Clostridioides Difficile Infection Is a Rare Cause of Infectious Pouchitis

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Keywords

Clostridioides difficile · Ileal pouch anal anastomosis · Pouchitis · Cuffitis

Abstract

Introduction: The true incidence of *Clostridioides difficile* infection (CDI) in patients with an ileal pouch is unknown, and there is little published on its associated risk factors. **Objective:** We aimed to evaluate the rate and risk factors of CDI in pouch patients. **Methods:** This was a retrospective review conducted at a single tertiary care inflammatory bowel disease (IBD) center. All ulcerative colitis or IBD-unspecified (IBD-U) patients who underwent total proctocolectomy with ileal pouch anal anastomosis for medically refractory disease or dysplasia between 2008 and 2017 were identified. Symptomatic patients tested for CDI were included. Demographic, disease, and surgical characteristics were collected. Non-parametric methods were used to compare continuous outcomes, and χ^2 and Fisher's exact tests were used to compare patients with and without CDI as appropriate. **Results:** A total of 154 pouch patients had postoperative *C. difficile* stool testing for symptoms of fever, urgency, increased stool frequency, hematochezia, incontinence, and abdominal and/or pelvic pain. CDI was diagnosed in 11 (7.1%) patients a median of 139 days (IQR 34–1,170) after the final surgical stage.

Ten patients (90.9%) received oral vancomycin for 10 days and 1 patient (9.1%) received oral metronidazole for 2 weeks. Ten patients (90.9%) reported improvement in symptoms at completion of therapy. Nine patients (81.8%) were retested for CDI for recurrent symptoms and found to be negative. No patient had CDI recurrence. There was no significant difference in demographic and surgical characteristics, previous antibiotic or proton pump inhibitor use, or previous hospital admission among the patients with and without CDI. **Conclusions:** CDI is a rare cause of infectious pouchitis and treatment with oral vancomycin improves symptoms.

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Introduction

Approximately 10–15% of ulcerative colitis (UC) patients will require surgery during their disease course for medically refractory disease or dysplasia [1, 2]. The preferred surgery is staged total proctocolectomy (TPC) with ileal pouch anal anastomosis (IPAA) and is associated with improved quality of life and good long-term functional outcomes [3–6].

Pouchitis is the most common complication after IPAA with cumulative incidence rates of 25% at 1 year, 35% at 3 years, and 45% at 5 years [7]. In the majority

of patients, pouchitis is idiopathic and is associated with dysbiosis of the pouch microbiome in the setting of mucosal metaplasia [8]. In a subset of patients, pouchitis is secondary to specific causative factors such as *Clostridioides difficile* infection (CDI), cytomegalovirus infection, NSAID use, ischemia, or autoimmune disorders [9].

There is little data published on the incidence and risk factors of CDI of the pouch. Three previous studies have reported pouch CDI rates of 10–18% and associated risk factors such as male gender, preoperative left-sided colitis, and medical comorbidities [10–12]. Common risk factors for CDI in the general population such as antibiotic use, immunosuppression, or gastric acid suppression therapy have not been associated with CDI of the pouch [10–12].

Less is known about the impact of CDI of the pouch on clinical outcomes. The treatment of CDI with metronidazole and/or vancomycin has been associated with clinical improvement of pouchitis symptoms; however, recurrence rates as high as 57% have been reported [10, 11]. A single-center retrospective review identified 15 pouch patients with CDI, only one of whom required temporary loop ileostomy due to refractory disease [13]. There have been no studies since that have examined the impact of CDI on pouch failure.

Given the limited available data, the aims of this study were to describe the rate and associated risk factors of CDI in pouch patients.

Methods

Study Population

We performed a retrospective analysis of a cohort of pouch patients from a large tertiary care inflammatory bowel disease (IBD) center. All UC or IBD-unspecified (IBD-U) patients who underwent TPC with IPAA for medically refractory disease or dysplasia between January 2008 and December 2017 were identified through hospital electronic medical records. Patients less than 18 years of age at the time of colectomy were excluded.

Data Collection and Variables

Clinical information was abstracted from the medical record using a standardized data collection sheet. Collected patient demographics and disease characteristics included sex, age at colectomy, BMI at colectomy, preoperative diagnosis (UC or IBD-U), preoperative extent of disease, diagnosis of primary sclerosing cholangitis, medical comorbidities (hypertension, hyperlipidemia, diabetes, chronic kidney disease, and/or cirrhosis), and preoperative CDI. Collected surgical characteristics included indication, procedures and stages, type of anastomosis (handsewn or stapled), and length of residual cuff. All postoperative *C. difficile* stool studies,

indications, results, and prescribed medications were recorded. Antibiotic or proton pump inhibitor use within the 6 weeks before, and hospital admissions within the 3 months before, *C. difficile* stool testing were recorded.

