

CLINICAL PRACTICE UPDATES

AGA Clinical Practice Update on Management of *Clostridioides difficile* Infection in Inflammatory Bowel Disease: Expert ReviewSahil Khanna,¹ Jessica R. Allegretti,² Jana G. Hashash,³ and Paul Feuerstadt⁴¹Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota; ²Division of Gastroenterology and Hepatology, Brigham and Women's Hospital, Boston, Massachusetts; ³Division of Gastroenterology and Hepatology, Mayo Clinic, Jacksonville, Florida; and ⁴Division of Gastroenterology and Hepatology, Yale University, New Haven, Connecticut

DESCRIPTION: *Clostridioides difficile* infection (CDI) remains a significant driver of disease flares and poor outcomes in patients with inflammatory bowel disease (IBD), leading to increased hospitalization, intensified or failed therapy, and higher surgical rates. Compared with the non-IBD population, patients with IBD face greater CDI risk and severity and higher recurrence risk, creating clinical dilemmas when considering antibiotic selection and the timing or necessity of IBD-related therapy adjustments. Emerging evidence highlights microbiota-based therapies such as unapproved fecal microbiota transplantation or US Food and Drug Administration–approved donor-derived therapies as a promising therapeutic avenue for recurrent CDI in patients with IBD, reflecting a growing emphasis on microbiome-directed interventions. This review examines the evolving literature, considering the diagnosis and management strategies and offering pragmatic guidance to optimize outcomes for patients with IBD challenged by concomitant CDI and recurrent CDI. **METHODS:** This Expert Review was commissioned and approved by the American Gastroenterological Association (AGA) Institute Clinical Practice Updates Committee and the AGA Governing Board to provide timely guidance on a topic of high clinical importance to the AGA membership and underwent internal peer review by the Clinical Practice Updates Committee and external peer review through standard procedures of *Gastroenterology*. These practical Best Practice Advice statements were drawn from a review of the best available published evidence, including existing clinical studies, systematic reviews and practice guidelines, and expert opinion. Because a formal systematic review was not performed, these Best Practice Advice statements do not carry formal ratings of the quality of evidence or strength of the presented considerations. The focus is on the management of both CDI and IBD in patients with underlying IBD who develop CDI.

BEST PRACTICE ADVICE STATEMENTS

BEST PRACTICE ADVICE 1: In patients with IBD who have new or worsening diarrhea, CDI should be excluded, especially among those with colonic involvement, as they are at increased risk of CDI. Clinicians should consider and treat CDI in patients with end ileostomy or ileo-anal pouch anastomosis with worsening diarrhea. **BEST PRACTICE ADVICE 2:** In patients with IBD and suspected CDI, a multi-step toxin-based assay should be used for diagnostic evaluation. **BEST PRACTICE ADVICE 3:** In patients with IBD and recent CDI who have been treated successfully with antibiotics, recurrent diarrhea should prompt retesting for CDI. **BEST PRACTICE ADVICE 4:** In patients with IBD who develop an initial episode of CDI, clinicians should preferentially use fidaxomicin or use vancomycin if fidaxomicin is unavailable or cost-prohibitive. Metronidazole should not be used. **BEST PRACTICE ADVICE 5:** Clinicians should strongly consider hospitalization for patients with IBD and CDI who

demonstrate features of severe colitis or systemic toxicity (eg, more than 6 bowel movements per day, severe abdominal pain, marked leukocytosis, hemodynamic instability, or other evidence of sepsis). **BEST PRACTICE ADVICE 6:** When selecting an immunosuppressive therapy to treat IBD, no class or mechanism of action has a differential risk of CDI and, therefore, clinicians should choose the therapy that is best to treat the IBD. **BEST PRACTICE ADVICE 7:** In patients with IBD and acute CDI, concurrent treatment of IBD is critical and clinicians should continue therapy with the required immunosuppressive therapies (ie, immunomodulators, biologics, or small molecules). Steroids can also be used if deemed necessary while CDI is treated with antibiotics. **BEST PRACTICE ADVICE 8:** Clinicians should consider endoscopic evaluation for IBD activity and exclusion of concomitant cytomegalovirus infection if symptoms persist 48–72 hours after initiation of treatment for CDI. **BEST PRACTICE ADVICE 9:** Clinicians may consider loperamide in patients with improving inflammation and infection but ongoing diarrhea. **BEST PRACTICE ADVICE 10:** Clinicians should offer microbiome-based therapies (eg, fecal microbiota, live-jslm, fecal microbiota spores, live-brpk, or unapproved fecal microbiota transplantation) to patients with IBD with at least 1 recurrence of CDI to prevent future infection. **BEST PRACTICE ADVICE 11:** In patients with IBD, clinicians should not advise probiotics for primary or secondary prevention of CDI. **BEST PRACTICE ADVICE 12:** In patients with IBD and a history of CDI who are receiving systemic antibiotics, clinicians may consider oral vancomycin prophylaxis as secondary prevention.

