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AGA Clinical Practice Update on Management of *Clostridioides difficile* Infection in Adults: Expert Review

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DESCRIPTION: ***Clostridioides difficile*** **infection is a common cause of clinically significant diarrhea, often becomes recurrent, and can be fatal when severe or fulminant. The purpose of this America Gastroenterological Association (AGA) Clinical Practice Update Expert Review is to provide best practice advice for** ***C difficile*** **infection management.**

METHODS: **This expert review was commissioned by the 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. The review was developed from expert opinion and a review of the published literature. Because systematic reviews were not performed, these best practice advice statements do not carry formal ratings regarding the quality of evidence or strength of the presented considerations. The review underwent internal peer review by the Practice Updates Committee and external peer review through standard procedures of** ***Clinical Gastroenterology and Hepatology.***

BEST PRACTICE ADVICE STATEMENTS

BEST PRACTICE ADVICE 1: **Prevention of** ***C difficile*** **infection should include proper barrier protection and disinfection with United States Environmental Protection Agency–approved sporicidal agents in health care settings. Patients should be counseled on the importance of handwashing and to consider disinfecting areas of the home potentially contaminated with** ***C difficile*** **spores, to prevent reinfection. Reassurance should be provided that** ***C difficile*** **infection transmission to unaffected family members is uncommon.**

BEST PRACTICE ADVICE 2: ***C difficile*** **infection is a clinical diagnosis that requires compatible symptoms (typically acute diarrhea, following antibiotics) in combination with supportive laboratory testing. Multistep testing is preferred for best diagnostic accuracy; however, patients with discordant testing who have a high clinical suspicion for** ***C difficile*** **infection should be treated.**

BEST PRACTICE ADVICE 3: **Clinicians should classify hospitalized patients with** ***C difficile*** **infection as having nonsevere, severe, or fulminant disease at diagnosis. White blood cell count >15,000 cells/uL and/or creatinine >1.5 × baseline are indicative of severe** ***C difficile*** **infection and increased risk for recurrence and poor outcomes. Patients with additional findings of shock, ileus, or megacolon have fulminant** ***C difficile*** **infection, which can be fatal.**

BEST PRACTICE ADVICE 4: **Fidaxomicin (200 mg twice daily oral for 10 days) is a narrower spectrum agent, and given lower recurrence rates, is favored as first-line therapy for nonfulminant** ***C difficile*** **infection. However, given practical considerations, vancomycin (125 mg 4 times daily oral for 10 days) is also acceptable therapy. Metronidazole should not be used outside of fulminant disease.**

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Abbreviations used in this paper: AGA, America Gastroenterological Association; BPA, Best Practice Advice; CDI, *Clostridioides difficile* infection; FDA, United States Food and Drug Administration; FMT, fecal microbiota transplant; IBD, inflammatory bowel disease; OVP, oral vancomycin prophylaxis; PCR, polymerase chain reaction; PPI, proton pump inhibitor; RCT, randomized controlled trial.

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BEST PRACTICE ADVICE 5: **Cholestyramine and other bile acid–binding agents should not be used as monotherapy or concurrently with oral vancomycin or fidaxomicin. Psyllium fiber can be used to bulk stools in patients who have recovered from the infection.**

BEST PRACTICE ADVICE 6: **Following treatment of *C difficile* infection, clinicians should not perform routine test of cure. Stool testing should only be performed for persistent worsening of diarrheal symptoms.**

BEST PRACTICE ADVICE 7: **First *C difficile* infection recurrence (second episode) within 8 weeks of completing anti–*C difficile* infection therapy should be treated with either a tapering course of vancomycin or fidaxomicin. Treatment of *C difficile* infection should include a risk assessment for *C difficile* infection recurrence and consideration of microbiota restoration therapy to prevent recurrence.**

BEST PRACTICE ADVICE 8: **Fecal microbiota-based therapies (fecal microbiota spores, live-brpk, fecal microbiota, live-jslm, or conventional fecal microbiota transplant) should be offered after treatment of a second recurrence (third *C difficile* infection episode). Microbiota restoration therapy may be considered after treatment of an initial infection or first recurrence in patients who are at high risk for further recurrence or in patients whose initial *C difficile* infection episode was particularly morbid or difficult to treat.**

