



Management of Recurrent *Clostridioides* Infection: A Difficile Problem in Inflammatory Bowel Disease Patients

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Case Presentation

Background

A 24-year-old woman with pancolonic ulcerative colitis (UC), complicated by primary sclerosing cholangitis (PSC) requiring orthotopic liver transplant (OLT), history of rotavirus infection, and *Clostridioides difficile* infection (CDI), was evaluated for ongoing care. Her past therapies for UC included 6-mercaptopruine, infliximab, and adalimumab. Her current therapy includes vedolizumab and tacrolimus monotherapy as an antirejection therapy. She reports 8 bowel movements per day which are soft and liquid, including 1–2 bowel movements at night. She reports trace blood in the stool, mild right-sided abdominal cramping, and occasional urgency. Prior colonoscopies revealed moderate–severe pancolitis. Multiple prior stool tests in the prior 1–2 years have been negative for CDI. Her calculated simple clinical colitis activity index (SCCAI) was 6 (≤ 2 signifies remission). Using shared decision making, potential changes in therapy were discussed. A *C. difficile* stool test ordered prior to initiating any changes in therapy was positive.

Clinical Course

After a 2-week course of oral vancomycin, bowel movements improved to 2–3/day. Her symptoms recurred after a month, and she received an extended 6-week vancomycin

taper which again reduced her bowel movements to 2–3 per day. Three months after completing the prolonged taper of oral vancomycin, she became symptomatic from a colitis standpoint; repeat testing for *C. difficile* was negative. Vedolizumab drug concentration was adequate at 15.4 with no antibodies present. Colonoscopy demonstrated a Mayo 3 subscore pancolitis with pathology showing chronic and focally active colitis throughout the colon. *Clostridioides difficile* checked after this colonoscopy was now positive. The patient received an additional course of oral vancomycin with a reduction in bowel movements to 3/day and is currently on a prolonged taper as the next steps are determined.

Case Discussion

Clostridioides difficile is a Gram-positive, spore-forming anaerobic bacillus that causes colitis and approximately 25% of all antibiotic-associated diarrhea, with symptoms ranging from mild diarrhea to severe disease (high fever, ileus, colonic dilation, or megacolon possibly complicated by perforation). Frequently implicated antibiotics include clindamycin, ampicillin, amoxicillin, and cephalosporins, though all antibiotics have been associated with *C. difficile* infection [1]. Other known risk factors include older age (> 65 years old), prolonged hospitalization, female gender, and multiple comorbidities [2, 3]. Immunosuppression and systemic infection are recognized risk factors for fulminant *C. difficile* colitis [2]. While *C. difficile* is responsible for a broad spectrum of disease, it also colonizes asymptomatic individuals [4]. CDI is defined as the presence of detectable *C. difficile* toxin in the stool with clinical manifestations of infection, including diarrhea and abdominal pain. The coexistence of *C. difficile* in the setting of inflammatory bowel disease (IBD) and immunosuppression is particularly challenging. Not only is it difficult to distinguish an IBD flare from *C. difficile* infection, the inflammation and immunosuppression typical of IBD may predispose to *C. difficile*.

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Furthermore, patients with coexisting *C. difficile* and IBD have inferior outcomes than those with IBD alone.

How Common Is *C. difficile* in Inflammatory Bowel Disease?

The incidence of CDI has been increasing in the general population; patients with IBD are at higher risk [5]. In a small study of consecutive IBD patients who underwent stool testing during disease flares, 19% tested positive for *C. difficile* [6]. In a larger study of hospital admissions from 1998 to 2004, CDI incidence increased over time and was higher in IBD patients than non-IBD patients [2]. Rates approximately doubled in Crohn's disease (CD) and tripled in UC. Another single-center study showed that the proportion of IBD patients with CDI increased from 7% in 2004 to 16% in 2005, with most infections contracted in the outpatient setting [5]. Data from the Nationwide Inpatient Sample (NIS) showed that the proportion of IBD hospitalizations nationwide complicated by CDI rose from 1.4% in 1998 to 2.3% in 2004 and 2.9% in 2007 [7]. In the same patient population, the prevalence of *C. difficile* was 37.3 per 1000 among UC patients and 10.9 per 1000 among CD patients, and 4.5 per 1000 among patients without IBD [8].