Keywords: Crohn's Disease; Ulcerative Colitis; *Clostridioides Difficile*; Immunosuppression; Microbiome; Antibiotics.

Clostridioides difficile infection (CDI) is caused by an anaerobic, spore-forming, gram-positive bacillus that occurs with antibiotic use and increasing age.¹ Patients

Abbreviations used in this paper: AGA, American Gastroenterological Association; CDI, *Clostridioides difficile* infection; EIA, enzyme immunoassay; FDA, US Food and Drug Administration; FMT, fecal microbiota transplantation; GDH, glutamate dehydrogenase; IBD, inflammatory bowel disease; NAAT, nucleic acid amplification test; OVP, oral vancomycin prophylaxis; PCR, polymerase chain reaction; RBL, fecal microbiota, live-jslm; rCDI, recurrent *Clostridioides difficile* infection; VOS, fecal microbiota spores, live-brpk.

 Most current article

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with comorbid conditions such as inflammatory bowel diseases (IBD) are at risk of developing CDI, regardless of age or antibiotic exposure (Supplementary Table 1). Because asymptomatic *C difficile* colonization is more prevalent among patients with IBD, stool assay results should be interpreted cautiously. Patients with IBD experience disease exacerbations secondary to CDI, leading to increased hospitalizations, escalation of IBD therapy, and surgery. Symptoms do not distinguish CDI from IBD flare, underscoring the need for cautious decision making.²

Areas requiring consideration include choice and timing of antibiotic and IBD therapies. We summarize the existing literature and provide management guidance for patients with IBD and with CDI via 12 Best Practice Advice statements. Table 1 outlines the management of CDI in patients with IBD. Table 2 outlines common pitfalls in the co-management of CDI and IBD. Figure 1 provides a management algorithm for CDI in IBD.

Best Practice Advice 1: In patients with IBD who have new or worsening diarrhea, CDI should be excluded, especially among those with colonic involvement, as they are at increased risk of CDI. Clinicians should consider and treat CDI in patients with end ileostomy or ileo-anal pouch anastomosis with worsening diarrhea.

Patients with IBD presenting with new or worsening diarrhea should be promptly evaluated for CDI, particularly those with colonic involvement, due to a higher CDI risk, up to 8 times the general population even in the absence of antibiotic use.^{3,4} Apart from prior CDI (which confers a higher CDI risk), there are no other clinical features that distinguish possible CDI complicating IBD from an IBD flare.

Patients with an end ileostomy or ileal pouch-anal anastomosis who develop worsening diarrhea or increased ostomy or pouch output should be evaluated for CDI and treated when testing is positive. In patients with ileal pouch-anal anastomosis, CDI has been detected in 10%–18% of patients.⁵ In patients with end ileostomy, *C difficile* enteritis is recognized increasingly with high stoma output.^{6,7}

The pathogenesis of CDI in IBD involves complex interactions between host and microbiome factors. Disruption of the colonic microbiota or dysbiosis, whether from underlying IBD or antibiotics, diminishes colonization resistance and facilitates *C difficile* growth. Toxins A and B trigger a cascade of inflammatory responses and mucosal injury, mimicking or exacerbating an IBD flare. In IBD, the ratio of primary and secondary bile salts is reversed, with higher primary bile acids in the colon, enhancing *C difficile* spore germination.⁸

Although IBD assessments, serum inflammatory markers, fecal calprotectin, and imaging are frequently obtained in this setting, their diagnostic performance is altered during active CDI. Inflammatory markers may be elevated due to infection-related systemic inflammation with limited specificity for IBD activity. Fecal calprotectin is elevated in CDI as a result of neutrophil-mediated mucosal inflammation, resulting in reduced positive predictive value

for identifying an IBD flare during CDI. Imaging may demonstrate nonspecific inflammatory changes and is more useful for identifying complications. These tests should be viewed as adjunctive rather than discriminatory tools in patients with IBD and CDI. Infection-control precautions should be instituted for suspected or confirmed CDI in IBD (Supplementary Table 2).

Best Practice Advice 2: In patients with IBD and suspected CDI, a multistep toxin-based assay should be used for diagnostic evaluation.