Outcomes

Acute CDI pouchitis was defined as symptoms of fever, urgency, increased stool frequency, hematochezia, incontinence, and abdominal and/or pelvic pain in the setting of a positive result on enzyme immunoassay (EIA) for toxin A/B or nucleic acid amplification testing (NAAT) for toxin A/B. Chronic pouchitis was defined as the aforementioned symptoms lasting longer than 4 weeks and requiring chronic antibiotic or anti-inflammatory therapy, with four or more episodes per year. [14] Pouch failure was defined as the construction of a permanent end ileostomy, with or without pouch excision. [14]

Statistical Analysis

Descriptive statistics were performed to describe baseline characteristics of the study population and were reported as proportions or medians (with interquartile range, IQR) for categorical and continuous variables, respectively. Nonparametric methods were used to compare continuous outcomes and χ^2 and Fisher's exact tests were used to compare patients with and without CDI as appropriate. A significance level cutoff of <0.05 was established a priori. SPSS version 24 (IBM Corp., Armonk, NY, USA) was used for all analyses. Further results were stratified between the two test types NAAT and EIA for a positive CDI test.

Results

A total of 621 patients aged 18 years or older underwent TPC with IPAA between January 2008 and December 2017. Of these, 205 (52.1%) developed symptoms of fever, urgency, increased stool frequency, hematochezia, incontinence, and abdominal and/or pelvic pain during a median length of follow-up of 3.9 years (IQR 2.0–6.4) after the final surgical stage. *C. difficile* stool testing was performed in 154/205 patients (75.1%) via EIA for toxin A/B or NAAT for toxin A/B. Patient demographic and surgical characteristics are given in Table 1. The majority of patients were male (54.5%) and had a preoperative diagnosis of UC (92.9%). Colectomy indication was medically refractory disease in 124/154 patients (80.5%) and dysplasia in 3/154 (19.5%). The most common procedure was the three-stage restorative proctocolectomy, performed in 90/154 patients (58.4%).

CDI was diagnosed in 11 patients (7.1%) a median of 139 days (IQR 34–1,170) after the final surgical stage. CDI diagnosis was made via EIA for toxin A/B in 5/11 patients (45.5%) and NAAT for toxin A/B in 6/11 (54.5%). Only one patient had pouchoscopy at the time of diagnosis that revealed ulceration, erythema, and friability of the pouch

Table 1. Clinical characteristics of symptomatic IPAA patients with *Clostridioides difficile* stool testing (*n* = 154)

Sex	
Male	86 (55.8)
Female	68 (44.2)
Age at colectomy, years	37 (27–51)
BMI at colectomy, kg/m ²	22.2 (18.9–26.7)
Preoperative diagnosis	
Ulcerative colitis	144 (93.5)
IBD-U	10 (6.5)
Disease extent	
Left-sided	23 (16.1)
Extensive	120 (83.9)
PSC	8 (5.2)
Medical comorbidities	98 (63.6)
Preoperative CDI	10 (12.3)
Surgical indication	
Medically refractory disease	124 (80.5)
Dysplasia	30 (19.5)
Stages	
One-stage IPAA	7 (4.5)
Two-stage IPAA	57 (37.0)
Three-stage IPAA	90 (58.4)
Anastomosis	
Stapled	122 (79.2)
Handsewn	32 (20.8)

Data are presented as *n* (%) or median (interquartile range), as appropriate. BMI, body mass index; IBD-U, inflammatory bowel disease unspecified; PSC, primary sclerosing cholangitis; CDI, *Clostridioides difficile* infection; IPAA, ileal pouch anal anastomosis. One-stage IPAA: total proctocolectomy with IPAA construction during one procedure. Two-stage IPAA: total proctocolectomy with immediate IPAA construction and diverting ileostomy with subsequent ileostomy closure. Three-stage IPAA: subtotal colectomy with end ileostomy followed by completion proctectomy with IPAA construction and diverting ostomy 3–6 months later, and subsequent ostomy closure.

without pseudomembranes. No patient met the criteria for severe CDI or required admission for CDI management. Diagnostic stool studies were not positive for other infectious pathogens at the time of sampling.