Which IBD Patients Are at Greatest Risk for *C. difficile* Infection?

In addition to traditional *C. difficile* risk factors, a prospective study of IBD patients from 2015 to 2016 identified healthcare exposures (primarily emergency room visits and hospitalizations) as significant risk factors for CDI [9]. Another retrospective study of 813 patients hospitalized for active IBD in France found that recent nonsteroidal anti-inflammatory drug (NSAID) intake was an independent risk factor for development of CDI associated with IBD [10]. While some studies have reported immunomodulator therapy as an independent risk factor for CDI [2, 5], this remains controversial given conflicting data in the literature [11, 12]. A large cohort study of 10,662 IBD patients found that corticosteroid initiation tripled the risk for CDI independent of dose and duration but did not show any relationship with infliximab [13]. Anatomically, IBD with colonic involvement (such as UC and Crohn's colitis) confers a higher risk of CDI [5, 8] than in those with intestinal involvement only. UC patients with pancolitis are at the highest risk [14], suggesting that the extent of colonic involvement is also important. Despite this, patients who have had colectomies with ileal pouch–anal anastomosis (IPAA) are still at risk for CDI with 10.7% of patients with diarrhea diagnosed with CDI at a single pouchitis clinic [15]. Another notable patient population at higher risk for CDI in this case includes solid organ

transplant recipients, such as this patient, with a prevalence five times higher compared to general medicine patients [16, 17].

How Does *C. difficile* Infection Impact IBD Severity?

Patients with IBD and CDI are at higher risk for subsequent IBD flares and need for therapy escalation, failure of medical therapy for *C. difficile* and recurrence, longer hospitalizations, and more frequent emergency room visits, as well as an increased risk of surgery and mortality [11, 18–21]. Based on data from the NIS, patients with both *C. difficile* and IBD had four times greater mortality than patients admitted for IBD alone and two times greater mortality than patients admitted for *C. difficile* alone [22]. These increased risks were driven by patients with underlying UC more than CD [8]. UC patients had higher rates of mortality, endoscopy, and surgery than did patients with CD [22]. Furthermore, CDI is associated with higher mortality even after hospital discharge in one study evaluating 5-year adjusted risks of deaths in hospitalized UC patients (HR 2.40, 95% CI 1.37–4.20) [20].

When Should *C. difficile* Be Suspected and Tested for in IBD Patients?

Colitis due to IBD or *C. difficile* commonly manifest with abdominal pain, fever, and diarrhea, though more likely to be bloody in IBD [18]. As the clinical presentation of an acute IBD colitis and acute *C. difficile* colitis share several similarities, all patients with IBD who have worsening diarrhea or symptoms suggestive of a colitis flare should initially be tested for the presence of toxigenic *C. difficile* in the stool [18, 23]. Given the diagnostic challenge inherent in differentiating colitis from CDI versus active IBD, initial treatment for CDI with vancomycin is recommended after a positive stool test, followed by intensification of IBD therapy if no clinical response occurs after antibiotic therapy [18]. Withholding immunosuppression is not recommended in CDI in patients with acute severe IBD, though should be considered carefully given the potential worsening of infection. This patient responded to vancomycin therapy, suggesting that most of her symptoms were likely driven by *C. difficile* infection and not IBD; thus, no IBD medication changes are planned at this time.

What Is the Standard Treatment for Initial and Recurrent *C. difficile* Infection in IBD Patients?