Diagnosing CDI in those with IBD is challenging due to overlapping symptoms and higher rates of asymptomatic colonization (ie, presence of bacteria) but not actively releasing toxin, making *C difficile* an unlikely source of symptoms.^{9,10} Because treatments of IBD flare and CDI are different, differentiating a carrier with an IBD flare from active CDI is essential¹¹ (Figure 1, Tables 1 and 2).

Clinicians rely on clinical history and stool assays to identify CDI.¹² Patients with CDI present with at least 3 liquid stools in a 24-hour period, for 2 consecutive days. Stool enzyme-linked immunoassay (EIA) for toxins A/B detects toxin and EIA for glutamate dehydrogenase (GDH), and nucleic acid amplification test (NAAT) and polymerase chain reaction (PCR) identify the presence or absence of the organism. Compared with the gold-standard cytotoxicity neutralization assay, these available tests have variable sensitivity and specificity, while the gold-standard assay itself is time-consuming, expensive, and impractical.

A 2-step approach, first attempting to detect the organism with a highly sensitive assay via GDH or PCR/NAAT is preferred. If this is positive, then a highly specific assay, the EIA detecting toxins A/B, can confirm active infection.¹³ If the NAAT/PCR is positive but the EIA for toxins A/B is negative, then the patient is likely a carrier and is not releasing toxin, so is assumed not to have active CDI.¹⁰ However, is it possible for the EIA for toxins A/B to have a false-negative result and, if suspicion is high, clinical judgment must be exercised.

The GDH assay detects any *C difficile*, not necessarily toxin-producing bacteria. A scenario of a positive GDH and negative EIA for toxins A/B could imply presence of non-toxin-producing *C difficile*. However, given the low sensitivity of EIA for toxins A/B, PCR assay that detects the toxin-producing genes is performed to arbitrate, either confirming or refuting the diagnosis in the context of symptoms.

Best Practice Advice 3: In patients with IBD and recent CDI who have been treated successfully with antibiotics, recurrent diarrhea should prompt retesting for CDI.

Recurrent CDI (rCDI) is typically defined as the recurrence of diarrhea in addition to a confirmatory positive test for CDI within 8 weeks of CDI treatment.¹⁴ A 2-step testing algorithm is preferred in this patient population, given the prevalence of *C difficile* colonization.^{10,13} Testing should be done at least 72 hours after stopping vancomycin to avoid false-negative results.

In the non-IBD population, approximately 20%–30% of patients overall develop an initial recurrence, and rates of

Table 1. Outline for Management of *Clostridioides Difficile* Infection and Inflammatory Bowel Disease**1. Risk factors and patient assessment**

- Medication history
 - Recent or ongoing antibiotic therapy
 - Current immunosuppressive therapy
 - Proton pump inhibitor use
- Disease status
 - Active IBD flare or recent hospitalization
 - Chronic comorbidities
- Health care exposure
 - Frequent clinic or hospital visits
 - Recent surgery or procedures

Action: Identify and minimize modifiable risk factors (eg, stop unnecessary antibiotics, consider de-escalation of proton pump inhibitors if possible).

2. Diagnostic considerations

- Symptom check
 - New-onset or worsening diarrhea (3 or more loose stools per day)
 - Abdominal pain, fever, elevated inflammatory markers (eg, C-reactive protein and white blood cell count)
- Diagnostic tests

Understand the testing available to you and use a stepwise algorithm to differentiate true CDI from colonization, especially in symptomatic IBD flares.

1. GDH + toxin EIA algorithm
 - GDH + toxin EIA: If both GDH and toxin are positive, diagnose CDI. If both GDH and toxin are negative, rule out CDI. If GDH is positive and toxin is negative, confirm with NAAT (PCR).
2. NAAT (PCR) alone for *C difficile* toxin genes
 - Highly sensitive but can detect colonization rather than active infection; interpret with caution in patients with IBD.
3. NAAT (PCR) plus toxin EIA algorithm
 - Because NAAT alone can detect colonization, positive EIA with NAAT confirms diagnosis. Positive NAAT and negative EIA should be interpreted with caution due to low sensitivity of EIA.
4. Toxin EIA
 - More specific but less sensitive than NAAT.
5. Flexible sigmoidoscopy (select cases)
 - Might be indicated to rule out other causes of colitis flare or if diagnosis is uncertain.

Action: Assess response to CDI antibiotic therapy and escalate care as needed.