BEST PRACTICE ADVICE 9: **Prolonged, low dose, suppressive vancomycin regimen (125 mg daily) for secondary prophylaxis may be considered in patients with multiple recurrent episodes who are not candidates for fecal microbiota-based therapies due to ongoing comorbidities, limited life expectancy, or ongoing/frequent systemic antibiotics or who have failed multiple courses of fecal microbiota-based therapy.**

BEST PRACTICE ADVICE 10: **Fulminant *C difficile* infection should be managed by a multidisciplinary team (gastroenterology/infectious disease, surgery, medicine/critical care) and treated with high-dose vancomycin 500 mg every 6 hours (oral or enteral), with metronidazole 500 mg intravenously every 8 hours, and if ileus is present, rectal vancomycin 500 mg every 6 hours should be added.**

BEST PRACTICE ADVICE 11: **Multi-dose fecal microbiota transplantation (fresh-directed donors, or institutional stool banks) delivered via lower endoscopy, should be considered in individuals with fulminant *C difficile* infection. Fecal microbiota, live-jslm (Rebyota), and fecal microbiota spores, live-brpk (Vowst) have not been studied and are not approved for treatment of severe and/or fulminant *C difficile* infection. Due to high risk of *C difficile* infection recurrence, patients who recover from severe or fulminant *C difficile* infection should be maintained on a suppressive vancomycin regimen until a final fecal microbiota transplantation can be administered as an outpatient.**

BEST PRACTICE ADVICE 12: **Use of vancomycin is not advised during systemic antibiotic administration to prevent *C difficile* infection. Probiotics are not advised to prevent an initial or recurrent *C difficile* infection. To promote restoration of healthy gut microbiota, patients should be instructed to consume a healthy diet including a variety of fruits and vegetables, rich in both soluble and insoluble fiber.**

BEST PRACTICE ADVICE 13: **During the treatment of *C difficile* infection or the prevention of its recurrence, the use of proton pump inhibitors should be evaluated. If a legitimate indication exists for their use, proton pump inhibitor discontinuation is not necessary.**

BEST PRACTICE ADVICE 14: **Individuals with a history of *C difficile* infection should be specifically counseled to avoid unnecessary antibiotic therapy.**

Keywords: Prevention; Treatment; Fulminant Disease; Severe; Recurrence; Fecal Microbiota Transplant.

Clostridioides difficile infection (CDI) is a common disease with approximately 365,200 cases diagnosed in the United States annually.[1] CDI can be clinically challenging, as some patients experience multiple recurrences or become critically ill. Severe or fulminant CDI can be morbid or even fatal.[2–8] Our understanding of CDI has grown in the past decade with the publication of multiple observational studies and clinical trials.

Management of CDI is rapidly changing, with some therapies no longer available and several new therapies clinically available. The purpose of this American Gastroenterological Association (AGA) Clinical Practice Update is to provide practical and evidence-based advice for the clinicians who care for patients with CDI.

Best Practice Advice 1: Prevention of CDI should include proper barrier protection and disinfection with United States Environmental Protection Agency–approved sporicidal agents in health care settings. Patients should be counseled on the importance of handwashing and to consider disinfecting areas of the home potentially contaminated with *C difficile* spores, to prevent reinfection. Reassurance should be provided that CDI transmission to unaffected family members is uncommon.

Preventing CDI recurrence requires a multifaceted approach combining strict hygiene, environmental disinfection, and patient education (reviewed in Table 1). CDI can be transmitted within households due to the persistence of *C difficile* spores, although the absolute risk of household acquired infection is low (<5%).[15] Patients with CDI become less contagious with resolution of diarrhea, as formed stool decreases spore spreading and environmental contamination. Individuals with CDI risk factors (eg, older age, recent antibiotic use, immunocompromised state, underlying inflammatory bowel disease [IBD]) are at significantly increased risk, and preventative measures are prudent to minimize the risk of CDI transmission as well as reinfection. Although household contact with CDI increases the relative risk compared with those without exposure, reassurance should be provided that CDI rarely spreads to family members as long as they have intact gut microbiota homeostasis. If proper disinfection of the bathroom is regularly performed, separate bathrooms are not necessary or advised.[16] A patient cleaning guide is included in the Supplementary Materials. The guide is most useful for patients with multiple recurrences of CDI who may be experiencing reinfection from ongoing spore exposure at home.

