

Diagnosis and Management of *Clostridioides difficile* in Inflammatory Bowel Disease

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Patients with inflammatory bowel disease (IBD) have an increased risk of *Clostridioides difficile* infection (CDI), which can lead to worse IBD outcomes. The diagnosis of CDI in patients with IBD is complicated by higher *C. difficile* colonization rates and shared clinical symptoms of intestinal inflammation. Traditional risk factors for CDI, such as antibiotic exposure, may be lacking in patients with IBD because of underlying intestinal microbiota dysbiosis. Although CDI disproportionately affects people with IBD, patients with IBD are typically excluded from CDI clinical trials creating a knowledge gap in the diagnosis and management of these 2 diseases. This narrative review aims to provide a comprehensive overview of the diagnosis, treatment, and prevention of CDI in patients with IBD. Distinguishing CDI from *C. difficile* colonization in the setting of an IBD exacerbation is important to avoid treatment delays. When CDI is diagnosed, extended courses of anti-*C. difficile* antibiotics may lead to better CDI outcomes. Regardless of a diagnosis of CDI, the presence of *C. difficile* in a patient with IBD should prompt a disease assessment of the underlying IBD. Microbiota-based therapies and bezlotoxumab seem to be effective in preventing CDI recurrence in patients with IBD. Patients with IBD should be considered at high risk of CDI recurrence and evaluated for a preventative strategy when diagnosed with CDI. Ultimately, the comanagement of CDI in a patient with IBD requires a nuanced, patient-specific approach to distinguish CDI from *C. difficile* colonization, prevent CDI recurrence, and manage the underlying IBD.

KEYWORDS: Crohn's disease; ulcerative colitis; fecal microbiota transplant; bezlotoxumab

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INTRODUCTION

Clostridioides difficile is responsible for approximately 500,000 infections in the United States annually (1). Its potential to cause symptomatic disease is determined by a permissive metabolomic milieu in the intestine that is dependent on the activity of the host gut microbiota and host immunity factors. In the setting of inflammatory bowel disease (IBD), the presence of *C. difficile* presents a particularly difficult diagnostic and therapeutic challenge.

Patients with IBD are 5 times more likely to develop *C. difficile* infection (CDI) than patients without IBD (2). Approximately 5%–13% of patients with IBD presenting with new-onset symptoms will test positive for *C. difficile* and will have worse outcomes including increased risk of surgery and prolonged hospitalization (3–10). It is unclear whether CDI leads to worse IBD outcomes or whether individuals with more aggressive IBD are more likely to have CDI. Both situations may exist.

Although the diagnostics and treatment options for CDI in the general population have improved, CDI in the context of IBD remains a special circumstance requiring therapeutic strategies that recognize the synergy between the 2 disease processes. Unfortunately, patients with IBD are typically excluded from CDI clinical trials (11). This review will outline a methodical approach needed for the successful diagnosis and management of CDI in people with IBD and highlight key knowledge gaps.

PATHOPHYSIOLOGY OF CDI IN IBD

C. difficile enters the gastrointestinal tract in the form of spores, and their fate is determined by the capacity for colonization resistance by the host's microbiota. The spores may merely "pass through" or germinate into vegetative cells that may colonize the large intestine either transiently or persistently (12). Thus, patients are colonized with *C. difficile* in that the organism is detected in the absence of symptoms attributable to CDI (13). Some of the factors resulting from antibiotic-induced dysbiosis that favor *C. difficile* spore germination and vegetative growth include increased nutrient availability, altered bile acid composition, and reduction in short-chain fatty acids, tryptophan-derived antibiotics, and bacteriocins (14–16). IBD-driven dysbiosis shares many of the same elements. In addition, host immunity dysfunction associated with IBD, such as decreased production of antimicrobial peptides, defects in autophagy and inflammatory function, altered cytokine responses, and effector/regulatory T-cell ratios, may contribute to weakened protection against *C. difficile*.

Patients with IBD are more likely to be colonized with *C. difficile*. The frequency of toxigenic *C. difficile* colonization in patients with IBD is estimated at 8%–17% vs 1%–3% of non-IBD controls (17,18). *C. difficile* colonization may be asymptomatic or lead to symptomatic infection. Development of symptoms

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depends on actual production of *C. difficile* toxins, their interaction with the receptors in the gut, and the quality of the immune response toward the microbial products penetrating the gut barrier. Not all *C. difficile* are toxigenic, and within varying toxigenic strains, some are more virulent than others (19). The relationship between asymptomatic carriage of *C. difficile* and the exacerbation of CDI or IBD is complex and not fully understood. Induction of antibodies against *C. difficile* toxins may be protective (20). Antibodies to *C. difficile* toxin B are associated with asymptomatic colonization in hospitalized patients, and higher levels of IgG to toxin A decrease the risk of developing CDI after exposure (21,22). Impairments in the humoral immune responses may limit this protective effect in IBD (23). Even in the general population, the bulk of evidence suggests that colonization with toxigenic *C. difficile* likely increases the risk of subsequent CDI development by 5–6 times (13).