3. Antibiotic management

- First-line treatment
 - Oral fidaxomicin (preferred due to lower recurrence rates)
 - Oral vancomycin if fidaxomicin is unavailable or cost-prohibitive
 - Do not use metronidazole
- Duration
 - Typically 10 days; consider fidaxomicin EXTEND regimen (eg, 200 mg PO bid for 5 days followed by 200 mg once every other day for days 7–25). Consider prolonged vancomycin (21–42 days) for initial infection or vancomycin taper-pulse regimens for complicated/recurrent cases ([Supplementary Table 3](#)).

Action: Adjust antibiotic choice fidaxomicin over vancomycin.

4. Management of IBD therapy during active CDI

- Assess disease activity
 - Distinguish CDI from IBD flare to avoid premature escalation of immunosuppression.
- Corticosteroids
 - May be continued or initiated if there is a high concern for concurrent moderate to severe IBD flare but use caution and closely monitor infection response.
- Immunomodulators/biologics/small molecules
 - Continue if clinically indicated for IBD control. Avoid abrupt cessation, if possible, because uncontrolled IBD can also worsen outcomes.
 - In cases of fulminant CDI, consider a temporary hold of nonessential immunosuppressants until there is some clinical improvement of CDI.^a

Action: Balance risk of infection worsening with risk of unchecked IBD inflammation. Individualize decisions on the basis of severity of both CDI and IBD.

Table 1. Continued

5. Recurrent or difficult to treat CDI microbiome therapies and adjuncts
- Extended taper of oral vancomycin ([Supplementary Table 3](#))
 - Fidaxomicin for recurrence
 - Often effective for first or second recurrences
 - Microbiome-based therapies
 - Used after completion of antibiotics and a washout (eg, 1–3 days off antibiotics) for rCDI
 - FMT^b
 - Considered for multiple recurrent (2 or more episodes) CDI or fulminant CDI not responding to standard therapies
 - Efficacy in active IBD remains high
 - FDA-approved donor-derived therapies
 - Have shown efficacy and safety in CDI complicating IBD^c
 - Probiotics
 - Do not use

Action: Use FMT for rCDI or refractory CDI per established protocols; counsel patients on potential benefits and risks.

6. Supportive care and follow-up
- Hydration and electrolytes
 - Ensure fluid resuscitation and correct electrolyte imbalances
 - Follow-up testing
 - Routine “test for cure” not advised unless symptoms persist
 - Monitor for recurrence (new or worsening symptoms)
 - IBD activity monitoring
 - Close follow-up with gastroenterology to assess IBD disease activity and ensure adequate disease control during and after CDI treatment

Action: Emphasize adequate hydration, symptom tracking, and timely follow-up to detect recurrence or IBD flare early.

bid, twice per day; PO, per os (by mouth).

^aFulminant CDI is defined as severe CDI accompanied by hypotension, shock, ileus, or megacolon.

^bFMT may not be readily available at most sites across the United States as of 2025.

^cFDA-approved donor-derived therapies include RBL and VOS. Data for CDI in IBD available for RBL as of the writing of this article in 2025.

recurrences increase significantly after each one.¹⁵ The rates of rCDI are 33% higher among patients with IBD than non-IBD patients.¹¹ In patients with IBD, diarrhea can be present for multiple reasons, including postinfection IBS or an IBD flare. Given that treatments vary, rCDI always needs to be excluded. Clinicians should not assume the patient is experiencing rCDI and miss an opportunity to optimize IBD therapy.

Best Practice Advice 4: In patients with IBD who develop an initial episode of CDI, clinicians should preferentially use fidaxomicin or use vancomycin if fidaxomicin is unavailable or cost-prohibitive. Metronidazole should not be used.

Most trials investigating CDI treatment exclude patients with IBD due to the inability to identify end points. There are limited published data from retrospective studies regarding antibiotic use for CDI in patients with IBD. Fidaxomicin is preferred for CDI in patients with IBD.^{14,16–18} Fidaxomicin is a narrow-spectrum antibiotic that targets *C difficile* and preserves gut microbiota diversity. This is important in patients with IBD who have dysbiosis due to underlying inflammation and compromised mucosal integrity. [Supplementary Table 3](#) outlines antibiotic regimens for CDI in IBD in different phases of care.