As of updated guidelines from the Infectious Diseases Society of America (IDSA) in 2018, either vancomycin or fidaxomicin is recommended over metronidazole for an initial episode of CDI [24]. These guidelines reflect prior

recommendations for management of CDI in IBD patients [18], given evidence supporting the superiority of vancomycin to metronidazole for CDI based on randomized, placebo-controlled trials [25, 26]. In cases of fulminant CDI (characterized by hypotension, shock, ileus, or megacolon), IV metronidazole is recommended in addition to oral and/or rectal vancomycin, particularly if ileus is present [24]. Worsening leukocytosis or lactic acidosis in patients with fulminant CDI is associated with higher mortality and can be used as markers to identify patients who may benefit from early surgery with subtotal colectomy.

When compared to the general medical population, patients with IBD are 33% more likely to develop recurrent CDI with drug exposures to antibiotics, 5-ASA, steroids, and biologics found to be predictors [27]. In patients with a first recurrence of CDI, a tapered and pulsed course of oral vancomycin, or a standard course of fidaxomicin, is recommended over a standard 10-day course of vancomycin [24]. If patients have had more than one recurrence of CDI, antibiotic options include a tapered and pulsed regimen of oral vancomycin, a standard course of vancomycin followed by rifaximin, or fidaxomicin. In clinical practice, vancomycin is most commonly used as a first-line therapy. One practical limitation to the use of fidaxomicin is cost-effectiveness [28].

What Is the Utility of Fecal Microbial Transplantation (FMT) for Treating Recurrent *C. difficile* Infection in IBD?

Over the past decade, FMT has also emerged as a highly effective treatment for recurrent CDI that is refractory to antibiotic therapy [29]. CDI is characterized by an altered intestinal microbiota composition with decreased alpha diversity and altered metabolic profiles, which enable colonization by *C. difficile* [30, 31]. FMT is the process of instilling the stool from a healthy individual into an individual with a perturbed microbiota by colonoscopy, enema, nasogastric tube, or capsules. In CDI, the introduction of healthy microbial communities by FMT improves CDI-related dysbiosis and metabolic derangements, thereby reestablishing resistance to colonization by *C. difficile* [32]. FMT has emerged as the best treatment for refractory CDI, with several randomized controlled studies supporting its safety and efficacy in patients with recurrent CDI, with a cure rate of nearly 90% [33–35].

Studies suggest that FMT is less effective in IBD patients than in the general population, with one study reporting that a single colonoscopic FMT cleared CDI from 74.4% of patients with IBD compared to 92.1% of patients without IBD ($p=0.0018$) [36]. A number of other small, retrospective cohort studies over the past few years examining the efficacy of FMT for recurrent CDI in IBD patients have reported

cure rates ranging from 60 to 90% [37]. One of the larger retrospective studies included 67 IBD patients, 35 (52%) with CD, 31 (46%) with UC, and 1 with indeterminate colitis. A total of 43 (64%) were receiving immunosuppressive therapy at the time of FMT. Initial FMT was successful in 53 (79%) patients. Following FMT, IBD disease activity was improved in 25 (37%), unchanged in 20 (30%), and worse in 9 (13%) patients. Few adverse events (AEs) occurred, none of which were directly attributable to FMT [38].

The ICON study is the first prospective cohort trial examining outcomes of IBD patients who developed recurrent CDI and received FMT. A total of 34/37 (92%) patients were *C. difficile* negative at week 8. In the CD cohort (14/37), 64% (9/14) patients had IBD improvement and 35% (5/14) had no change in their disease at week 12. In the UC cohort (23/37), 57% (12/23) patients had IBD improvement, 40% (9/23) had no change, and 4% (1/23) experienced UC flare. No patients experienced severe AEs [39].

Given the high efficacy and relatively good safety profile of FMT in CDI, weighed against the high complication rates for CDI in patients with IBD, FMT may be considered for recurrent CDI for patients with IBD [40].

Does FMT for Recurrent *C. difficile* Infection Also Treat Underlying IBD?