Best Practice Advice 2: CDI is a clinical diagnosis that requires compatible symptoms (typically acute diarrhea, following antibiotics) in combination with supportive laboratory testing. Multistep testing is preferred for best diagnostic accuracy; however, patients with discordant testing who have a high clinical suspicion for CDI should be treated.

Infection can never be determined solely by the presence of an organism. An accurate diagnosis requires a thorough clinical evaluation for CDI: typically, new-onset unexplained diarrhea (≥3 unformed stools in 24 hours). Overreliance on laboratory tests alone, especially in patients with atypical symptoms, risks overdiagnosis due to high *C difficile* colonization rates.[17–21] Healthy adult colonization rates in the community range from 4% to 15%; hospital colonization rates vary widely from 3% to 21%, with rates as high as 50% in residents of long-term care facilities.[20,22] After establishing new-onset symptoms compatible with CDI, supportive laboratory testing should be pursued.

Testing for CDI is described in Figure 1. The specificity of polymerase chain reaction (PCR) testing alone is limited due to high *C difficile* colonization rates. Multistep laboratory testing, screening with a highly sensitive test for the presence of *C difficile* followed by a test to detect toxin production, can help to distinguish *C difficile*

Table 1. Counseling for Household Prevention of CDI

Hand hygiene is foundational	Alcohol-based sanitizers are ineffective against spores; mechanical handwashing with soap and water remains essential.[9] Patients should wash their hands thoroughly, especially after using the bathroom and before meals.[9]
Environmental cleaning is critical	*C. difficile* spores can survive up to 6 months on surfaces and resist alcohol, drying, and temperature. EPA-approved sporicidal agents (eg, diluted bleach: 1 part bleach to 9 parts water) should be used on high-touch areas (toilets, faucets, doorknobs, etc), allowing at least 10 minutes of contact time. Bedding and clothes should be dried on high heat, and professional cleaning is advised for soiled carpets and upholstery.[10]
Household practices matter	Shoe soles frequently carry spores; patients and family members should remove shoes at the door.[11,12] Pet paws may also carry spores and should be wiped clean. Asymptomatic pets and children under age 2 may harbor toxigenic strains.[13] Thorough washing of produce under running water is advised, as root vegetables and leafy greens may serve as environmental sources and vectors of *C. difficile* infection.[14]
Risk to others	Although the relative risk of CDI among household members is increased, the absolute risk remains very low.[15] Reassure that healthy family members are unlikely to be affected due to intact microbiota and host defenses. A healthy gut microbiome is the best defense. CDI arises predominantly in those with disrupted colonization resistance due to antibiotics or other medical conditions. Effective education and proactive environmental hygiene can significantly reduce the risk of reinfection.

NOTE. See also Patient Cleaning Guide in the Supplementary Materials.
CDI, *Clostridioides difficile* infection; EPA, United States Environmental Protection Agency.