Fidaxomicin has cure rates similar to those for vancomycin, but significantly lower recurrence, a critical

consideration given the high risk of rCDI among patients with IBD. Although data for fidaxomicin use in patients with IBD are limited, studies suggest that fidaxomicin is effective and safe (cure rates are approximately 80%–90%).¹⁶ Pharmacokinetic data from a phase IIIb/IV study indicated that fidaxomicin and its primary metabolite OP-1118 have minimal systemic absorption in patients with IBD with high stool concentrations.¹⁷ An open-label trial demonstrated that an extended-pulsed fidaxomicin regimen was superior to a standard 10-day vancomycin regimen in older inpatients with CDI without IBD, achieving a sustained clinical cure in 70% vs 59% with vancomycin.¹⁸ Patients with active CDI on concomitant systemic antibiotics may benefit from fidaxomicin instead of vancomycin to prevent rCDI.¹⁹

Vancomycin is superior to metronidazole for CDI for initial clinical response.²⁰ Metronidazole is not recommended for CDI, owing to high resistance and treatment failure.²¹ Longer duration vancomycin regimens (21–42 days) have been found to reduce CDI recurrence in patients with IBD compared with standard 10- to 14-day courses.²²

The decision to favor fidaxomicin over vancomycin in patients with IBD is driven by both clinical efficacy and ability to preserve the intestinal microbiota. Clinicians should consider fidaxomicin as first-line treatment for a new episode of CDI in patients with IBD, while ensuring

Table 2. Common Pitfalls in the Co-Management of *Clostridioides Difficile* Infection and Inflammatory Bowel Disease

Pitfall	Why it occurs	Mitigation strategies
Failing to suspect CDI in IBD flare	New or worsening diarrhea in a patient with IBD is sometimes attributed solely to an IBD flare, leading to delayed CDI testing.	Maintain high level of suspicion for CDI in any IBD flare with increased stool frequency. Prompt testing for <i>C difficile</i> (eg, GDH/toxin or NAAT).
Misinterpretation of positive PCR/colonization vs infection	NAAT (PCR) positivity may reflect colonization rather than true infection, especially in an IBD population.	Use a 2-step diagnostic approach (eg, GDH + toxin EIA, then PCR if discrepant or PCR screen followed by EIA/GDH confirmation) to confirm active CDI. Interpret PCR results in the clinical context (presence of symptoms).
Inappropriate choice of CDI treatment	Persisting with metronidazole or using suboptimal regimens for severe or recurrent CDI (eg, not opting for fidaxomicin over vancomycin).	Follow updated guidelines recommending fidaxomicin (preferred) or vancomycin over metronidazole for most CDI cases.
Delaying IBD therapy escalation when needed	Clinicians may fear using immunosuppressants or biologics during CDI, which can result in undertreatment of an active IBD flare.	Differentiate active CDI from active IBD. Give 2–3 days of standard of care antibiotics before escalating IBD therapy Collaboration between gastroenterology and/or infectious disease teams to adjust IBD therapy as clinically indicated.
Abruptly stopping immunomodulators or biologics	Stopping IBD treatments out of fear of worsening infection can lead to an uncontrolled IBD flare.	Evaluate severity of infection vs IBD activity before altering immunosuppressive regimens. Consider temporary hold only if clinically justified.
Overuse of PPIs	PPIs can increase CDI risk through changes in gastric pH and gut microbiota but are frequently prescribed for gastrointestinal symptoms without ongoing need.	Re-evaluate indication for PPI at each visit. Use lowest effective dose or discontinue if no clear indication.
Lack of follow-up after CDI treatment	Patients may not be monitored closely post-treatment, risking missed recurrences or complications in an IBD population with baseline gastrointestinal symptoms.	Schedule follow-up appointments to assess symptom resolution or recurrence. Encourage prompt reporting of new or worsening diarrhea.
Delayed or underused microbiota-based therapies	rCDI in patients with IBD can be severe; clinicians may be slow to implement FMT due to concerns about possible IBD flares or lack of familiarity with FMT protocols.	Consider microbiota-based therapies after initial or multiple recurrences or failure of first-line treatments. Coordinate with experienced centers for optimal patient selection and procedure safety.

PPI, proton pump inhibitor.

that treatment regimens are integrated with the broader management strategies for IBD to optimize patient outcomes. Oral vancomycin can be used if fidaxomicin is unavailable or cost-prohibitive.

Best Practice Advice 5: Clinicians should strongly consider hospitalization for patients with IBD and CDI who demonstrate features of severe colitis or systemic toxicity (eg, more than 6 bowel movements per day, severe abdominal pain, marked leukocytosis, hemodynamic instability, or other evidence of sepsis).

Patients with IBD and CDI who exhibit these signs are at high risk of rapid deterioration. Although these markers have not been studied in a single retrospective model, these are individually associated with development of medically refractory colitis and a higher likelihood of progression to fulminant CDI. Timely hospitalization facilitates close monitoring and prompt escalation of care preventing complications such as

surgery and mortality. A large cohort study found that CDI was associated with higher in-hospital death rates in patients with IBD.²³

Management of fulminant CDI in patients with IBD requires a multidisciplinary approach involving infectious disease specialists, gastroenterologists, and surgeons. For patients who fail conventional treatment, early surgical consultation is advised, as timely colectomy can be life-saving in cases of toxic megacolon or refractory colitis.

