis to specified outcomes of interest and to initiation of therapy was determined from the last positive *C. difficile* assay. Therapy escalation was defined as initiation of new corticosteroid or biologic medication or an increase in pre-CDI dose of these medications.

Complicated CDI was defined as patients meeting at least 1 of the following criteria: admission to an intensive care unit, hypotension (mean arterial pressure <65 mmHg), ileus and/or significant abdominal distension, mental status change, or serum lactate >2.2 mmol/L. Hypoalbuminemia was defined as albumin <2.5 mg/dL. Elevated C-reactive protein (CRP) and ESR were defined as >1 mg/dL and >20 mm/h.

Statistical Analyses

Continuous variables were compared between groups using the *t* test. Categorical variables were compared using the Pearson chi-square test or the Fisher exact test. Bivariate associations were performed to compare clinical CDI outcomes at 30 and 90 days between groups that received and did not receive escalation of IBD therapy. Multivariable logistic regression was performed to determine the relationship between severe outcomes and escalation of immunosuppressive therapy after adjusting for covariates. Variables included in the multivariable analysis include status of IBD medication escalation, inpatient status, and age. Other variables, including laboratory markers

and comorbidities, were excluded due to limited numbers of outcomes within the patient cohort.

RESULTS

A total of 207 adult patients with a confirmed diagnosis of IBD were identified with at least 1 positive assay for *C. difficile.* Patient demographics are listed in Table 1. The median age of the cohort was 42.8 ± 19.8 years, 94 (45.4%) were male, and 158 (76.3%) were diagnosed with CDI in the inpatient setting. Thirty patients (14.6%) had a prior CDI (more than 30 days before the current infection). Proton pump inhibitor use within 1 month (n = 39, 18.8%) and exposure to antibiotics within 3 months before CDI (n = 68, 32.9%) were recorded in a minority of patients. Thirty-one patients (15.0%) were classified as having complicated CDI, as determined by clinical and laboratory parameters described in the "Methods." Prior exposure to various IBD therapies is detailed in Supplementary Table 1.

Sixty-two patients (30.0%) underwent escalation of IBD therapy within 90 days of the last positive *C. difficile* assay, of whom 41 (66.1%) were escalated in the inpatient setting. Details of therapy initiated within 30 and 90 days after CDI diagnosis are indicated in Table 2. By 90 days, corticosteroids and biologic therapy were initiated in 28 (13.7%) and 30 patients (14.7%), respectively, with an additional 4 patients (2.0%) receiving combination therapy with both biologic and immunomodulator therapy. The median time to escalation of IBD therapy (range) was 13 (0–90) days, with escalation for 21 patients, representing 33.9% of those in the therapy escalation cohort, occurring within 7 days (Fig. 1).

A composite of "severe outcomes," including death, sepsis, and/or colectomy, was used to assess differences among groups. Within 30 days after CDI diagnosis, 44 patients underwent therapy escalation (Supplementary Table 2), with severe outcomes occurring in 1 (2.3%) patient in the escalation cohort, as compared with 15 (9.2%) patients in the nonescalation cohort. With the exception of more frequent worsening of IBD, as determined by physician assessment (including history and

TABLE 1. Patient Demographics

		Total	n = 207
Demographic	No.	No.	%
Age, mean (SD), y	207	42.8 (19.8)	
Male sex	207	94	45.4
Inpatient CDI diagnosis	207	158	76.3
Ethnicity	197[a]		
Caucasian		94	47.7
African American		47	23.9
Hispanic or Latino		32	16.2
Asian or Pacific Islander		13	6.6
Other		11	5.6
CDI treatment	207		
PO metronidazole		90	45.2
PO + IV metronidazole		16	8.0
PO vancomycin		85	42.7
Fecal microbiota transplant		1	0.5
Combination or other		7	3.5
Unknown		8	4.0
Mean duration of IBD (SD), y	172[a]	7.6 (9.6)	
IBD subtype	207		
Crohn's disease		91	44.2
Ulcerative colitis		111	53.9
Indeterminate colitis		4	1.9
Unknown		1	0.5
Prior *C. difficile* infection	206[a]	30	14.6
PPI use past mo	207	39	18.8
Antibiotic use past 3 mo	200[a]	68	32.9
Complicated *C. difficile* infection[b]	207	31	15.0
Current IBD therapy			
Aminosalicylates[c]	205[a]	156	76.1
Corticosteroids	205[a]	48	23.4
Immunomodulators	204[a]	13	6.4
Biologics	205[a]	20	9.8
Escalation of therapy (within 90 d)	204[a]	62	31.4

Abbreviations: IV, intravenous; PO, postoperative; PPI, proton pump inhibitor.
[a]Values smaller than 207 reflect missing data for specific demographic variables.
[c]Complicated CDI was defined as patients meeting at least 1 of the following criteria: admission to an intensive care unit, hypotension, ileus and/or significant abdominal distension, mental status change, or serum lactate >2.2 mmol/L.
[b]Current or past use of aminosalicylates.