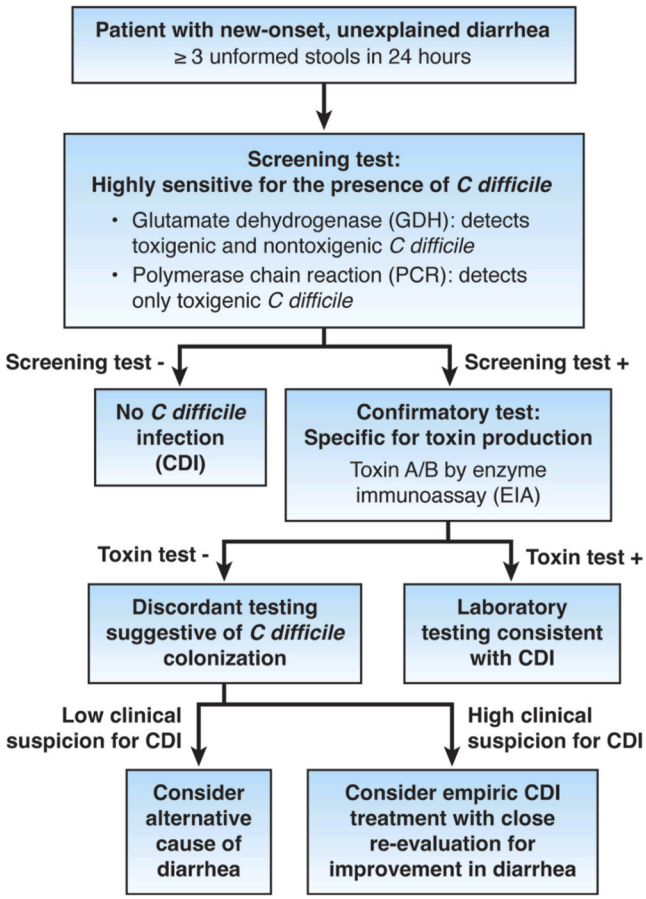

Figure 1. Testing for CDI.

colonization from CDI. Both glutamate dehydrogenase and PCR testing are acceptable initial tests. If positive, we advise confirmation by toxin A/B enzyme immunoassay.[23] However, it is important to recognize that the toxin test may be negative due to low fecal levels of toxin, or improper sample collection/processing.[21,24] In case of discordant results (eg, PCR+/toxin−), if clinical suspicion remains high, treatment should not be withheld only due to negative toxin results.

Best Practice Advice 3: Clinicians should classify hospitalized patients with CDI as having nonsevere, severe, or fulminant disease at diagnosis. White blood cell count >15,000 cells/uL and/or creatinine >1.5 × baseline are indicative of severe CDI and increased risk for recurrence and poor outcomes. Patients with additional findings of shock, ileus, or megacolon have fulminant CDI, which can be fatal.

Following a diagnosis of CDI, assessing disease severity is important for guiding appropriate treatment and predicting prognosis. Although there is no universally accepted, validated definition of CDI severity, expert consensus has long relied on laboratory parameters. A white blood cell count >15,000 cells/μL and a serum creatinine >1.5 mg/dL (or 1.5 × the premorbid baseline) are commonly cited as key markers of severe disease.[18,19] CDI managed in the outpatient setting is more likely to be nonsevere; therefore, additional laboratory assessment for severity should be performed on a case-by-case basis.

In contrast to mild or severe disease, fulminant (Latin *fulminare*, to strike with lightning) CDI represents the most extreme and life-threatening end of the clinical spectrum, occurring in 1% to 3% of all CDI cases.[25] Fulminant CDI is defined by the presence of systemic toxicity and/or end-organ dysfunction attributable to CDI. Hallmark features include hypotension or shock, ileus, and toxic megacolon. In the authors' experience, pseudomembranes are universally present in this setting, and their absence should prompt investigation for an alternative cause of symptoms.[26,27] Prompt recognition of fulminant disease is essential as the mortality rate is between 30% and 40%, with higher rates among those requiring surgery or with multiple comorbid conditions.[25,28]

Best Practice Advice 4: Fidaxomicin (200 mg twice daily oral for 10 days) is a narrower spectrum agent and, given lower recurrence rates, is favored as first-line therapy for nonfulminant CDI. However, given practical considerations, vancomycin (125 mg 4 times daily oral for 10 days) is also acceptable therapy. Metronidazole should not be used outside of fulminant disease.

Metronidazole was shown to be inferior in older patients, those hospitalized for treatment of CDI, and in those with multiple comorbidities.[29] Furthermore, metronidazole is associated with a higher risk for recurrence.[30,31] Therefore, it is no longer recommended to be used, except in combination with vancomycin for the treatment of fulminant disease (see Best Practice Advice [BPA] 10).

