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Epidemiology, Diagnosis, and Management of *Clostridium difficile* Infection in Patients with Inflammatory Bowel Disease

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Abstract

Clostridium difficile infection (CDI) is a major source of morbidity and mortality for the US healthcare system, and frequently complicates the course of inflammatory bowel disease (IBD). Patients with IBD are more likely to be colonized with *C. difficile* and develop active infection than the general population. They are also more likely to have severe CDI and develop subsequent complications such as IBD flare, colectomy, or death. Even after successful initial treatment and recovery, recurrent CDI is common. Management of CDI in IBD is fraught with diagnostic and therapeutic challenges, since the clinical presentations of CDI and IBD flare have considerable overlap. Fecal microbiota transplantation can be successful in curing recurrent CDI when other treatments have failed, but may also trigger IBD flare and this warrants caution. New, experimental treatments including vaccines, monoclonal antibodies, and non-toxicogenic strains of *C. difficile* offer promise but are not yet available for clinicians. A better understanding of the complex relationship between the gut microbiota, CDI, and IBD is needed.

Keywords

Ulcerative colitis; Crohn's disease; inflammatory bowel disease; *Clostridium difficile*; microbiota

Introduction

Clostridium difficile is a Gram-positive, spore-forming, obligate anaerobe and bacillus that was first identified in the 1970s as the cause for the then-rare condition of pseudomembranous colitis (1). Since then, *C. difficile* infection (CDI) has become one of the most frequent causes of nosocomial diarrhea and colitis and its incidence has been increasing over the past decade. *C. difficile* is now responsible for nearly 450,000 cases and 35,000 deaths annually in the US (2). This increased incidence and morbidity is due, in part, to the emergence of epidemic strains, including some with increased virulence (3–5).

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CDI has become particularly problematic for patients with inflammatory bowel disease (IBD). The prevalence of IBD in the US is estimated at 238 per 100,000 population for UC and at 201 per 100,000 for Crohn's, which amounts to over 1 million affected individuals (6). There is a higher prevalence of asymptomatic *C. difficile* carriage in patients with IBD (7, 8), the incidence of symptomatic CDI is higher in this population and has been increasing (9), and patients with IBD are at increased risk for adverse outcomes from CDI, which can also impact the management of the underlying IBD (10). These factors complicate both the diagnosis and management of CDI in patients with IBD and, thus, are the focus of this review.

Pathogenesis of CDI

The pathogenesis of CDI was previously covered in detail in an *Inflammatory Bowel Diseases* review by Monaghan et al. (11) and, therefore, will only be summarized briefly here. Although the complete pathophysiological mechanisms underlying CDI have not been elucidated, it is known that toxin production by *C. difficile* is required and, consequently, non-toxigenic strains are not associated with clinical disease (12, 13). The basic paradigm of infection, shown in Figure 1, first involves loss of colonization resistance and establishment of susceptibility (14, 15). This is usually mediated by exposure to antimicrobials, which alter the gut microbiota to a susceptible state, discussed further below. Ingested *C. difficile* spores can then germinate, establish themselves in the colon, and produce toxins that inactivate the Rho family of proteins through glycosylation, which leads to disruption of the gut endothelial cells' cytoskeletons and cell death(16). One or both of two principal toxins, TcdA and TcdB, are found in most pathogenic strains (16). Some strains, most notably including the epidemic strains known by their various classification schemata as ribotype 027, North American pulsed field gel electrophoresis pattern 1, or restriction endonuclease pattern BI, also produce the binary toxin, CDT (17). Although the precise pathophysiologic role of binary toxin is not known, its presence is associated with increased severity of CDI and mortality (18–20).

In addition to the pathogen's virulence factors, host characteristics also play a role in the susceptibility to CDI. The humoral immune response is important, as patients without antibodies to *C. difficile* toxins are at increased risk of primary CDI and recurrence (21, 22). Relevant to IBD, immunocompromised patients are also at higher risk of CDI and subsequent adverse outcomes (23–26) In other populations, host and treatment-related features, such as healthcare exposure, increased comorbid disease, exposure to proton pump inhibitors, advanced age, and decreased functional status, all impact the risk of CDI and/or the subsequent clinical course (26–30). Although immunosuppression is common, patients with IBD have additional, distinct risk characteristics from these traditional risk factors, including younger age, outpatient care, and lack of antibiotic exposure immediately preceding CDI onset, yet still experience a high incidence of CDI (31).

One putative explanation for the high incidence of CDI in the IBD population, even without presence of classic risk factors for CDI, lies with the gut microbiota. The relationship between the gut microbiota, the disruption caused by antimicrobials (termed dysbiosis), and increased susceptibility to CDI has been established and includes features such as decreased

diversity and alterations in the gut microbial taxa (14, 15, 32–41). In IBD, dysbiosis can occur independently of antimicrobial exposure, and *C. difficile* carriage can occur in this setting, suggesting a mechanism by which IBD itself can predispose to colonization by *C. difficile* (42–46).