TABLE 2. Therapy Escalation After CDI

Type of Therapy		No.	%
Escalation of therapy (within 30 d)		44	22.6
Corticosteroids		24	11.8
Biologics[a]	Total	18	8.8
	Infliximab	10	4.8
	Adalimumab	1	0.5
	Vedolizumab	6	2.9
Combination therapy[b]		2	1.0
Escalation of therapy (within 90 d)		62	30.4
Corticosteroids		28	13.7
Biologics[c]	Total	30	14.7
	Infliximab	13	6.3
	Adalimumab	5	2.4
	Vedolizumab	10	4.8
Combination therapy[b]		4	2.0

The type of therapy initiated or escalated in patients after CDI is listed for patients undergoing therapy intensification within 30 and 90 days after last positive assay for CDI.
[a]One biologic type is unknown.
[b]Combination therapy indicates both immune modulator and biologic medication.
[c]Two biologic types are unknown.

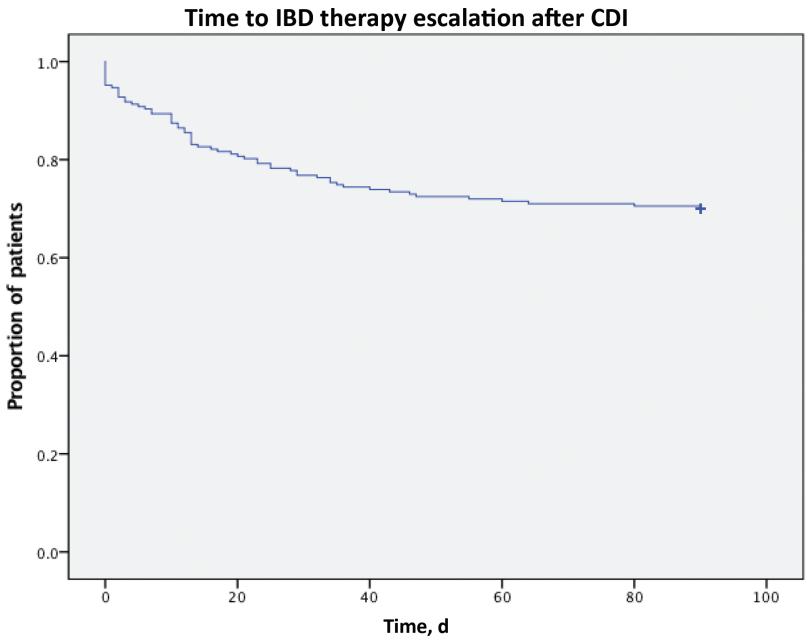

FIGURE 1. Time from last positive *C. difficile* assay to escalation of IBD therapy.

physical examination findings, laboratory assessment, endoscopy, and/or radiologic studies), within the escalation cohort (36.4% vs 17.3%; $P < 0.01$), there were no significant differences between primary and secondary outcomes (severe outcomes, recurrence of CDI, or rehospitalization) between groups at 30 days. There was a trend toward decreased length of hospital stay in the escalation cohort (4.3 days vs 5.2 days; $P = 0.49$).

At 90 days (Table 3), severe outcomes occurred in 21 (15.6%) patients in the nonescalated cohort and 1 (1.8%) patient in the cohort undergoing therapy escalation ($P < 0.01$). In addition to the composite end point of severe outcomes, sepsis as an individual outcome was significantly increased within the nonescalated cohort (n = 15, 11.2%, vs n = 1, 1.8%; $P = 0.04$). One patient undergoing escalation from oral to intravenous corticosteroids developed sepsis and underwent colectomy 8 days after diagnosis with CDI.

There was no difference in *C. difficile* recurrence or rehospitalization among patients undergoing therapy escalation as compared with no escalation (Table 4). Twenty-five patients (41.7%) within the escalation cohort had worsening of IBD activity, nearly double that of nonescalated patients (n = 28, 21.2%; $P < 0.01$). Type of therapy escalation (corticosteroids vs biologic) was not associated with worsening of IBD, but there was a nonsignificant trend toward higher rehospitalization in those escalated to corticosteroids (n = 7, 31.3%, vs n = 5, 15.2%; $P = 0.19$), and CDI recurrence was numerically greater in patients escalated to biologics (n = 5, 15.2%, vs n = 0, 0.0%; $P = 0.07$) (Table 5). Four patients who developed recurrent CDI were treated with anti-TNF agents and 1 with vedolizumab. Of note, all adverse events, including recurrence of CDI, rehospitalization, and worsening of IBD activity within the escalation cohort, were observed in patients undergoing escalation at least 1 week after CDI.