Fidaxomicin is generally favored as first-line therapy for nonfulminant CDI (Figure 2*A*). Guidelines recommend fidaxomicin for first-line treatment of CDI, citing decreased risk for recurrent infection rates (ranging from 6% to 11% fewer events vs vancomycin).[20,32] This is related to the narrower spectrum of activity of fidaxomicin and preservation of beneficial anaerobic commensals. In a randomized trial comparing fidaxomicin with vancomycin for the treatment of CDI, rates of clinical cure with fidaxomicin were noninferior to those with vancomycin in both the modified intention-to-treat analysis (88.2% vs 85.8%) and the per-protocol analysis (92.1% vs 89.8%).[33] In a Cochrane review, fidaxomicin was more effective than vancomycin for achieving a symptomatic cure without recurrence at 1 month (71% cure with fidaxomicin compared with 61% with vancomycin; relative risk, 1.17; 95% confidence interval, 1.07–1.27).[34] Of note, a generic version of fidaxomicin is United States Food and Drug Administration (FDA)-approved and may improve access to therapy.

Vancomycin is also a reasonable option for treatment. When determining use of vancomycin or fidaxomicin, providers and patients should engage in shared decision-making, considering risk factors for recurrence,

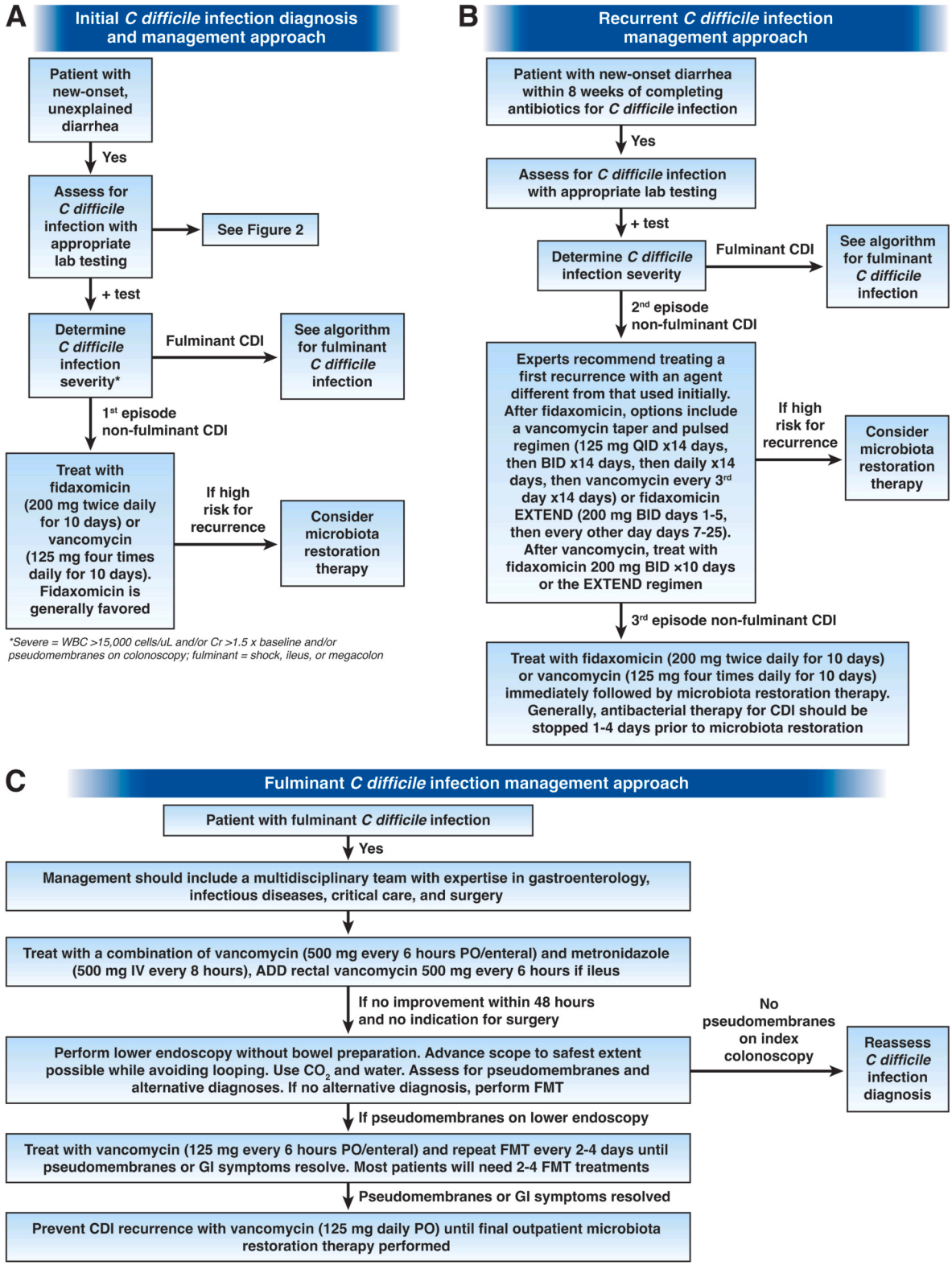

Figure 2. (*A*) Initial CDI diagnosis and management approach; (*B*) Recurrent CDI management approach; (*C*) Fulminant CDI management approach. BID, twice daily; IV, intravenous; PO, orally; QID, 4 times daily.

ease of dosing, access, and cost. When oral vancomycin is prescribed 4 times daily, doses may be given during waking hours; patients do not need to wake overnight to take it exactly every 6 hours.

Patients should demonstrate a symptomatic response, defined as at least a 50% reduction in the number of loose or liquid bowel movements per day, to fidaxomicin or vancomycin within 3 days (and no later

than 5 days) of therapy initiation. If this degree of symptomatic improvement is not observed within 3 to 5 days, alternative explanations for diarrhea should be considered, including inadequate response to therapy, other infection, or noninfectious etiologies such as irritable bowel syndrome.