Clinical presentation and natural history of CDI

The classic presentation of mild, symptomatic CDI includes diarrhea without systemic signs of infection (47). On endoscopy, pseudomembranes may also be present (Figure 2), though this is uncommon in IBD patients (48). Severe CDI occurs when systemic signs of infection such as fever, leukocytosis, and acute kidney injury are present (49). Complicated CDI results when hypotension, shock, ileus, and/or toxic megacolon are present (49). Although mild CDI may be self-limited, improving upon withdrawal of the inciting antimicrobials alone (50–52), symptomatic improvement often requires treatment as outlined below. Severe and complicated cases of CDI can carry significant morbidity, requiring admission to an intensive care unit and even colectomy. Despite treatment, 8–53% (median 19%) of patients with CDI will die within 30 days of initial disease (26).

Even among those that successfully recover from CDI, recurrence within eight weeks is common and occurs in up to 25% of the general population (26). This incidence of recurrent CDI is considerably higher in older adults (26), and happens in up to 34% of patients with IBD (10, 53). Of those with a first recurrence, 30–45% will experience a second recurrence, with 45–60% of those experiencing a third recurrence, and 5% of patients entering a chronic cycle of seemingly endless recurrences (Figure 1) (54).

Among those that do not recur, asymptomatic shedding of *C. difficile* spores can continue for up to six weeks, complicating the diagnosis of recurrent CDI (55). Furthermore, up to 35% of patients will experience symptoms of a functional bowel disorder in the first two weeks after resolution of CDI (56). Although this is transient and rarely persists, approximately 4% of patients can develop a post-infectious irritable bowel syndrome lasting >3 months from CDI onset (56). Distinguishing a functional bowel disorder with shedding of spores from recurrent CDI remains a clinical challenge without a clear solution.

Standard diagnostic algorithms for CDI

Diagnosis of CDI requires 1) presence of diarrhea (≥ 3 unformed stools in a 24 hour period) or radiographic evidence of ileus/toxic megacolon and 2) a positive stool test result indicating the presence of toxigenic *C. difficile* or colonoscopic/histopathologic findings demonstrating pseudomembranous colitis (47). There are a number of techniques used to identify the presence of toxigenic *C. difficile*, but the most common utilize either an enzyme immunoassay (EIA) for presence of *C. difficile* glutamate dehydrogenase and toxin (TcdA and/or TcdB) or real-time polymerase chain reaction (PCR) for the *tcdB* gene. Since PCR is quite sensitive for the presence of toxigenic *C. difficile*, it may increase detection of asymptomatic colonization and shedding (47). Thus, most experts recommend testing only diarrheal stool with laboratory-based rejection of formed specimens (57). Furthermore, there

are proponents of multistep testing algorithms that start with EIA-based tests with a reflex to the PCR test for discordant EIA results (Figure 3) (47, 58).

Diagnostic dilemmas surrounding CDI in IBD

As noted above, some individuals can carry toxigenic *C. difficile* asymptotically. This leads to one of the major challenges in diagnosing CDI in the IBD population, since there is a high incidence of asymptomatic colonization. Clayton et al. evaluated outpatients with IBD who were in clinical remission and had no recent exposure to antimicrobials, corticosteroids, immunomodulatory agents, or hospitalizations (7). These patients had toxigenic *C. difficile* carriage rates of 8.2%, compared to only 1% of the healthy outpatient population. Furthermore, there was a higher prevalence of *C. difficile* carriage in UC patients (9.4%) than in CD patients (6.9%). Although there are reference standards such as cytotoxicity assay and toxigenic culture that definitively establish the presence of toxigenic *C. difficile* in stool (47), there is no gold standard for diagnosis of symptomatic CDI short of positive testing for the organism plus a histopathologic diagnosis of pseudomembranous colitis. However, pseudomembranes are only present in up to 13% of CDI cases with underlying IBD (48).

Further compounding this dilemma is the considerable overlap seen in the clinical syndromes of CDI and IBD flare (10, 59). It is often impossible to distinguish the two on clinical grounds alone. In addition, the two conditions are not mutually exclusive as they can co-exist temporally, and CDI can even trigger an IBD flare and complicate the subsequent IBD course (53, 59). Strategies for navigating these issues and deciding on the optimal treatment course are discussed below.

Treatment of CDI, IBD, or both?

In patients with IBD, given the clinical conundrum introduced above that often precludes definitively identifying the source of a patient's diarrhea when toxigenic *C. difficile* is present in stool, there are multiple approaches that can be entertained. A survey of American and Canadian gastroenterologists on the topic found them split on the issue, with 46% electing to use antibiotics alone to treat the CDI and 54% electing to use both antibiotics and immunomodulators together (60). One might speculate that "hedging your bets" and treating for both conditions would be the safest approach, however a retrospective, multicenter study in Europe noted an increased risk of mortality in patients treated with both antibiotics and immunomodulators (defined as prednisone >20 mg/day, azathioprine, 6-mercaptopurine, methotrexate, biologics, cyclosporine, or tacrolimus)(61). Although this study had several limitations, including a small sample size, lack of randomization, and non-standardized antibiotics for CDI, this warrants caution in starting or escalating immunosuppression without appropriate antimicrobials against CDI.

Given this uncertainty and lack of guidance from the literature, we have proposed an algorithm to approach treatment of patients with IBD presenting with diarrhea and toxigenic *C. difficile* in their stool that balances the uncertainty and risk in this population (Figure 4). We suggest that patients who present with a clinical syndrome consistent with CDI be

evaluated with appropriate stool testing. If they test negative, immunosuppressive therapy should be initiated (62). If they test positive, appropriate treatment for CDI should begin, as detailed below. If there is no response to the treatment for CDI after 48 hours, then concurrent immunologic therapy can be started/escalated.

Treatment of CDI: initial measures

Asymptomatic carriers of toxigenic *C. difficile* should not be treated as this does not impact the risk of subsequent disease, and may even promote shedding and increase transmission to other individuals (63, 64). Intriguingly, carriers may actually be at lower risk of subsequent CDI. Shim et al. followed asymptotically colonized and non-colonized patients weekly and noted symptomatic CDI occurred in 1% and 3.6%, respectively (65).

Since there are no prospective clinical trials on treating CDI in IBD, evidence from the general population is used to guide management. Initial measures that have been recommended include cessation of other concomitant antimicrobials, antimotility agents, and proton pump inhibitors (47). Though any antibiotic can adversely impact the gut microbiota, penicillins, cephalosporins, clindamycin, and fluoroquinolones are particularly associated with CDI (66–68). Historically, withdrawal of offending antibiotics as monotherapy was sufficient to achieve cure of CDI in up to 15% of patients (50, 51, 69). Both antimotility agents such as loperamide and proton pump inhibitors have been associated with complicated CDI and/or recurrence (70, 71); thus, it is prudent to stop these agents when possible. Cholestyramine has been tested for its role in binding toxins produced by *C. difficile* (discussed below), however it can also bind antibiotics used to treat CDI such as vancomycin and should be stopped prior to starting such therapy (49).

Treatment of CDI: pharmacologic management

Primary CDI mild and severe CDI

The typical management of CDI involves first assigning a severity category and determining if criteria for a recurrent episode are met, followed by selection of the appropriate antimicrobial agent and course (Table 1)(47). Metronidazole has been promoted by numerous guidelines and reviews as the first line agent for mild, uncomplicated CDI, and vancomycin is only recommended for severe CDI and/or recurrence (47, 49, 72, 73). Prior literature has suggested that there is no difference in cure between vancomycin and metronidazole for mild disease (74). However, in 2014 Johnson et al. conducted a pooled analysis of two clinical trials and found metronidazole to be inferior to vancomycin (odds ratio for clinical success 1.58, 95% confidence interval 1.04–2.4, $P = .034$), even after adjustment for disease severity (75). Thus, given the higher likelihood of adverse events from CDI in IBD, many experts have argued for the use of vancomycin first-line in the IBD population, though no prospective data demonstrating a benefit over metronidazole exist (76, 77).

Fidaxomicin is the newest antimicrobial approved for treatment of primary and first recurrence of CDI (78). Fidaxomicin is minimally absorbed from the gut, leading to little systemic exposure and has a very narrow spectrum of activity, leading to little disruption of

the microbiota with use (78). In a meta-analysis of the two phase 3 clinical trials that led to approval of fidaxomicin by the US Food and Drug Administration (FDA) for treatment of CDI, it was found to have a lower incidence of recurrence of CDI when compared to vancomycin (78). The FDA granted a superiority designation for this indication. Despite these encouraging data, widespread use of fidaxomicin for primary CDI and first recurrence of CDI has been hampered by its cost and lack of incorporation into national guidelines. Several studies have examined the cost effectiveness of fidaxomicin and have reached contradictory conclusions (79–81). Furthermore, the efficacy of fidaxomicin in the IBD population has not been well-established.

Complicated CDI

Although there is a paucity of high quality data on the treatment of complicated CDI, expert opinion and guidelines favor higher doses of oral vancomycin along with intravenous (IV) metronidazole (Table 1) (47, 49, 72, 73). There are also case reports suggesting that rectally administered vancomycin may be of benefit when ileus is present and this is thus also recommended (Table 1) (82, 83). Both IV metronidazole and rectally administered vancomycin should be used in combination with oral vancomycin and not in lieu of it, as rectal vancomycin does not reach the entire colon and treatment failures are reported with IV metronidazole monotherapy. (51, 83, 84)

Recurrent CDI

The treatment of recurrent CDI beyond the first recurrence is often initiated through tapering and/or pulsed doses of vancomycin (Table 1). The specific construction of the tapering schedule has not been optimized through any prospective studies, however experts generally suggest reducing the dosing frequency by one administration per day per week, ending with three times weekly dosing (pulsing) (47). The pulsed-dosing strategy may have higher efficacy than tapering alone, based on a secondary analysis of two clinical trials with a 31% incidence of recurrence with a tapering course versus 14.3% with pulsed dosing (85). Given the known significant disruption of the gut microbiota from oral vancomycin, some experts recommend use of a “chaser” with a narrower spectrum of activity following vancomycin which still prevents CDI from relapsing while allowing the microbiota to recover (47). Two studied agents for this indication are rifaximin and fidaxomicin, though neither has high quality evidence in support of their use in the “chaser” role (86–88).

Treatments not recommended for CDI

There are several treatments that have been tested over the years for CDI that are currently not recommended. These include intravenous immunoglobulin and toxin binders such as tolevamer, colestipol, and cholestyramine (47, 75, 89), none of which have demonstrated efficacy in high quality studies, and the latter may actually bind antibiotics used to treat CDI (90). Tolevamer has actually been shown to be inferior to both metronidazole and vancomycin in a randomized, controlled clinical trial (RCT) (75). Tigecycline has been efficacious in case reports for severe CDI but its role remains unclear and, thus, it cannot be recommended at present (91). Nitroimidazole has been studied and does show promise for patients who fail metronidazole, but noninferiority to vancomycin has not been

demonstrated (92–94). Therefore, patients who fail metronidazole should still receive vancomycin next (Table 1).

Probiotics

Probiotics are live microorganism preparations that are used to treat dysbiosis in various conditions. The role of probiotics in CDI remains poorly defined, based on a paucity of high quality evidence. Meta-analyses of numerous small studies have suggested an adjunctive role when taken alongside other antimicrobials in prevention of initial episodes and recurrence (95–98). One large RCT was unable to demonstrate a benefit of probiotics in reducing incident CDI, but did observe a trend toward reduction and with only 1% of the study population developing CDI, it was likely underpowered to detect a true difference (99). In response to an outbreak, a hospital in Canada noted a significant reduction in both incidence and severity of CDI after implementation of a probiotic prophylaxis bundle for patients started on antibiotics (100). However, the entire patient population moved to a new facility mid-way through the study, and much of the reduction was seen following this relocation, casting doubt on the veracity of the results. A recent case series suggests that daily administration of kefir, a fermented milk drink, alongside staggered, tapered doses of vancomycin or metronidazole was beneficial for recurrent CDI (101). Although probiotics are generally safe and well-tolerated, some risk for bacteremia and fungemia exists and has been described in immunocompromised and critically ill patients (102).

Fecal Microbiota Transplantation

Recurrent CDI

Fecal microbiota transplantation (FMT) delivers donated stool into the gut of an affected individual in order to correct dysbiosis and restore the microbiota to a healthy state. In the US, without an investigational new drug application, FMT can only be used for the treatment of CDI (103). The preponderance of data on FMT for CDI is in the treatment of CDI recurrence. Although initially consisting of only case reports and case series, there are now several high quality RCTs demonstrating efficacy (104–108). Although the optimal parameters for FMT administration have not been rigorously tested, the route, stool preparation methods, amount of stool infusate, and donor characteristics all vary considerably between studies and FMT is up to 92% effective irrespective of these variations (54). One recent trial compared fresh to frozen stool and both were highly efficacious, which is encouraging given the convenience of frozen stool banks that obviate the need for individual clinicians to select and screen donors (107). The recent evidence of the effectiveness of frozen, capsulized stool preparations promises to further reduce the logistical barriers to FMT (109). A popular stool bank, OpenBiome (openbiome.org, Medford, MA), initially made available frozen stool capsules for use by investigators in clinical trials, and recently made this treatment option available to all clinicians based on encouraging preliminary data (110).

Primary CDI

There are few studies examining the use of FMT for primary, non-recurrent CDI aside from case reports (54, 111). However, a mathematical model where FMT was used for primary CDI in an intensive care unit suggested a decrease in the mean incidence of recurrent CDI in patients compared to antimicrobial therapy alone (112). This suggests that despite the increased cost and logistical difficulties, there may be benefit to using FMT in lieu of conventional therapy in a population at high risk of recurrence. A major limitation of this study, in addition to being a mathematical model, was the lack of incorporation of known risk factors for CDI. A non-randomized, open label, before/after prospective study of FMT for primary CDI was conducted by Lagier et al. (113) They compared a period utilizing only conventional therapy with one promoting early FMT via nasogastric infusion. This shift in treatment strategies occurred at their institution due to an outbreak of CDI from a ribotype 027 strain that had a 50.8% mortality rate, prompting clinicians to try non-conventional measures to combat the disease. Mortality in the FMT group was 18.8% versus 64.4% ($P < .01$). Since this was an older cohort with a mean age of 84 and during an epidemic, the findings may not be generalizable to treatment of primary CDI in other settings.

Severe and Complicated CDI

FMT for severe CDI (both primary and recurrent) similarly has little evidence, though the published case reports show efficacy (114–117). Furthermore, although the study discussed above by Lagier et al. does not provide data on severity classification, the high mortality rate suggests some of the patients who benefited from FMT met the severity definition (113). There was one death reported following FMT for complicated CDI discussed further below (118), and this warrants caution before widespread use can be recommended for this indication.