Bivariate analysis was performed to determine associations between variables of interest and severe outcomes (Table 6). Laboratory findings associated with severe outcomes were elevated serum lactate and hypoalbuminemia, but not elevated serum or stool markers of inflammation, including CRP, ESR, and fecal calprotectin. Clinical variables significantly associated with the occurrence of severe outcomes were systemic hypotension, ileus and/or abdominal distension, mental status change, and admission to an intensive care unit, all of which were also variables included as criteria for the composite variable complicated CDI. Patients with severe outcomes were significantly older than those with nonsevere outcomes (median age ± SD, 58.1 ± 24.3 vs 40.1 ± 18.4 years; $P < 0.01$). Although the presence of 1 or more comorbid medical conditions was not associated with the occurrence of severe outcomes (nonescalation cohort: n = 117, 68.4%; escalation cohort: n = 17, 77.3%; $P = 0.40$), cardiovascular disease, chronic kidney disease, and rheumatologic disease were significantly associated with severe outcomes. Malignancy, other gastrointestinal conditions, pulmonary disease, genitourinary disease, hematologic conditions, neuropsychiatric disorders, and other autoimmune diseases were not associated with severe outcomes (Table 7).

To investigate differences in clinical status of patients undergoing therapy escalation vs those not receiving intensified IBD therapy, surrogate markers of IBD disease activity and of the severity of CDI were compared between these 2 groups (Supplementary Table 3). There were no significant

TABLE 3. 90-Day Clinical Outcomes According to IBD Therapy Escalation After CDI

Outcome Within 90 d	No Escalation (n = 142[a])	Escalation (n = 62[a])	*P*
Death (n = 194[b])	7 (5.2)	0 (0.0)	0.10
Sepsis (n = 191[b])	15 (11.2)	1 (1.8)	0.04
Colectomy (n = 191[b])	9 (6.8)	1 (1.7)	0.29
Severe outcome[c] (n = 192[b])	21 (15.6)	1 (1.8)	<0.01

The number of patients experiencing death, sepsis, colectomy, or a composite (severe outcome) within 90 days is listed according to the presence of therapy escalatation. Percentages are listed within parentheses.
[a]Therapy escalation data missing for 3 subjects (n = 204).
[b]Values smaller than 204 reflect further missing data for specific outcome variables.
[c]Severe outcomes were defined as death, sepsis, and/or colectomy.

TABLE 4. Secondary Outcomes According to Treatment Escalation. Frequency of Secondary Outcomes According to Therapy Escalation

	No Escalation, No.	n = 142,%	Escalation,No.	n = 62,%	Total, No.	n = 204,[a] %	*P*
CDI recurrence (n = 188[b])	8	6.1	5	8.8	13	6.9	0.54
Worsening of IBD (n = 192[b])	28	21.2	25	41.7	53	27.5	<0.01
Rehospitalization (n = 187[b])	29	22	12	21.8	41	21.9	0.98

TABLE 5. Secondary Outcomes According to Treatment Escalation. Frequency of Secondary Outcomes According to Escalation to Corticosteroids or Biologic Therapy

	Escalation to Corticosteroids, No.	n = 28, %	Escalation to Biologics, No.	n = 34, %	P
CDI recurrence	0	0.0	5	15.2	0.07
Worsening of IBD	13	48.2	12	36.4	0.36
Rehospitalization	7	31.8	5	15.2	0.19

[a]Therapy escalation data missing for 3 subjects.
[b]Values smaller than 204 reflect further missing data for specific outcome variables.

differences in these variables between patients undergoing therapy escalation and those not escalated, including leukocytosis (n = 11, 18.3%, vs n = 30, 21.7%; *P* = 0.59), elevated serum creatinine (n = 2, 3.4%, vs n = 5, 3.6%; *P* = 1.00), intensive care unit (ICU) admission (n = 1, 1.6%, vs n = 7, 5.1%; *P* = 0.44), hypotension (n = 1, 1.6%, vs n = 6, 4.4%; *P* = 0.68), or the presence of complicated CDI (n = 6, 9.7%, vs n = 24, 16.9%; *P* = 0.18). Additionally, no difference between baseline ESR/CRP, stool calprotectin, serum lactate, or serum albumin was detected between groups, although data for these indicators of disease activity were not available for >10% of the patients in the cohort. Lastly, there was no difference between the escalation and nonescalation cohorts in the rate of recurrent CDI (11.3% vs 16.2%; *P* = 0.36) (data not shown).