Best Practice Advice 6: When selecting an immunosuppressive therapy to treat IBD, no class or mechanism of action has a differential risk of CDI and, therefore, clinicians should choose the therapy that is best to treat the IBD.

Immunosuppressive therapy is a known risk factor for both CDI and other gastrointestinal infections among patients with ulcerative colitis.^{24,25} Vedolizumab selectively inhibits lymphocyte trafficking to the intestine, raising

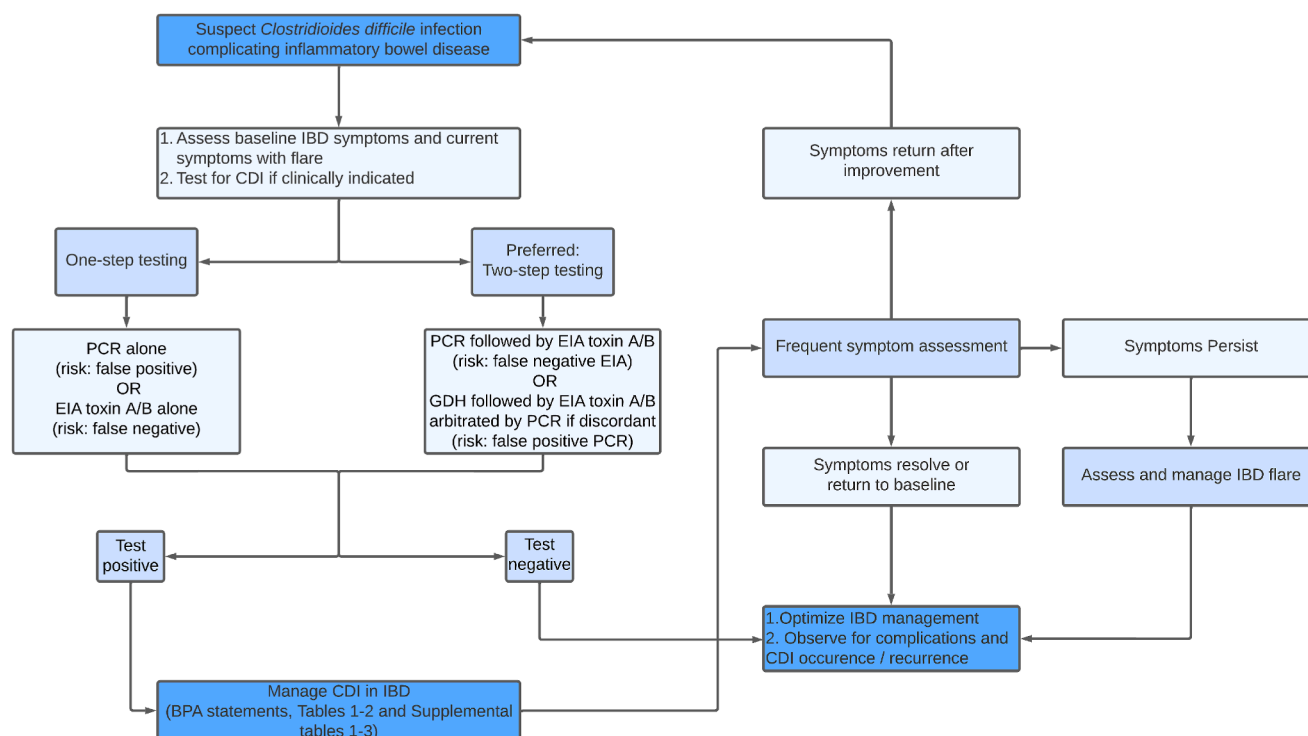


Figure 1. A proposed management algorithm for CDI in patients with IBD.

concern for increased gastrointestinal infections, but no association between CDI and vedolizumab vs anti-tumor necrosis factor has been found.²⁵ The risk of CDI associated with each class of biologics and small molecules has not been assessed. Based on limited data, selection of a biologic or small molecule for the management of IBD should not be made on the basis of risk of CDI, but rather on the basis of what is best for each patient's IBD.

Best Practice Advice 7: In patients with IBD and acute CDI, concurrent treatment of IBD is critical and clinicians should continue therapy with the required immunosuppressive therapies (ie, immunomodulators, biologics, or small molecules). Steroids can also be used if deemed necessary while CDI is treated with antibiotics.