DIAGNOSING CDI IN IBD

Distinguishing colonization from infection in IBD is confounded by the underlying intestinal inflammation related to IBD (Figure 1). *C. difficile* may act as a bystander, instigator, or perpetuator of inflammation in IBD. In each possible situation, the treating provider cannot ignore the underlying IBD when considering diagnosis and treatment of CDI. As the distinction between colonization and CDI is dependent on the clinical attribution of symptoms to *C. difficile*, laboratory tests alone cannot reliably distinguish *C. difficile* colonization from CDI, and clinical history is of paramount importance.

Clinical presentations of CDI in IBD

Patients with IBD are more likely to present without traditional risk factors for CDI. Specifically, they present at a younger age, often without recent antibiotic use, and are more likely to experience community-onset CDI compared with non-IBD controls

(24). Although the presence of traditional risk factors, such as antibiotic use, should raise the pretest probability of CDI, many patients with IBD will lack them. However, a key limitation of most studies examining CDI risk factors in IBD is the lack of a gold standard to discriminate between CDI and an IBD exacerbation with *C. difficile* colonization. However, with that caveat, any colonic involvement (either ulcerative colitis [UC] or Crohn’s disease) is an important risk factor for the development of CDI (25). As with the general population, the risk of CDI is likely directly correlated to the severity of intestinal dysbiosis; in the general population, dysbiosis is frequently driven by antibiotics, whereas patients with IBD (in particular with colonic involvement) have inherent dysbiosis.

The clinical symptoms of CDI in patients with IBD also differ from CDI in the general population. Bloody diarrhea is more common with CDI and IBD (24,26). Endoscopically, CDI in a patient with IBD is generally indistinguishable from a CDI-independent IBD flare, and pseudomembranes are rarely seen in patients with IBD with CDI. Occasionally, histopathology may offer some distinguishing features of CDI (27), and acute colitis alone (without chronicity) suggests CDI to be the predominant driver of inflammation.

As with the diagnosis of CDI outside of IBD, the patient’s medical history is essential to making an accurate diagnosis. The knowledge of distribution and activity of IBD preceding *C. difficile* testing is extremely valuable. However, with any new onset or worsening of IBD symptoms, *C. difficile* should be entertained as a contributor, and stool testing should be performed.

Laboratory evidence of CDI

The most common laboratory diagnostics for CDI performed are polymerase chain reaction (PCR)-based tests to detect the presence of genes that encode for toxin (*tcdA* and/or *tcdB*) and enzyme immunoassays (EIAs) to detect the presence of glutamate

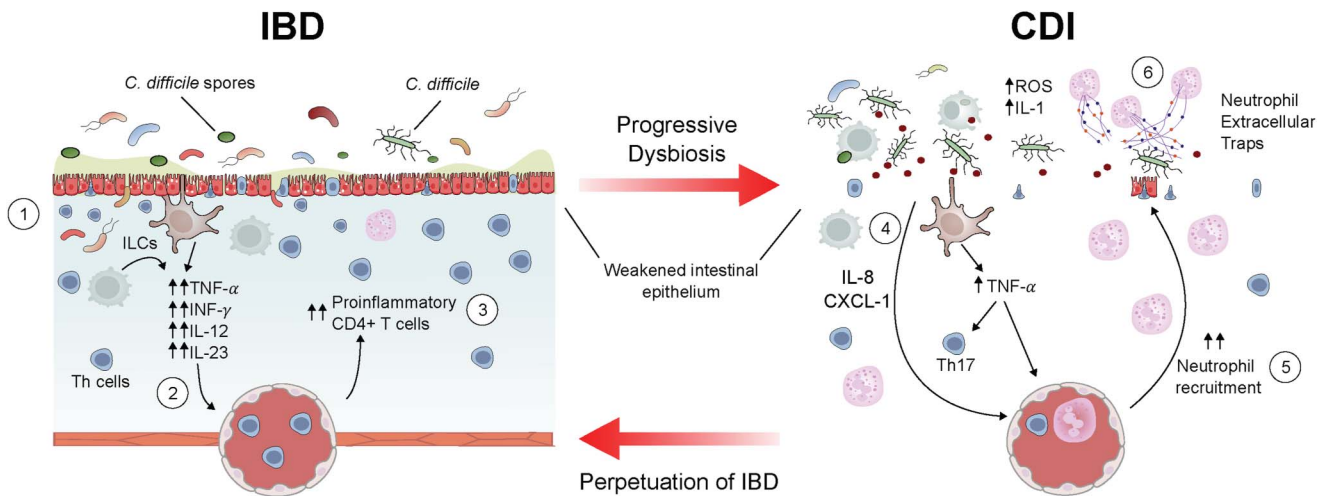


Figure 1. IBD and CDI have distinct but overlapping pathophysiology. In active IBD, there is a chronic immune response against the indigenous microbiota (1) leading to release of proinflammatory cytokines from innate intestinal lymphoid cells (2). The subsequent inflammatory response is T-cell-mediated (3) leading to chronic inflammation with crypt abscesses, progressive dysbiosis, and a weakened intestinal epithelial barrier. Patients with IBD have higher rates of *C. difficile* colonization. Over time, dysbiosis progresses and colonization resistance is lost. In this setting, *C. difficile* can produce toxins. Toxin-mediated colonocyte death induces a neutrophilic response mediated by IL-8 and CXCL-1 (4) but also induces Th17 cells through TNF-α. The subsequent inflammatory response is predominately neutrophilic (5). Extravasated neutrophils release DNA to form extracellular traps (6). The resulting luminal inflammation may stimulate or perpetuate an already dysregulated immune response in people with IBD. CDI, *Clostridioides difficile* infection; CXCL-1, CXC chemokine ligand-1; IBD, inflammatory bowel disease; IL, interleukin; Th17, T-helper 17; TNF, tumor necrosis factor.

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dehydrogenase (GDH) and toxin A/B production. GDH is a component of all *C. difficile* strains and thus unable to arbitrate between toxigenic and nontoxigenic *C. difficile*. PCR is a sensitive test and can accurately identify toxigenic *C. difficile*, but does not provide information on toxin production. Although the optimal laboratory stool testing in patients with IBD is unknown, it is the opinion of the authors that a PCR-based test should be performed first, and if positive, followed by the confirmative toxin EIA test (Figure 2), as suggested by the 2021 ACG Clinical Guidelines on CDI (28). We prefer the initial screening test of PCR over GDH because PCR is a more sensitive test. Approximately 10%–15% of individuals who are PCR+ are GDH-. Similarly, to non-IBD populations, laboratory testing should only be pursued when a patient presents with new-onset suggestive symptoms.

PCR-

A negative PCR test has a high negative predictive value, but like all tests can be falsely negative and clinical judgment is imperative. Some exceptions include early infection (29) or acute severe/fulminant colitis with ileus (30). In the latter, stool testing may be unreliable. Flexible sigmoidoscopy with colonic washings may be helpful. Empiric treatment for CDI in this situation is unlikely to be harmful, whereas definitive treatment of the underlying severe IBD should not be delayed.

PCR+/toxin EIA+

New-onset GI symptoms with a positive toxin EIA test in a patient with IBD should prompt treatment for CDI. If performed for new onset or acute worsening of symptoms, a false-positive PCR and toxin EIA test is unlikely. However, it is important to note that although this testing pattern represents toxin production, the

underlying inflammation could be attributed to either CDI, IBD, or both.

PCR+/toxin EIA-

In the general population, individuals with discordant CDI testing (i.e., PCR+/toxin EIA-) have favorable outcomes relative to those who are toxin EIA positive (31). Patients with IBD who are toxin EIA positive are significantly more likely to have a clinical response to anti-*C. difficile* antibiotics than those who are PCR+/toxin EIA- (32). However, patients with IBD who are PCR+/toxin EIA- may have early or mild infection. The distinction between colonization and infection is based on the provider's attribution of new-onset symptoms to *C. difficile* or IBD. Given the overlapping symptoms, it may not be possible to make that determination. In such cases, the symptomatic response to antibiotic therapy can be a reasonable diagnostic test. A substantial improvement in diarrheal symptoms from anti-*C. difficile* antibiotics suggests CDI, although IBD activity may transiently benefit from antibiotic treatments in absence of CDI. On the other hand, administering antibiotics can worsen intestinal dysbiosis and is not currently an evidence-based strategy.

Additional supportive testing

Procalcitonin is a biomarker for acute bacterial inflammatory conditions that is neither elevated by IBD nor affected by immunosuppressive medications. It may have diagnostic benefits in distinguishing colonization from CDI in patients with IBD, although the observational evidence is controversial (33,34). Although not used clinically, stool cytokines, such as interleukin 1β, may help distinguish between *C. difficile* colonization and CDI (35).

Ultimately, no single clinical symptom, sign, or laboratory test can definitively diagnose CDI. IBD providers must balance the pros and cons of treating CDI with or without concurrent IBD treatment. In many cases, it may be better to err on the side of treating for CDI.

TREATMENT OF CDI IN IBD

Once a diagnosis of CDI has been made, treatment generally follows the protocols used for the general population. More narrow-spectrum antibiotics may be preferred in IBD to limit exacerbation of dysbiosis, and advanced nonantibiotic therapies may be considered earlier to prevent CDI recurrence.

Metronidazole is not recommended in patients with IBD, and its use is associated with worse outcomes relative to vancomycin (28,36–38). Fidaxomicin has the theoretical advantage of being bactericidal and more selective in antimicrobial coverage. In patients without IBD, fidaxomicin was noninferior to vancomycin for an initial clinical CDI cure and had lower CDI recurrence rates (39). Unfortunately, patients with IBD were excluded from the trial. In a prospective pharmacokinetic study of fidaxomicin, 80% of patients with IBD had a clinical response with no safety signals noted (40). Fidaxomicin absorption and metabolism seemed similar to those in the general population. Retrospective observational studies of fidaxomicin report initial cure rates between 61% and 100% in patients with IBD, with a CDI recurrence rate of 19%–30% (41–43).

Concurrent treatment of the underlying IBD is of critical importance when managing CDI. An intuitive decision to hold immunosuppressive medications is highly problematic because many therapies for IBD have a prolonged half-life and cannot be

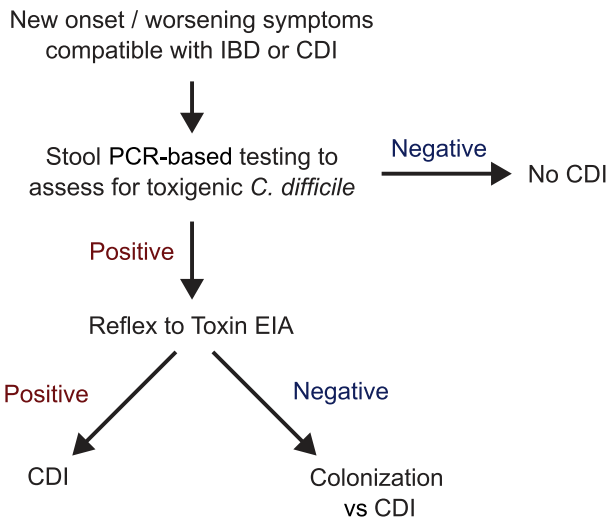


Figure 2. Diagnostic algorithm for interpreting PCR/reflex toxin EIA testing. A negative PCR for toxigenic *C. difficile* has a high sensitivity for ruling out CDI. Positive PCR tests should undergo reflex testing given the high toxigenic *C. difficile* colonization rates in patients with IBD. A positive toxin supports a CDI diagnosis. Although a negative toxin supports colonization with toxigenic *C. difficile*, CDI is still possible. A diagnosis of CDI should not be made on isolated laboratory testing, but an appropriate clinical context with supportive laboratory data. CDI, *Clostridioides difficile* infection; EIA, enzyme immunoassay; IBD, inflammatory bowel disease; PCR, polymerase chain reaction.

easily turned off. More importantly, continued inflammatory activity driven by IBD worsens dysbiosis and further disrupts the gut barrier function, factors that synergize with CDI pathogenicity. Thus, rather than holding IBD medications, we prefer to continue the underlying IBD therapy with a plan to re-evaluate the IBD after CDI and optimize IBD treatment if needed.

PREVENTION OF CDI RECURRENCE IN PATIENTS WITH IBD

Patients with IBD should be considered “high” risk of CDI recurrence because of the underlying IBD-driven dysbiosis. After initial antibiotic treatment, it is important to consider preventative strategies that mitigate future CDI. Persistent inflammation driven by IBD results in progressive dysbiosis after fecal microbiota transplantation (FMT) despite initial engraftment of donor microbiota and eventual CDI recurrence (44,45). Therefore, it may be best to suppress *C. difficile* with extended antibiotics while the underlying IBD therapy is optimized before FMT. It is also possible that early aggressive FMT protocols may diminish IBD-driven inflammation and improve control of CDI. The optimal timing of FMT should be individualized based on the patient’s history considering factors as an antibiotic trigger for CDI, the inflammatory status before CDI, and the symptomatic response to CDI therapy. Availability of FMT material should be also considered when deciding on which approach to take. Ultimately, additional data from clinical trials are needed to determine the most beneficial protocols in this complex clinical situation.

Extended antibiotic regimens

Longer duration vancomycin is associated with lower *C. difficile* toxin gene detection by PCR with compared with standard duration (46), and low-dose vancomycin has been effective at preventing CDI recurrence in high-risk individuals (47). Therefore, it is possible to extend vancomycin administration while the management of the underlying IBD is being optimized. Once clinical and endoscopic remission of IBD is achieved, vancomycin may be simply discontinued or punctuated by a microbiota-based therapy or bezlotoxumab to further mitigate the chance of recurrence.

Microbiota-based therapies

FMT has emerged as a highly effective strategy to prevent CDI recurrence, and it is endorsed by numerous gastroenterology and infectious disease societies (28,38,48). Notably, early studies identified a significantly lower CDI cure rate for patients with IBD compared with patients without IBD (74.4% vs 92.1%, $P = 0.001$) (49). However, a subsequent meta-analysis did not reach statistical significance (81% IBD vs 89% non-IBD, $P = 0.06$) (50). A pooled analysis of 16 retrospective and 1 prospective, single-arm study of adults with IBD and CDI estimated the CDI cure rate to be 78% (95% confidence interval 73%–83%) after a single FMT administration (51). The overall cure rate of CDI in patients with IBD was 88% (95% confidence interval 81%–94%), including repeat FMT administration. Variation in the underlying IBD activity and the accuracy of CDI diagnosis constitute important concerns in interpreting these results.

Currently, there are 2 microbiota-based products that have been approved by the FDA for the prevention of CDI recurrence: Vowst (fecal microbiota spores, live-brpk) and Rebyota (fecal microbiota, live-jslm). Although some patients with IBD were

included in the phase III trial for Vowst (ECOSPOR III), analysis based on comorbidities was unable to assess outcomes specific to IBD (52,53). Patients with IBD were excluded from the PUNCH CD3 trials that lead to approval of Rebyota (54). Because of lack of evidence, recent American Gastroenterological Association (AGA) guidelines recommended FMT for use in prevention of recurrent CDI for mild-to-moderately immunocompromised individuals, but not fecal microbiota spores live-brpk or fecal microbiota live-jslm (48). As most patients with IBD fall under mild-to-moderately immunocompromised, FMT should be preferred over the 2 current commercial products.

Ultimately, our expert opinion suggests that FMT for the prevention of CDI recurrence has similar effectiveness to that in the general population, provided the IBD is under control. FMT should be performed after antibiotic therapy for CDI. Practically low-dose suppressive antibiotics may be required until 1–3 days before the FMT procedure (depending on if a bowel purgative was used). The AGA Clinical Practice Guidelines on FMT outline the salient implementation considerations (48). As FMT may be beneficial in the management of IBD, especially UC, it may seem reasonable to pursue earlier FMT to both prevent CDI recurrence and treat IBD. However, the studied FMT regimens for IBD are much more intensive, requiring multiple repeated administrations. Therefore microbiota-based therapies to prevent CDI recurrence should not be relied on to treat the underlying IBD.

Bezlotoxumab

Bezlotoxumab is a monoclonal antibody against *C. difficile* toxin B. It is FDA-approved for the prevention of CDI recurrence (55). Patients with IBD who received bezlotoxumab had a non-significant trend toward lower CDI recurrence at 12 weeks (26.7% vs 53.8%) (56). The analysis was limited by the small sample size (44 patients with IBD) but represents a promising potential therapy. Bezlotoxumab should be administered over the course of antibiotic therapy (55). Interestingly, the combination of bezlotoxumab and FMT was not superior to bezlotoxumab alone in preventing CDI in patients with IBD in randomized trials of 61 patients, although more patients were decolonized from *C. difficile* in the bezlotoxumab + FMT arm (57).

SPECIAL SITUATIONS

Acute severe ulcerative colitis

Acute severe UC (ASUC) is a medical emergency requiring the prompt initiation of intravenous steroid therapy. CDI can complicate ASUC, and the clinical picture of severe/fulminant CDI and severe/fulminant UC may be indistinguishable. The presence of *C. difficile* in the setting of ASUC is associated with worse outcomes including an increased risk of colectomy, postoperative infections, and death (58,59). As with other forms of IBD exacerbations, it remains unknown whether the presence of *C. difficile* is related to the severity of inflammation and subsequent dysbiosis or whether *C. difficile* exacerbates existing colonic inflammation. Scant literature exists on the optimal management strategy for this group. It is the authors’ opinion that both diseases should be treated promptly, and definitive IBD therapy (such as infliximab or colectomy) should not be avoided. There is no evidence that intravenous steroids for ASUC worsen concurrent CDI. Interestingly, before the identification of *C. difficile*, steroids were used to treat pseudomembranous colitis (in conjunction with tetracycline antibiotics, which had anti-*C. difficile* activity)

with reasonable efficacy (60). Some modern case reports exist where IV steroids have been used as adjunct CDI therapy, although this practice is not widely adopted (61). Salvage therapy for IBD should not be delayed either. In small case series of ASUC and CDI nonresponsive to steroids and antibiotics, prompt response was noted with salvage medical therapy using infliximab (62,63).

Although FMT seems effective for the treatment of severe/fulminant CDI (28,48) and is a promising treatment for active UC (64), there are no reports of FMT use for ASUC. A key concern about incorporating FMT into the treatment of ASUC is the delay of salvage therapy, which should be determined within 3–5 days of hospital admission (65). FMT for severe/fulminant CDI requires multiple administrations and thus could delay medical decisions for ASUC, leading to worsened outcomes. In our expert opinion, if CDI is felt to be contributing to the overall clinical picture, then concurrent treatment with sequential FMT while escalating immunosuppressive therapy can be considered. This should only be performed at centers with expertise in managing both ASUC and fulminant CDI and should not delay effective therapy for ASUC.

CDI of an ileoanal pouch

C. difficile toxins are recognized by receptors on colonic epithelial cells, endocytosed, and subsequently lead to colonic inflammation (19). Typically, the small bowel is spared; however, the ileoanal pouch mucosa undergoes an incomplete transition to colonic phenotype making CDI of the pouch possible (66–68). The prevalence of CDI in the pouch is estimated to be around 10% (69), although the data are mostly derived from retrospective, observational studies and rely on PCR-based diagnosis. When reported, toxin EIA accounts for 28%–46% of cases (70,71). No clear risk factors are known for CDI of the pouch, although recent hospitalization may increase the risk (72). Vancomycin is most commonly used with a good response (73).

FMT is a reasonable option to prevent CDI recurrence in the pouch. One case series found that FMT eradicated *C. difficile* from the pouch in the short term, but was only associated with 58% symptom improvement (74). Considerations for FMT of the pouch include the underlying inflammation, retention of FMT material, and route of administration. The addition of ursodeoxycholic acid after FMT may inhibit subsequent CDI (75). Bezlotoxumab, although not studied in CDI of the pouch, is a mechanistically reasonable approach. In general, we advocate for a similar diagnostic and management algorithm for CDI of the pouch as other forms of IBD.

CDI in an ostomy patient

There are 3 potential intestinal compartments to consider in a patient with an ostomy: a colostomy, an ileostomy, and a diverted colon. Patients with IBD with a colostomy should be managed as discussed above. CDI is unlikely to cause colitis in a diverted segment of the colon, although case reports exist (76), and rectal administration of anti-*C. difficile* antibiotics can be a diagnostic and therapeutic maneuver. CDI enteritis after colectomy is generally considered a rare event (77). For patients with increased ileostomy output who are *C. difficile* toxin EIA positive, treatment with oral vancomycin or fidaxomicin is reasonable, and symptomatic improvement is supportive of the diagnosis.

CONCLUSIONS

CDI and IBD have overlapping pathophysiology and symptoms and can jointly intensify intestinal inflammation. Discerning whether symptoms are being driven by CDI or IBD is a knowledge gap requiring additional study. It is critical to consider CDI in all cases of IBD exacerbations with a diagnostic approach that ideally includes a 2-step laboratory testing process. Future clinical trials with CDI therapeutics should be performed in patients with IBD specifically or included as an important subpopulation of interest. Ultimately, both CDI and IBD should be treated concurrently without interruption. The likelihood of CDI recurrence is lessened when inflammatory activity in the intestine is controlled.

CONFLICTS OF INTEREST

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