The primary and secondary outcomes were also assessed according to timing of initiation of biologic therapy (Supplementary Table 4). There were no severe outcomes among patients exposed to biologic medications. All adverse events (CDI recurrence, rehospitalization, and worsening of IBD) occurred in patients undergoing therapy escalation at least 1 week after CDI, with no occurrence of any of the secondary outcomes among patients receiving new biologic therapy within 7 days of CDI.

An adjusted logistic regression model was created to assess the effect of individual variables of interest on the development of severe outcomes after CDI (Table 7). Escalation of IBD therapy within 90 days of CDI was protective against severe outcomes when adjusting for other covariates (adjusted odds ratio [aOR], 0.12; 95% confidence interval [CI], 0.02–0.94). Age >65 years was significantly associated with the occurrence of severe outcomes (aOR, 4.55; 95% CI, 1.37–15.12).

DISCUSSION

In this real-world cohort of patients with IBD and infection with *Clostridium difficile*, escalation of immunosuppressive

TABLE 6. Bivariate Association of Clinical and Laboratory Variables With Severe Outcomes After CDI (n = 193[a])

	Nonsevere Outcome, No.	n = 171, %	Severe Outcome,No.	n = 22, %	*P*
Lactate > 2.2 (n = 123[b])	4	3.8	6	35.3	<0.01
Albumin < 2.5 (n = 181[b])	8	5.0	4	19.1	0.04
ICU admission (n = 190[b])	1	0.6	6	27.3	<0.01
Hypotension (MAP < 65) (n = 190[b])	2	1.2	4	18.2	<0.01
Ileus/abdominal distension (n = 192[b])	13	7.7	5	22.7	0.04
Mental status change (n = 192[b])	1	0.6	2	9.1	0.04
Complicated CDI[c] (n = 193)	19	11.1	10	45.5	<0.01
Age, mean (SD) (n = 193), y	40.1 (18.4)		58.1 (24.3)		<0.01
Inpatient (n = 193)	128	74.9	21	95.5	0.03
Presence of 1 or more comorbidities (n = 193)	117	68.4	17	77.3	0.4
Cardiovascular disease (n = 193)	29	17.0	11	50.0	<0.01
Chronic kidney disease (n = 193)	9	5.3	4	18.2	<0.01
Rheumatologic disease (n = 193)	5	2.9	4	18.2	0.01

[a]Severe outcome data missing for 14 subjects.
[b]Values smaller than 193 reflect further missing data for specific clinical and laboratory variables.
[c]Complicated CDI was defined as patients meeting at least 1 of the following criteria: admission to an intensive care unit, hypotension, ileus, and/or significant abdominal distension, mental status change, or serum lactate >2.2 mmol/L.

TABLE 7. Adjusted Logistic Regression Model for Severe Outcomes (n = 192[a])

	Adjusted Odds Ratio	95% CI
Escalated treatment within 90 d	0.12	0.02–0.94
Inpatient status	5.29	0.66–42.20
Age[b]		
35–65 y	2.00	0.64–6.26
>65 y	4.55	1.37–15.12

Odds ratio adjusted for the other covariates presented in the table.
[b]Age <35 years used as the reference group.
[a]Data were missing for 15 patients for the outcome variable and/or the covariates that were used during adjustment.

therapy with corticosteroids or biologic agents was not associated with adverse events. The occurrence of severe outcomes, including death, sepsis, and/or colectomy at 90 days, was almost exclusively observed in patients in whom IBD therapy was not escalated after CDI diagnosis. Although it is not possible from this retrospective study to attribute improvement in clinical outcomes directly to therapy escalation, it could be speculated that a subset of patients in whom IBD activity remains significant after antibiotic therapy for *C. difficile* may benefit from intensified therapy with corticosteroids or biologic agents. Delaying treatment of active IBD symptoms in patients in whom therapy is required may risk the development of adverse outcomes, including sepsis, colectomy, and/or death.