A major challenge is that in many hospitalized patients with IBD with an acute flare, their CDI status is initially uncertain. In some centers, waiting for CDI test results may delay treatment of severe colitis. When clinical suspicion of an IBD flare is high, particularly in patients who are systemically ill or at risk of rapid deterioration, initiation of advanced therapy or corticosteroids should not be withheld due to pending CDI diagnostics. If CDI test results are expected to be delayed, starting CDI-directed antibiotics (after a stool sample is obtained) at the same time is appropriate to treat both inflammatory drivers. Obtaining a stool test after initiation of antibiotics may lead to false-negative results.

Retrospective analyses suggest that continuing or even escalating immunosuppression in patients with IBD who have CDI is safe when indicated, although randomized trials are lacking. Data from patients on anti-tumor necrosis

factor therapies suggest that maintaining or increasing immunosuppression does not worsen CDI outcomes and remains necessary to control against an underlying IBD flare. Data regarding the safety of newer biologics and small molecules (eg, Janus kinase inhibitors) are lacking. Further research is needed to provide more definitive guidance on whether to hold, continue, or escalate newer IBD agents during an acute CDI.

Corticosteroids have been associated with higher rates of adverse outcomes in patients with IBD, including increased infection risk and worsening of CDI. Although steroids may sometimes be required to manage IBD flares, clinicians should exercise caution and aim to start steroids and appropriate CDI-directed antibiotic therapy. If CDI test results will be delayed, then steroids can be started while waiting, if suspicion for IBD flare is high.²⁶ Meticulous risk-benefit assessments must be made on a case-by-case basis, given that poorly controlled IBD flares can be life-threatening if not treated in a timely manner.

Best Practice Advice 8: Clinicians should consider endoscopic evaluation for IBD activity and exclusion of concomitant cytomegalovirus infection if symptoms persist 48–72 hours after initiation of treatment for CDI.

Once a patient with IBD is diagnosed with CDI, treatment with standard of care antimicrobials such as vancomycin or fidaxomicin is indicated. If a patient is not responding within 48–72 hours, then other diagnoses should be entertained.¹⁴ The differential diagnosis includes an IBD flare or other opportunistic infections such as cytomegalovirus.²⁷ A flexible sigmoidoscopy or colonoscopy should be performed, depending on the patient's

historical IBD distribution and clinical status, as this provides mucosal assessment, insight on distribution of colitis, and histology to guide accurate diagnosis.¹⁴ Patients with CDI and IBD rarely have pseudomembranes, but will have mucopurulent exudate, further complicating our ability to differentiate these entities.²⁸ Histology and historical appearance of the patient's colitis are both important considerations.

Best Practice Advice 9: Clinicians may consider loperamide in patients with improving inflammation and infection but ongoing diarrhea.

It has been considered taboo to use antimotility agents (eg, loperamide) in patients with ongoing CDI. Although not studied, this was advised due to theoretical concerns that bacterial toxins would be retained in the colon and increase the risk of toxic megacolon. Patients who experienced complications or died in the setting of CDI were given antimotility agents alone initially, without an appropriate antibiotic.²⁹ In a study of patients with mild to moderate CDI who received metronidazole or vancomycin and an antimotility agent, no complications were seen, although the addition of the antimotility agent did not decrease symptom duration.³⁰ Clinicians should avoid antimotility agent use while workup is underway in those with untreated CDI or fulminant infection. Once patients have initiated anti-CDI antibiotics and are clinically improving, clinicians may use loperamide safely in outpatients with ongoing diarrheal symptoms if other systemic symptoms are improving.

Best Practice Advice 10: Clinicians should offer microbiome-based therapies (eg, fecal microbiota, live-jslm, fecal microbiota spores, live-brpk, or unapproved fecal microbiota transplantation) to patients with IBD with at least 1 recurrence of CDI to prevent future infection.

Recurrence of CDI in patients with IBD is a major challenge, with an estimated 33% increased likelihood compared with the general population.³¹ Hence, add-on therapies to reduce recurrence are very effective. Bezlotoxumab is a monoclonal antibody against *C difficile* toxin B, reducing rCDI, particularly in high-risk populations, including IBD.³² Bezlotoxumab was discontinued for commercial reasons, not due to safety or efficacy concerns.