FMT is actively being studied as a potential treatment for IBD, with some signal that there may be efficacy, particularly in UC [41]. Four randomized controlled trials over the past few years examining FMT as a treatment of UC have been published, all of which used multiple doses of FMT with numerous delivery methods and dosing schedules [41]. Though FMT for treatment of CDI may incidentally help IBD disease activity, it is unlikely that a single FMT used for the treatment of CDI will have a meaningful impact on IBD disease activity [37]. Based on FDA guidance, FMT cannot be given for the exclusive treatment of ulcerative colitis without an approved investigation new drug (IND) application to the FDA. In this patient with IBD, FMT would be permitted without an IND after adequate counseling on the risks, given that it would be used to treat recurrent *C. difficile*.

What Are the Risks of FMT?

Though FMT is an effective treatment for recurrent CDI, it is not without risk. A meta-analysis that included 50 original articles on FMT found that the total incidence rate of AEs was 28.5%. The most common AE was abdominal discomfort. Serious AEs occurred in 9.2% of patients, including death (3.5%, 38/1089), infection (2.5%, 27/1089), relapse of IBD (0.6%, 7/1089), and CDI (0.9%, 10/1089) [42].

In 2019, a report was published in the *New England Journal of Medicine* describing two immunocompromised patients who developed extended spectrum beta-lactamase producing *Escherichia coli* infection after receiving FMT in two independent clinical trials, resulting in death in one of the patients. Both cases were linked to the same donor, who had not been screened for multidrug-resistant organisms prior to donating stool [43]. The FDA has since mandated updated screening guidelines for donating stool for FMT with public stool banks updating screening to ensure all FMT is appropriately screened for these pathogens.

A more recent potential risk is transmission of the SARS-CoV-2 coronavirus, which can be shed in the stool. Although information is evolving and the risk of transmission is unknown, several stool banks have implemented protocols that include nasopharyngeal swab screening of stool donors for the presence of SARS-CoV-2 every 30 days. Furthermore, based on FDA guidance, no FMT material collected after December 1, 2019, should be used therapeutically until it can be affirmatively cleared of SARS-CoV-2 risk. The FDA recommends using stool donated for FMT prior to December 1, 2019, until that occurs. The FDA also recommends adding to the informed consent process that healthy asymptomatic stool donors may potentially be infected with SARS-CoV-2 and advising FMT recipients as to the limitations of testing and risk mitigation strategies.

Finally, a unique risk to the IBD population is the risk for flare of underlying IBD, which in one study was reported to be as high as 25.6% in IBD patients receiving FMT for recurrent CDI [36]. Nevertheless, a different study examining FMT in IBD patients with recurrent CDI reported no serious AEs [44]. A Cochrane meta-analysis examining FMT as a treatment for IBD included an analysis of 277 patients for serious AEs, indicating that 10/140 (7%) who received FMT experienced a serious AE compared to 7/137 (5%) in the control group (RR 1.40, 95% CI 0.55–3.58, I²=0%) [45]. Additional studies are needed to elucidate the true incidence of serious AEs of FMT in the IBD patient population. Nevertheless, at this time, given poor outcomes associated with *C. difficile* in IBD patients, patients with recurrent infections who otherwise meet criteria for FMT based on *C. difficile* recurrence should not be denied FMT based on the presence of IBD.

Key Messages

- IBD patients are at higher risk for both initial and recurrent *C. difficile* infection (CDI)
- *Clostridioides difficile* infection in IBD is associated with escalation of therapy and need for surgery
- Vancomycin is the preferred treatment over metronidazole as first-line treatment for *C. difficile* infection in

IBD. Recurrences can be treated with a prolonged tapering course of vancomycin.

- Fecal microbial transplantation (FMT) may be considered for recurrent CDI for patients with IBD
- Success rates of FMT in IBD patients with recurrent CDI are slightly lower than in patients without IBD, with reports ranging from 60 to 90%.

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