One potential explanation for the observed differences in outcomes among patients in the escalation cohort is patient selection. Indeed, the therapy escalation cohort had a higher proportion of patients with increased IBD disease activity after CDI, suggesting that intensification of therapy was clinically indicated in this group (Table 4). However, markers of IBD severity at baseline were not significantly different between the nonescalation and escalation cohorts (Supplementary Table 3). Additionally, although nonsignificant, there was a trend toward more complicated CDI and recurrent CDI within the nonescalation cohort, which might explain why some patients were not recommended for IBD treatment intensification. It is likely that escalation was not appropriate for some patients, including those in whom sepsis, other infection, or end-organ involvement was a contraindication for such therapy. The presence of systemic illness in these patients may be associated with abnormalities in inflammatory markers, hemoglobin, and albumin, but these parameters do not necessarily indicate active IBD. However, it is also possible that delay in treatment escalation in some *C. difficile*–positive patients due to concern for complications of immunosuppressive therapy prevented timely treatment of active IBD, thereby leading to complications of CDI and/or IBD.

Consistent with previous studies in IBD patients,[13] we identified hypoalbuminemia and advanced age to be associated with worse outcomes after CDI. Additionally, patients with comorbid cardiovascular, renal, or rheumatologic disease more frequently had severe outcomes after CDI. These conditions have not been previously described as risk factors for severe CDI, and further data are needed to determine their association with adverse outcomes in IBD patients after CDI.

Due to the low number of severe outcomes after therapy escalation after CDI diagnosis, it is not possible to draw major conclusions regarding the relative safety of individual

immunosuppressive therapies. There was no difference in rehospitalization or worsening IBD activity in patients escalated to corticosteroids vs biologic therapies. There was a numeric difference in CDI recurrence between those escalated to corticosteroids vs biologics (0% vs 15.2%; $P = 0.07$). In contrast with the results of an analysis of CDI recurrence from the Food and Drug Administration Adverse Events Reporting System,[15] we did not find an increase in CDI recurrence in vedolizumab-exposed patients as compared with those receiving anti-TNF biologic therapy. These findings are limited by the small numbers of patients experiencing recurrent CDI and relatively short follow-up period.

A key question regarding the use of immunosuppressive medications after CDI is the timing of therapy initiation. Although it was not possible to draw conclusions regarding the optimal timing of therapy from this study, more than half of patients in the escalation cohort were initiated within 2 weeks of the last positive *C. difficile* assay. All patients undergoing therapy escalation within 7 days of CDI (n = 21) were treated with corticosteroids. One patient was initiated on both corticosteroids and adalimumab therapy 3 days after CDI and did not experience an adverse outcome. The 1 patient experiencing a severe outcome from the escalation cohort developed sepsis after transitioning from oral to intravenous corticosteroids 2 days after diagnosis of CDI, and subsequently underwent colectomy after salvage infliximab therapy was unsuccessful. Only 1 patient was escalated to biologic therapy within 7 days of CDI.

The strengths of this study include the use of a large, multicenter cohort of real-world patients encompassing a diverse patient population. This study adds to current knowledge by assessing a broad number of clinical outcomes after CDI in both inpatient and outpatient populations exposed to a variety of immunosuppressive medications. The small event rate for the primary outcome of interest limited the ability to perform multivariable analyses including additional variables. Although this is the largest cohort study to our knowledge to assess clinical outcomes in IBD patients undergoing treatment escalation after CDI, an increased cohort size would be needed to detect differences among type of immunosuppressive therapy and the timing of therapy initiation with outcomes. Lastly, in this retrospective cohort, CDI was defined as any positive assay for *C. difficile*, including PCR-based assays and EIA for toxin A/B and/or GDH. Distinction of active, toxin-producing infection from asymptomatic colonization was therefore not possible, and it is difficult to determine whether patients with IBD and a positive assay who had gastrointestinal symptoms were symptomatic of infection, active IBD, and/or both. Although the optimal method for making the determination of active infection vs colonization is not known, data suggest that detection of stool toxin with a cytotoxicity neutralization assay correlates with a higher bacterial load of *C. difficile* than GDH-based methods (Sorrentino et al. 2017), and could be used to assess symptomatic CDI in future prospective studies.

In conclusion, initiation of new immunosuppressive therapy or intensification of prior therapy for IBD in the setting of recent CDI was not associated with the occurrence of severe outcomes, including death, sepsis, and/or colectomy. In carefully selected patients without contraindications to dose escalation, treatment of active IBD with immunosuppressive medication appears to be safe. Our data are consistent with current ACG guidelines suggesting that early initiation of IBD-directed therapy is appropriate once suitable antibiotic treatment has been initiated.[9] The optimal timing and type of therapy escalation after CDI remain unknown, and prospective data are needed to further inform clinical decision-making in this setting.

SUPPLEMENTARY DATA

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

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