Microbiome-based therapies, such as fecal microbiota transplantation (FMT), restore intestinal microbial eubiosis to eradicate the spore phase of infection and reduce the risk of rCDI when given after antibiotics to prevent recurrence.³³ Antibiotics alone only treat the vegetative phase, leaving patients prone to rCDI.³⁴ In a recent study, FMT administered after antibiotics led to symptom resolution and reduced hospitalizations in patients with IBD with rCDI or refractory CDI.³⁵ The data on FMT's utility to prevent rCDI in patients with IBD are encouraging; 1 prospective trial reported 90% efficacy at 8 weeks.³⁶ Pathogenesis of IBD includes colonic microbiota dysbiosis, raising concern for an increased risk of IBD flare with FMT, but was not seen in this trial.³⁷ Although FMT is a promising adjunct for rCDI, its use in fulminant disease must be evaluated carefully with a plan that prioritizes both CDI and IBD management.

Fecal microbiota, live-jslm (RBL) and fecal microbiota spores, live-brpk (VOS) are the first 2 US Food and Drug Administration (FDA)-approved microbiota restoration therapies indicated to prevent rCDI. RBL is a broad consortium, single-dose enema given 1–3 days after completion of antimicrobials and VOS is an encapsulated selective group of *Firmicutes* spores administered as 4 capsules daily for 3 consecutive days, 2–4 days after antimicrobials and a bowel lavage.^{38,39} In a phase IIIb trial, colonoscopic administration of RBL for rCDI achieved a high success rate in preventing rCDI at 8 weeks.⁴⁰ With major stool banks in the United States no longer providing specimens to prevent rCDI, RBL and VOS are the main options for microbiota restoration.

The 2024 American Gastroenterological Association (AGA) guideline concluded that non-FDA-approved or “conventional” FMT and the FDA-approved treatments were safe and effective to prevent rCDI in those who are immunocompetent.⁴¹ For those with mild to moderate immunocompromised state, they suggested non-FDA-approved FMT, but not FDA-approved therapies.⁴¹ Since then, conventional FMT has become minimally available, and a large phase 3 open-label study of RBL that included 74 patients with IBD found safety and efficacy were consistent with conventional FMT.⁴² A treatment success rate of 78.9% at 8 weeks and a sustained clinical response rate of 91.1% at 6 months was found, comparable with outcomes in non-IBD participants.⁴³ There are no available data for VOS in those with CDI and IBD. Given similar mechanisms and response, it is reasonable to use either RBL or VOS in patients with IBD with mild to moderate immunocompromising medications. The benefits of prevention of rCDI outweigh the risks.

Best Practice Advice 11: In patients with IBD, clinicians should not advise probiotics for primary or secondary prevention of CDI.

Although probiotics are considered safe and are marketed for gut health, evidence does not support routine use of probiotics for either primary or secondary prevention of CDI in patients with IBD. Probiotics may have a role in treating acute infectious diarrhea, but data for either primary or secondary prevention of CDI in IBD are limited and contradictory. The AGA advises against the use of probiotics for the treatment of CDI, citing low quality of evidence.⁴⁴ Rare but serious adverse events like bacteremia and fungemia, especially among immunocompromised or severely ill populations, have been documented. Many commonly used probiotic strains, such as *Lactobacillus* and *Bifidobacterium* species, are susceptible to vancomycin. This susceptibility undercuts theoretical benefits of probiotics during CDI treatment. Clinicians should not prescribe probiotics for patients with IBD with CDI.

Best Practice Advice 12: In patients with IBD and a history of CDI who are receiving systemic antibiotics, clinicians may consider oral vancomycin prophylaxis as secondary prevention.

Oral vancomycin prophylaxis (OVP) is a potential strategy to prevent rCDI in high-risk populations.¹⁴ Retrospective studies and meta-analyses evaluating OVP in patients with a history of CDI receiving systemic antibiotics (secondary prevention) found that OVP may reduce the risk of rCDI in

high-risk patients, although the quality of evidence remains low.⁴⁵ A placebo-controlled, double-blind randomized clinical trial of 81 patients evaluated the efficacy of OVP for preventing rCDI (excluding patients with IBD) in adults who had completed CDI treatment within the past 180 days and were receiving systemic antibiotics.⁴⁶ Participants were randomized to receive 125 mg vancomycin daily or placebo during systemic antibiotics plus 5 days after. The rate of rCDI was 43.6% with OVP and 57.1% with placebo group, which was statistically insignificant, likely due to the study being underpowered. Vancomycin-resistant *Enterococcus* carriage was higher in the vancomycin group (50%) compared with placebo (24%) at 8 weeks post treatment.⁴⁶

Owing to weak evidence, such regimens (ie, vancomycin 125 mg once to twice daily, initiated with systemic antibiotics and continued until 5 days after completion of systemic antibiotics) may be used in high-risk patients after informed decision making.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at <https://doi.org/10.1053/j.gastro.2026.03.008>.

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Conflicts of interest

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