Best Practice Advice 5: Cholestyramine and other bile acid–binding agents should not be used as monotherapy or concurrently with oral vancomycin or fidaxomicin. Psyllium fiber can be used to bulk stools in patients who have recovered from the infection.

Cholestyramine and other bile acid–binding agents should not be used as monotherapy or concurrently with oral vancomycin or fidaxomicin, as they may bind the antibiotic and reduce its effectiveness. These agents are not active against CDI.

Low-fiber diets may contribute to prolonged susceptibility to CDI after antibiotics.[35] Psyllium fiber works by acting as a bulking agent to absorb excess liquid, improving stool consistency, and potentially supporting the gut microbiota.[36]

Patients often inquire about the use of antidiarrheal medications during treatment of CDI. Antimotility agents are contraindicated in untreated CDI, fulminant CDI infection, and severe colonic IBD. Although we do not suggest loperamide, if used, it should be limited to the shortest duration needed for symptom control, and only after anti-CDI therapy is initiated, to avoid the theoretical risk of toxin retention and toxic megacolon.[20,37]

Best Practice Advice 6: Following treatment of CDI, clinicians should not perform routine test of cure. Stool testing should only be performed for persistent worsening of diarrheal symptoms.

Asymptomatic carriage and persistent shedding of *C difficile* toxin for weeks after successful treatment of an infection is common, and currently available tests are not validated on formed stool and cannot accurately distinguish CDI from asymptomatic colonization.[38,39] Furthermore, negative PCR testing during or following treatment for CDI does not guarantee sustained cure.[40] For these reasons, testing for cure at the end of a course of anti-CDI therapy should not be performed. If a patient develops a relapse in diarrhea (3 or more watery stools per day), which is sustained over 2 or more days or worsening, and consistent with prior episodes, only then testing should be performed. Although patients who are suffering symptoms typical of their recurrent CDI are often prescribed anti-CDI therapy empirically, we strongly encourage laboratory testing to confirm a relapse. If stool testing is negative or discordant, patients should be evaluated for other etiologies of diarrhea, such as postinfection irritable bowel syndrome. