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MANAGEMENT OF CLOSTRIDIOIDES DIFFICILE IN IBD PATIENTS

Introduction

Clostridioides difficile (*C. difficile*) is an anaerobic, spore-forming, Gram-positive bacterium. *C. difficile* is the most frequently reported nosocomial pathogen.[1] *C. difficile* is also the most commonly identified pathogen associated with antibiotic-associated diarrhea, responsible for up to 30% of antibiotic-associated diarrhea.[2] Spores are transmitted via the fecal-oral route, and acquisition of *C. difficile* in the healthcare setting is generally by contaminated hands or surfaces. *C. difficile* has two monoglycosyltransferase virulence factors that are responsible for damage to the intestinal mucosa, enterotoxin A (TcdA) and cytotoxin B (TcdB). These two enzymes enter intestinal epithelium through receptor-mediated endocytosis and irreversibly inactive Rho GTPases. This ultimately disrupts the cytoskeleton and tight junctions, resulting in a loss of parenchymal polarity and eventual apoptosis.

A population-based study from Manitoba reported that individuals with inflammatory bowel disease (IBD) have a 4.8-fold increased risk of laboratory confirmed *C. difficile* infection (CDI) compared to individuals without IBD, with no difference in rates between those with ulcerative colitis (UC) or Crohn's disease (CD).[3] Among individuals with IBD, exposure to corticosteroids; use of anti-TNF agents; use of metronidazole; hospitalizations; numerous ambulatory care visits; shorter duration of IBD; and numerous comorbidities are associated with an increased risk of CDI.[3] The risk of CDI is increased among individuals of all ages with IBD. The incidence rate of hospitalization with CDI in a Canadian multi-provincial population-based incident cohort of children with IBD was reported to be 49.06 (95% CI 39.40-61.08) per 10,000 person-years and was nearly 70-fold that of age- and sex-matched children without IBD.[4] The reasons why IBD patients are more susceptible to CDI are not fully understood, but some possible factors include: frequent use of antibiotics and immunosuppressive drugs; increased exposure to healthcare settings where *C. difficile* is prevalent; altered gut microbiota; compromised mucosal barrier function due to inflammation; and genetic susceptibility.

Among patients with IBD, CDI is associated with worse clinical outcomes compared to individuals without IBD, including increased emergency room visits, longer hospitalizations, higher rates of colectomy, and increased mortality.[3,5-7] CDI may mimic an IBD flare and can precipitate an IBD flare. Given the clinical overlap between CDI and IBD exacerbations (e.g., increased frequency of loose stools, abdominal pain), it is difficult to differentiate CDI versus colonic colonization in patients with active IBD who test positive for *C. difficile*.[8] *C. difficile* colonization occurs in up to 15% of healthy adults and more than 20% of hospitalized adults.[9] In a prospective study, *C. difficile* colonization was higher among IBD patients (8.2%) in remission with no recent hospitalizations or recent exposure to corticosteroids, immunomodulators or antibiotics compared to healthy controls (1.0%).[10]

Diagnosing *Clostridioides difficile* Infection

Testing and treatment for *C. difficile* colonization is not recommended. Rather, testing for *C. difficile* should occur in patients where there is clinical suspicion for CDI (e.g., frequent and loose stools, abdominal pain, leukocytosis). Therefore, anyone with known IBD presenting with an acute flare associated with diarrhea should undergo testing for *C. difficile*.[11] All diagnostic tests have been validated for use on unformed stool only; as a result, most laboratories will not process formed stool.

The Infectious Disease Society of America (IDSA) and the American College of Gastroenterology (ACG) recommend multistep testing algorithms to diagnose CDI.[11,12] However, use of a multistep testing algorithm can fail to differentiate symptomatic CDI from asymptomatic colonization among individuals with IBD with symptoms due to IBD.[13]

Commercially available tests include nucleic acid amplification tests (NAAT), enzyme immunoassays (EIA), toxigenic culture, and next-generation sequencing (NGS). NAAT is a PCR that tests for the presence of toxin genes A and B. NAAT is regarded to have excellent sensitivity (up to 100%), but a specificity of 87% with a positive-predictive value of 45%,[14] therefore, there is risk of overdiagnosis in the setting of colonization. The EIAs test for the presence of toxin in stool and are regarded to have lower sensitivity but improved specificity compared to NAAT. Ultrasensitive protein-based stool tests have been developed that have improved diagnostic accuracy for CDI; however, they are not yet commercially available.[15] Certain laboratories may use EIA to detect stool glutamate dehydrogenase (GDH). However, this enzyme is produced by both toxigenic and nontoxigenic strains of *C. difficile*, therefore, a second confirmatory test is required.

Due to the issues with differentiating CDI vs colonization, a multistep algorithm is recommended by the ACG,[11] first using a highly sensitive NAAT or GDH test, followed by a more specific toxin EIA if the first test is positive. If both tests are positive, a diagnosis of CDI is reliably made. A problem arises when there is discordance between two tests. As toxin EIA is less sensitive, GDH positive, toxin negative can result in a false negative, where a CDI exists. The ACG guideline points out "Because no test is perfect, the diagnosis and decision to treat is a clinical one. Treatment should not be withheld when there is high clinical suspicion, based on laboratory testing alone". Therefore, a positive GDH with a negative EIA toxin test requires treatment in selected cases with severe symptoms and a high index of suspicion for CDI in IBD patients.

Treatment of *Clostridioides difficile* Infection

Following the diagnosis of a CDI in an individual with IBD involves treating the infection with antibiotics and optimizing management of the patient's immunosuppression.[7] The IDSA and ACG consider vancomycin or fidaxomicin as first-line antibiotics for non-severe or severe diseases (white blood count ≥15,000 cells/mL or serum creatinine >1.5x above baseline).[11,12] Vancomycin is dosed at 125 mg orally four times/day for 10 days, and fidaxomicin is dosed at 200 mg orally twice daily for 10 days. Vancomycin is generally preferred as the first-line antibiotic as fidaxomicin is much more expensive. However, fidaxomicin is associated with lower rates of CDI relapse and some cost-effectiveness analyses do favour fidaxomicin over vancomycin.[16,17]

There are limited data and randomized, controlled trials concerning treatment-specific regimens for CDI in individuals with IBD. In general, metronidazole is not recommended as monotherapy, and a prolonged course of vancomycin (14 days instead of 10 days) is favoured.[11] Fidaxomicin is also deemed a reasonable option. In the setting of a suspected or confirmed IBD flare with concurrent CDI, immunosuppressive therapy should not be held; conversely escalation of immunotherapy should be considered in those with no symptomatic improvement after three days of CDI treatment.

For fulminant CDI, defined as the presence of hypotension or shock, ileus, or megacolon, vancomycin 500 mg four times daily (orally or by nasogastric tube) is recommended. Vancomycin can be administered rectally as an enema if enteral administration is contraindicated and, in such cases, intravenous metronidazole 500 mg every eight hours should be added in addition to rectal vancomycin.[11,12]

C. difficile infection recurrence is defined as an episode of CDI occurring within 12 weeks of a previous CDI. For the first recurrent CDI, it is recommended that the treatment regimen be modified from the first, as follows: (1) vancomycin 125 mg orally four times daily for 10 days if metronidazole was used for the initial episode; (2) pulsed vancomycin plus taper (125 mg orally four times daily for 10-14 days, followed by twice daily for one week, then once daily for one week, then every two or three days for two to eight weeks if standard vancomycin dosing was used for the initial CDI; or (3) fidaxomicin 200 mg orally twice daily for 10 days if standard vancomycin dosing was used for the initial CDI.[11,12] For a second recurrence or any subsequent recurrence thereafter, vancomycin pulse

and taper or standard fidaxomicin are recommended, as outlined above. Standard 10-day dosing of vancomycin followed by rifaximin 400 mg three times daily for 20 days is also an option. However, all of these treatment regimens for the second CDI and recurrence thereafter is based on low quality of evidence and therefore is backed by weak strength of recommendation (**Table 1**).[12]

Other options for the treatment of CDI recurrence include bezlotoxumab, a monoclonal antibody targeting cytotoxin B (TcdB), and fecal microbiota transplantation (FMT). The ACG recommends reserving bezlotoxumab for individuals experiencing at least their second episode of CDI in the past six months, in those aged 65 or over, along with an additional risk factor, i.e., immunocompromised or severe CDI.[11]

FMT is has been shown to be beneficial in preventing CDI recurrence in IBD patients.[11] The ACG recommends that FMT be considered for patients with severe or fulminant CDI that is refractory to antibiotics, or for patients experiencing their second or further recurrence of CDI. It can be considered in IBD patients with their first CDI recurrence.[11] FMT is administered through a colonoscopy and should be combined with an antibiotic regimen as described above. Toxic megacolon is not considered an absolute contraindication to the administration of a FMT.[11] The colonoscope should be carefully advanced beyond the splenic flexure, and FMT repeated every 3-5 days until pseudomembrane resolution or discharge from hospital. Vowst™ is an orally administered fecal microbiota product that is FDA approved but not yet available in Canada. It is a capsule composed of purified Firmicutes spores from healthy donors, and is approved for CDI recurrence that is unresponsive to antibiotics.[18]

Additional Considerations

Probiotics are not recommended for the prevention of CDI or recurrent CDI due to a lack of conclusive evidence; this has been previously reviewed in detail.[11] Follow-up testing or so-called test of cures should not be done where there has been adequate treatment and symptom resolution as there can be clinically irrelevant toxin shedding for up to four weeks postinfection. Furthermore, there is insufficient evidence to suggest that proton pump inhibitors (PPIs) should be discontinued as a measure for preventing CDI.[11,12] *C. difficile* enteritis and pouchitis are rarely reported entities; however, *C. difficile* testing can be considered in IBD patients who have undergone colectomy and are unresponsive to conventional treatment for their underlying IBD.

Treatment	Dosing regimen
First CDI episode	
1. Vancomycin	125 mg orally four times daily for 14 days
2. Fidaxomicin	200 mg orally twice daily for 10 days
First CDI Recurrence (episode of CDI occurring within 12 weeks of a previous CDI)	
1. Vancomycin	pulsed + taper (125 mg orally qid for 14 days, followed by bid for one week, then once daily for one week, then every two or three days for two to eight weeks if standard vancomycin dosing was used for initial CDI
2. Fidaxomicin	200 mg orally bid for 10 days
Second CDI Recurrence (or any subsequent recurrence thereafter)*	
1. Vancomycin	pulsed + taper (125 mg orally qid for 14 days, followed by bid for one week, then once daily for one week, then every two or three days for two to eight weeks
2. Fidaxomicin	200 mg orally bid for 10 days
3. Vancomycin + rifaximin	Standard 14-day dosing (vancomycin) followed by 400 mg tid for 20 days (rifaximin)

Table 1. *First line drug regimens for the management of CDI in IBD; courtesy of Harminder Singh, MD and Jeffery M. Venner, MD*
** Low strength of evidence for these treatment regimens.*

Clinical Pearls
✓ C. difficile occurs much more commonly among people with IBD
✓ C. difficile Infection is associated with worse outcomes among people with IBD
✓ Individuals with colonic IBD with flare symptoms should be evaluated for C. difficile infection
✓ Vancomycin is the drug of choice for treating the first episode of C. difficile infection
✓ Metronidazole should no longer be used to treat C. difficile Infections among those with IBD
✓ Multistep testing algorithms (i.e., include both a highly sensitive and a highly specific assay) should be used to diagnose CDI. However, as noted by the ACG, clinicians should also be aware that "Because no test is perfect, the diagnosis and decision to treat is a clinical one. Treatment should not be withheld when there is high clinical suspicion based on laboratory testing alone".

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Financial Disclosures:
H.S.: Advisory boards/Consultation: Abbvie Canada, Amgen Canada, Roche Canada, Sandoz Canada, Organon Canada, Eli Lilly Canada, Takeda Canada, Pendopharm Inc, and Guardant Health, Inc

Research funding: Pfizer

J.V.: None declared

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