Of the 11 patients diagnosed with CDI, 10 (90.9%) received oral vancomycin for 10 days and 1 (9.1%) received oral metronidazole for 2 weeks. Ten patients (90.9%) (9 post-vancomycin use, 1 post-metronidazole use) reported improvement in symptoms of fever, urgency, frequency, hematochezia, incontinence, and abdominal and/or pelvic pain. Patients who tested negative for CDI did not receive vancomycin. The median length of follow-up for CDI patients was 4.7 years (IQR 1.9–6.6). Nine patients (81.8%) developed recurrent symptoms and were retested for CDI; however, these were found to be negative. Of

these, 5 (55.6%) were empirically treated with ciprofloxacin for pouchitis with resolution of symptoms. No patient had CDI recurrence. One patient (8.3%) developed chronic pouchitis 400 days following CDI diagnosis and 1 patient (8.3%) had pouch failure 8 days following CDI diagnosis.

There was no significant difference in demographic and surgical characteristics, pre-colectomy CDI, previous antibiotic or proton pump inhibitor use, or previous hospital admission among the patients with and without CDI (Table 2). No patient with CDI had primary sclerosing cholangitis. The majority of patients with CDI (10/11, 90.9%) had a stapled surgical anastomosis, though this was not statistically significant. There was no significant difference in median rectal cuff length between patients with CDI and those without.

Discussion

We observed a 7% rate of CDI in symptomatic ileal pouch patients within the first 3 months after the final surgical stage and no associated predictive risk factors. All CDI patients were treated with oral vancomycin or metronidazole with significant improvement in clinical symptoms. No patients had CDI recurrence after treatment, and rates of chronic pouchitis and pouch failure were low in CDI patients.

Although *C. difficile* has traditionally been thought to be a colorectal mucosal pathogen, we found no significant difference in rectal cuff lengths or type of surgical anastomosis among patients with and without CDI. In pouch patients, fecal stasis during pouch construction promotes gut microbial dysbiosis, colonic metaplasia of the ileal mucosa, and activation of the innate and adaptive mucosal immune system [15, 16]. These factors independently increase the risk of pouchitis and may predispose to *C. difficile* colonization of the ileal pouch. Separately, *C. difficile* has been shown to be capable of small bowel colonization, toxin release, mucosal damage, and inflammation [17]. Thus, even though there is no remaining colon or significant rectum after IPAA, CDI remains a risk for pouch patients.

In comparison to previous smaller studies, we did not observe male gender, preoperative left-sided colitis, lower BMI, or medical comorbidities to be risk factors for pouch CDI [18, 19]. Common risk factors for CDI in the general population include recent antibiotic use, gastric acid suppression therapy use, and hospital admission; however, none of these were observed to be significantly associated with pouch CDI in our population [10–12].

Table 2. Univariable analysis among patients with and without *Clostridioides difficile* infection stratified by type of positive test

Characteristics	CDI + NAAT (n = 6)	CDI- (n = 143)	p value	CDI- (n = 143)	CDI + EIA (n = 5)	p value
Sex						
Male	4 (33.3)	80 (55.9)	0.70	80 (55.9)	2 (40.0)	0.66
Female	2 (66.7)	63 (44.1)		63 (44.1)	3 (60.0)	
Age at colectomy, years	33 (21.2–28.6)	37.0 (27–50)	0.41	37.0 (27–50)	58 (41.5–73.5)	0.16
BMI at colectomy, kg/m ²	27.5 (20.5–28.6)	22.2 (18.8–26.4)	0.28	22.2 (18.8–26.4)	23.5 (22.0–29.2)	0.28
Preoperative diagnosis			0.35			0.32
Ulcerative colitis	5 (83.3)	134 (93.7)		134 (93.7)	5 (100)	1.00
IBD-U	1 (16.7)	9 (6.3)		9 (6.3)	0 (0)	
Disease extent			1.00			1.00
Left-sided	0 (0)	22 (16.5)		22 (16.5)	1 (20)	
Extensive	5 (100)	111 (83.5)		111 (83.5)	4 (80)	
Medical comorbidities	3 (50)	91 (63.6)	0.67	91 (63.6)	4 (80)	0.655
Preoperative CDI	0 (0)	9 (11.7)	1.00	9 (11.7)	1 (50)	0.24
Stages			0.83			0.08
One-stage IPAA	0 (0)	6 (4.2)		6 (4.2)	1 (20)	
Two-stage IPAA	2 (33.3)	55 (38.5)		55 (38.5)	0 (0)	
Three-stage IPAA	4 (66.7)	82 (57.3)		82 (57.3)	4 (80)	
Anastomosis			1.00			0.58
Stapled	5 (83.3)	112 (78.3)		112 (78.3)	5 (100)	
Handsewn	1 (16.7)	31 (21.7)		31 (21.7)	0 (0)	
Length of rectal cuff, cm	3.5	2.8 (1.0–4.0)	0.61	2.8 (1.0–4.0)	1 (1.0–1.0)	0.08
Antibiotic use	3 (50.0)	86 (60.1)	0.69	86 (60.1)	3 (60)	1.00
Proton pump inhibitor use	1 (16.7)	27 (18.9)	1.00	27 (18.9)	1 (20)	1.00
Hospital admission	4 (66.7)	86 (60.1)	1.00	86 (60.1)	5 (100)	0.07

Data are presented as *n* (%) or median (interquartile range), as appropriate. NAAT, nucleic acid amplification; EIA, enzyme immunoassay; BMI, body mass index; IBD-U, inflammatory bowel disease unspecified; CDI, *Clostridioides difficile* infection; IPAA, ileal pouch anal anastomosis. One-stage IPAA: total proctocolectomy with IPAA construction during one procedure. Two-stage IPAA: total proctocolectomy with immediate IPAA construction and diverting ileostomy with subsequent ileostomy closure. Three-stage IPAA: subtotal colectomy with end ileostomy followed by completion proctectomy with IPAA construction.

There is a higher incidence of CDI among patients with IBD thought to be secondary to underlying dysbiosis, altered humoral immune response, and epithelial dysfunction [20]. Despite the curative intent of TPC with IPAA for UC patients, these changes may persist postoperatively and predispose the pouch to CDI. Prospective studies are needed to define mucosal expression and microbiota patterns after IPAA to better understand the changes that occur postoperatively and how these may play a role in the development of pouchitis and CDI.

There is conflicting data related to pouch CDI recurrence after treatment. Li et al. [10] reported high rates of pouch CDI recurrence; however, this may have been due to the use of different vancomycin regimens and inadequate treatment in certain patients. We did not observe any recurrent episodes of CDI in our cohort after treatment and noted patients' symptomatic improvement with a standard 10-day course of vancomycin. However, approximately

81.8% of patients developed recurrent symptoms with subsequent negative CDI testing, suggesting that the initial CDI episode triggered further dysbiosis that manifested as pouchitis symptoms. One pouch patient with CDI developed chronic pouchitis despite having negative subsequent CDI testing, and one patient developed pouch failure. We were unable to determine the significance of CDI on the development of these outcomes due to their small number.

Our study had several strengths. First, all patients underwent surgery and clinical follow-up at one institution, and all CDI data were systematically reviewed by one investigator. Second, our study had a large sample size relative to previously published data and included long-term follow-up. Our study also had a number of limitations. First, the study was retrospective and only included patients who underwent CDI testing. Since not all symptomatic patients had CDI testing, the study is susceptible to selection bias and the rate of CDI may be different. Second, given that our

cohort is from a single, tertiary care IBD center, these results may not be broadly generalizable; however, the majority of IPAA surgeries and follow-up occur at tertiary care centers similar to our study location [21]. Third, our event rate was too small to adequately assess the impact of CDI on pouch outcomes such as chronic pouchitis and pouch failure. Fourth, certain data points such as rectal cuff length were not available for every patient, and hence the association between residual rectum and CDI may be different. Fifth, the true extent to which *C. difficile* is a pathogen or colonizer in pouch patients is unclear. The impact of CDI on pouch mucosa could not be studied because pouchoscopy data were not available for the majority of patients, and the assays used to detect CDI were not uniform and did not discriminate between active infection and colonization. While our patients' response to therapy suggests CDI was the cause of their symptoms, vancomycin may have been treating an alternative pathogen.

Conclusion

In conclusion, *C. difficile* is a rare cause of infectious pouchitis that can be managed with oral vancomycin. Pouch patients presenting with symptoms of fever, urgency, increased stool frequency, hematochezia, incontinence, and abdominal and/or pelvic pain should be tested for CDI and treated accordingly. Recurrence after treatment is uncommon; however, pouch dysbiosis and pouchitis may occur and responds to traditional antibiotic therapy.

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Statement of Ethics

This project was approved by the Mount Sinai Hospital Institutional Review Board.

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