Safety of FMT with IBD

FMT for CDI in the general population appears safe in the short term with serious adverse events being uncommon (54). Symptoms of an irritable bowel (cramping and bloating) shortly after FMT are reported but usually last less than 48 hours. However, there may be additional risk incurred in the IBD population. A recent case series of immunocompromised patients with CDI treated by FMT did not identify many adverse events overall (119). However, 14% of the subgroup of patients with IBD experienced adverse events including IBD flare, requiring hospitalization in some instances. Other studies have also reported an increased risk of IBD flare, fever, and elevated inflammatory markers after FMT, including one case of sepsis that developed after a home self-FMT (120). Currently, there are no tools to risk stratify patients in terms of these adverse outcomes and/or select donor stool based on microbiota characteristics. In contrast with the published cases, a recent RCT for patients with ulcerative colitis (without concurrent CDI) treated with FMT did not find any significant adverse events, highlighting the complexity of the interaction between IBD and the microbiota that can result in inter-study variability (121).

Much of the safety data, however, are garnered from studies of FMT for recurrent, non-severe CDI. Use of FMT in severe and complicated CDI has not been well studied in terms of efficacy, and thus there is a paucity of safety data to accompany these indications. In one

study, a patient developed complicated CDI including an associated septic shock and was treated with standard of care (Table 1) but still had loose stools after 18 days of therapy (118). He did have other milder markers of severity at that time, including pancolitis on visualized on computed tomography (CT) and elevated creatinine. He underwent FMT via gastrojejunostomy tube with stool donated by his wife, the procedure was uncomplicated, and antimicrobials were stopped with clinical stability for the first 48 hours. He subsequently developed septic shock and bacteremia from *Pseudomonas aeruginosa*, *Escherichia coli*, and *Lactobacillus casei*. A repeat CT revealed toxic megacolon and, despite resection, he died on the fourth day following FMT. The authors speculate that withdrawal of antibiotics active against CDI may have contributed to his clinical decline. Nevertheless, this case raises concerns over the safety of FMT in severe and complicated CDI.

Unlike the short-term effects, concerns about the long-term safety of FMT have been raised even in the general, immunocompetent non-IBD population (109). There are demonstrated associations between the gut microbiota and other conditions such as diabetes, obesity, and cancer (122). Animal models of colitis and obesity have even been able to “transmit” the disease phenotype through FMT (122–124). Thus, it is plausible that although effective and safe in the short run for treatment of CDI, FMT may be adversely altering the long-term risk profiles of various other diseases. Data on long-term follow-up of patients following FMT is lacking, but one study that followed 77 patients for 3–68 months (mean 17 months) observed the development of several new medical conditions including ovarian cancer and autoimmune disease (125). Although causality cannot be inferred from these data, the findings do highlight the need for additional studies on long-term outcomes in patients that underwent FMT. A systematic review and meta-analysis of any studies with >90 days of follow-up demonstrated an overall low incidence of late adverse events, and only a 1.7% cumulative incidence of late recurrence (126).

Experimental therapies and future directions

FMT

There are several clinical trials underway that may shed light on the safety and efficacy of FMT for primary CDI, severe CDI, and as prophylaxis against CDI for high risk patients on antimicrobials (127–131). Until the data from these studies are available, given the risk of IBD flare and at least one death following FMT seen in some studies and case reports on severe CDI, it is prudent to reserve FMT for recurrent, non-complicated CDI at this time.

There has also been an interest in the use of FMT to correct the underlying dysbiosis of IBD and induce clinical remission. Initial case reports on use of FMT for IBD outside the context of recurrent CDI were encouraging for treatment of UC (132–135). While patients without IBD have fecal microbial diversity that stably mimics the donor stool following FMT, by six months post-FMT, patients with IBD have stool microbiota that returns to the pre-FMT level of diversity, suggesting host-related mechanisms that modify the microbiota (136).

Subsequent reports have raised some concerns, however. In one prospective case series of five patients, none achieved clinical remission after FMT and only one had improvement in symptoms (137). There may also have been harm as all the patients had transient fever and elevation in serum C-reactive protein levels. Another study of six UC patients did note

transient clinical improvement in all of them following FMT, but none achieved remission (138).

Two RCTs have been published on the use of FMT for UC and both were stopped early due to futility, though enrolled patients were allowed to complete the studies (121, 139). Intriguingly, in one of these studies, of the nine patients that did achieve UC remission seven received their stool from the same donor (121). This suggests a donor- and microbiota-specific beneficial effect that has yet to be elucidated by basic research.

The data on use of FMT for CD are even sparser than for UC. One patient in a case report demonstrated clinical improvement only to relapse after 18 months (133). Another report noted clinical, endoscopic, and histologic remission after a single infusion of feces (140). Again, unlike FMT for CDI in the general population, where it appears to be generally effective irrespective of many other clinical and microbiological characteristics, there appears to be underlying characteristics for IBD in the donor, microbiota, and/or recipient that interact in a complex manner to produce the clinical outcome, and the details of this have yet to be determined.

Immunotherapy

There is a *C. difficile* vaccine in development for treatment of primary and recurrent CDI, but the outcomes data have not yet been released (141). Prior data had suggested monoclonal antibodies against *C. difficile* toxins may be efficacious in preventing recurrence (142). Recently, two phase 3 studies, MODIFY I AND MODIFY II evaluated the efficacy of two monoclonal antibodies, actoxumab (ACT) and bezlotoxumab (BEZ), with activity against TcdA and TcdB, respectively (143). The study arm with ACT alone was stopped early due to lack of efficacy in an interim analysis. The pooled analysis of the 2327 patients that received either ACT + BEZ or BEZ alone observed recurrent CDI in 15.4% and 16.5%, respectively, versus 26.6% in the placebo arm ($P < .001$). The safety profiles in the interventional arms were similar to the placebo arm. Although patients with IBD were not specifically included, analysis of other subgroups at high risk of recurrence, such as age ≥ 65 years, history of CDI, ribotype 027 infection, and severity, showed similar reductions in recurrence compared to placebo.

Non-toxicogenic *C. difficile*

Another strategy to prevent recurrent CDI involves administration of spores derived from non-toxicogenic strains of *C. difficile*. A phase 2 RCT studying strain VP20261 administered to patients with primary CDI or first recurrence of CDI found a dose-dependent reduction in recurrent CDI (144). Recurrent CDI overall occurred in 11% of patients receiving spores, compared to 30% in the placebo arm ($P = .003$). However, only the subgroups receiving 10^7 spores/day demonstrated a significant benefit, while those receiving 10^4 spores/day did not. Furthermore, colonization with the non-toxicogenic strain was transient, as all study arms had negative fecal cultures by week 26. Since TcdA and TcdB are not produced by this strain, the mechanism of action for protection is not well-understood, but it may be transient given the lack of persistent fecal colonization. Possible non-immunologic mechanisms for

resistance to recurrent CDI conferred by non-toxigenic strains include alterations in the microbiota or niche exclusion through physical occupation or competition for nutrients.

Summary and Conclusions

The management of CDI in patients with IBD presents both diagnostic and therapeutic challenges. Balancing the risk of certain treatment strategies is important given that CDI can present with severe features when IBD is present and can affect the subsequent course of IBD. Although FMT shows promise, the role of the microbiota in IBD is complex and initial studies warrant a cautious approach. A better understanding is needed of the specific features of the microbiota that promote IBD remission with or without concomitant CDI. New treatments on the horizon including vaccines, monoclonal antibodies, and spores of non-toxigenic *C. difficile* may soon give patients multiple additional options for management of what can be a difficult, recalcitrant disease.

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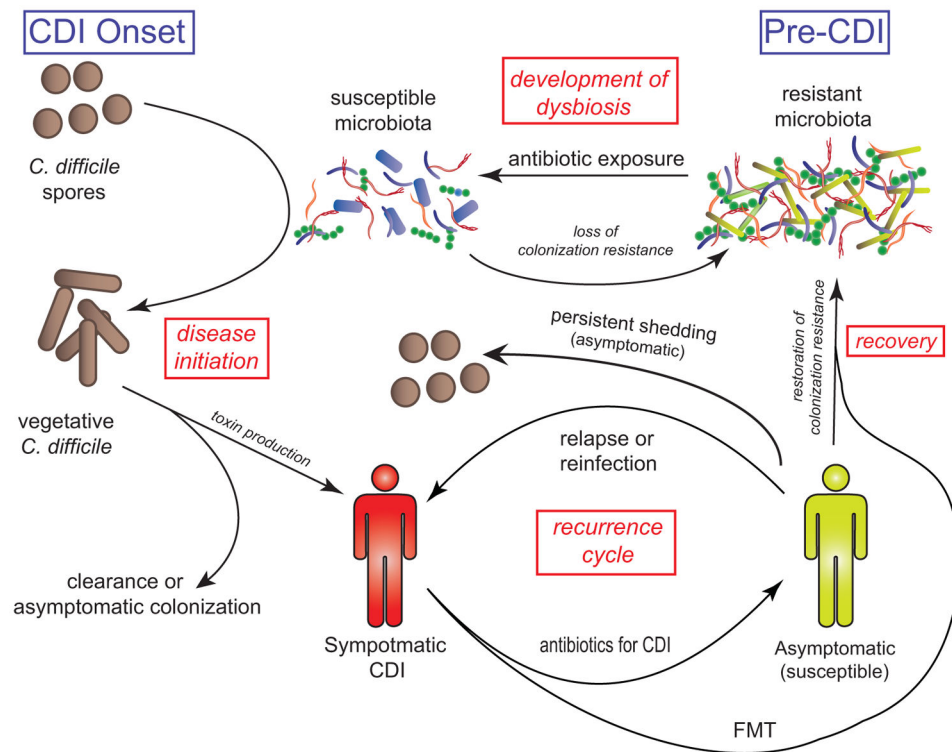


Figure 1. Life cycle of *Clostridium difficile* infection (CDI)

CDI first requires a susceptible host and microbiota, which often occurs following antibiotic exposure that decreases the diversity and composition of the gut's microbial community. Some patients never develop disease, either clearing the infection or becoming asymptotically colonized. Many patients shed spores asymptotically following CDI. Even after successful treatment, some patients remain susceptible and can have recurrences. Fecal microbiota transplantation can help restore colonization resistance and break the cycle of recurrence

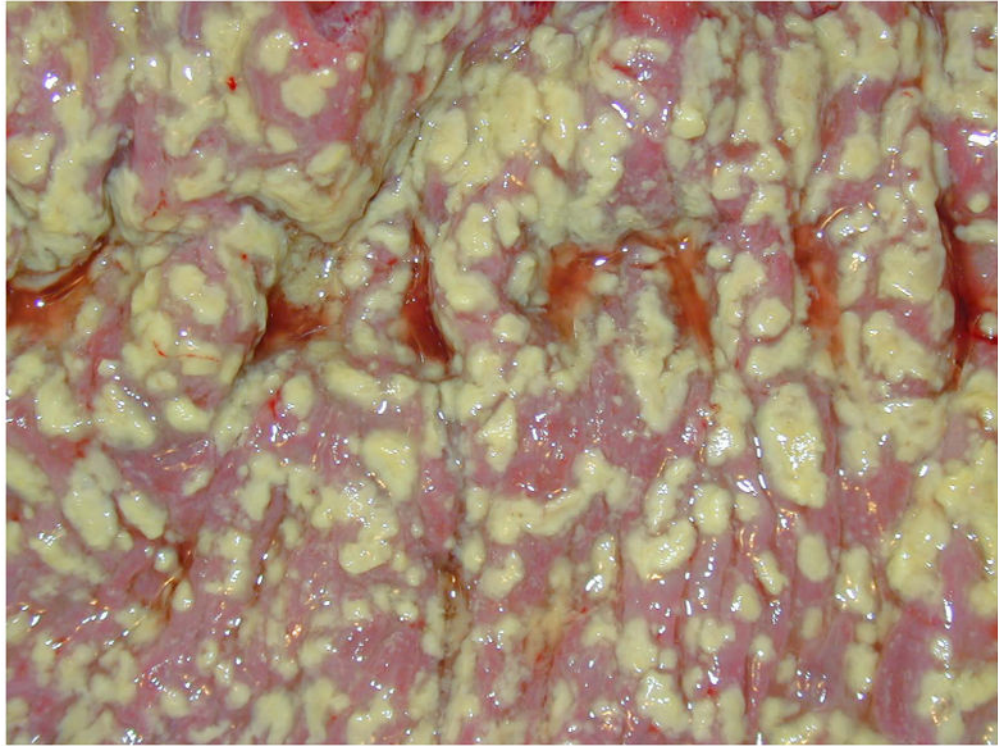


Figure 2. Pseudomembranous colitis seen on a pathological colon specimen

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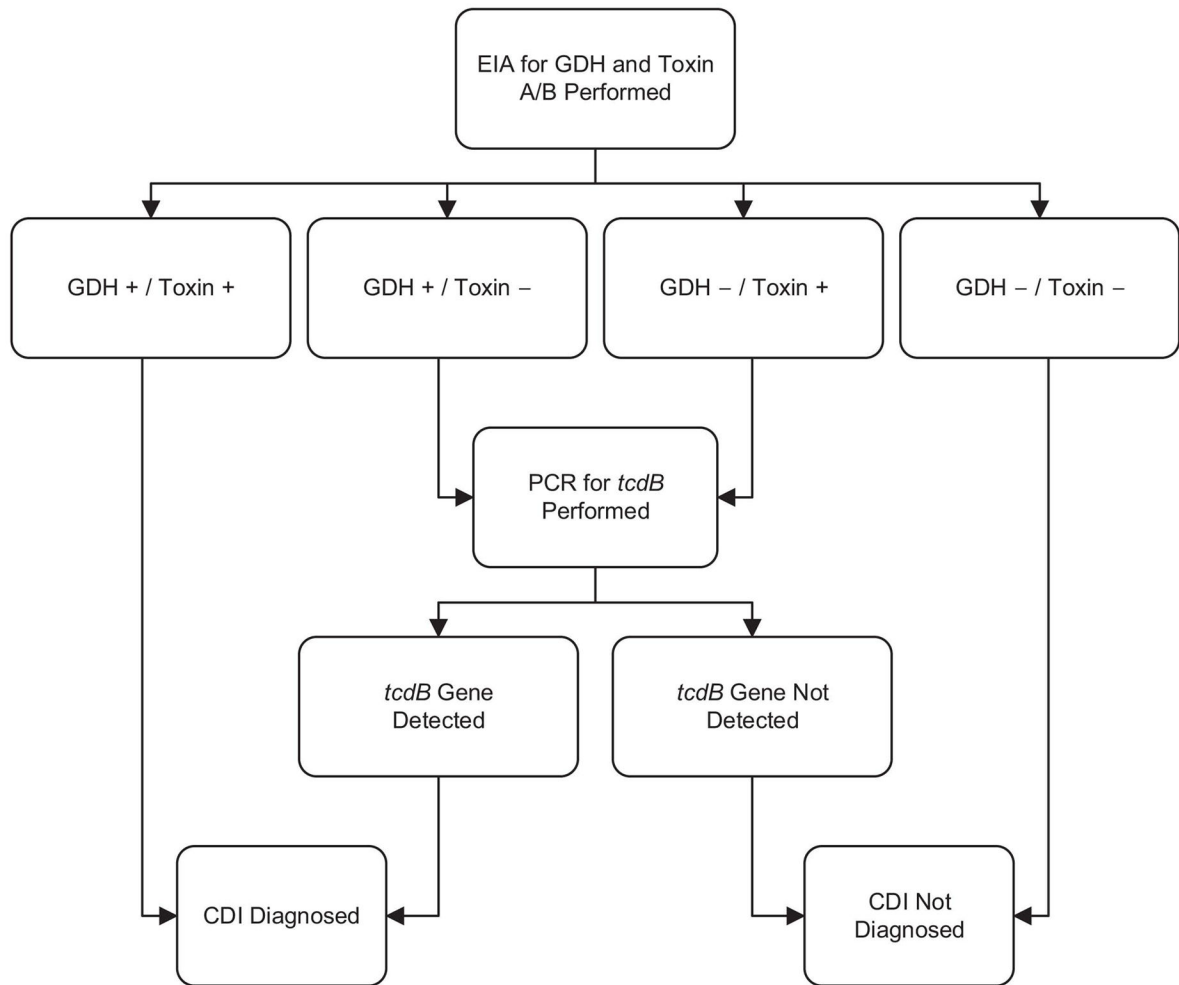


Figure 3. Sample multistep testing algorithm for diagnosis of *Clostridium difficile* infection

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Abbreviations. CDI, *Clostridium difficile* infection; EIA, enzyme immunoassay; GDH, glutamate dehydrogenase; PCR, polymerase chain reaction.

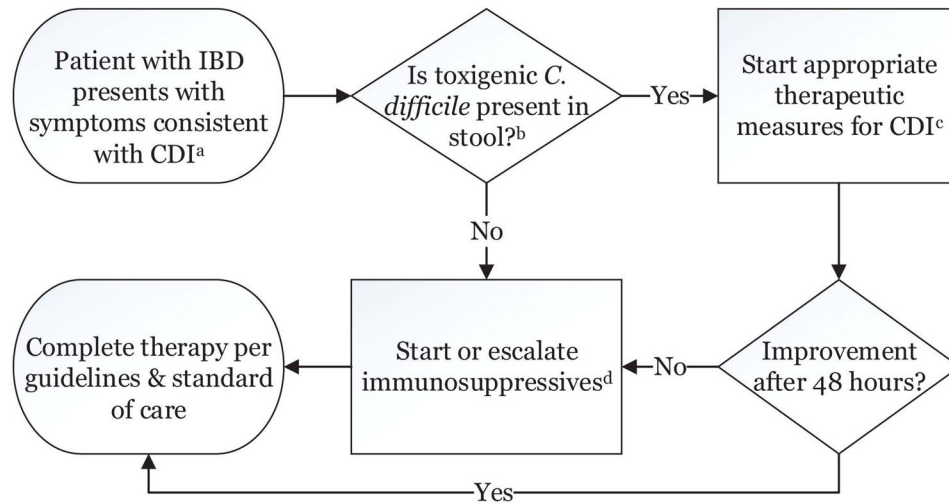


Figure 4. Suggested algorithm for management of patients with IBD presenting with symptoms consistent with CDI

Footnotes:

^aSee text for details on symptoms consistent with CDI.

^bWhile awaiting test results, empiric treatment for CDI and/or IBD flare may be appropriate with a severe presentation

^cSee table 1 for details.

^dThe management of IBD flare is beyond the scope of this review; see Kornbluth et al. 2010 (62) for suggestions on how to proceed.

Abbreviations: CDI, *Clostridium difficile* infection; IBD, inflammatory bowel disease.

Table 1

Classification and pharmacologic management of CDI.

Classification	Criteria	Treatment options
Primary CDI, non-severe	Diarrhea without signs of systemic infection, WBC <15,000 cells/mL, and serum creatinine <1.5 times the premorbid level	metronidazole 500 mg by mouth three times daily for 10–14 days OR vancomycin 125 mg by mouth three times daily for 10–14 days OR fidaxomicin 200 mg by mouth twice daily for 10 days ^a
Primary CDI, severe	Signs of systemic infection and/or WBC 15,000 cells/mL, or serum creatinine 1.5 times the premorbid level	vancomycin 125 mg by mouth three times daily for 10–14 days OR fidaxomicin 200 mg by mouth twice daily for 10 days ^a
Primary CDI, complicated	signs of systemic infection including hypotension, ileus, or megacolon	vancomycin 500 mg by mouth four times daily AND intravenous metronidazole 500 mg three times daily AND (if ileus is present) vancomycin 500 mg by rectum four times daily
Recurrent CDI	Return of symptoms with positive <i>C. difficile</i> testing within 8 weeks of onset, but after initial symptoms resolved with treatment	<u>First recurrence</u> : same as initial treatment, based on severity. <u>Second recurrence</u> : Start treatment based on severity, followed by a vancomycin pulsed and/or tapered regimen over six or more weeks

Footnotes.

^a fidaxomicin is not currently represented in US guidelines (49) but is FDA-approved for the treatment of CDI.Abbreviations: CDI, *Clostridium difficile* infection; WBC, white blood cell count.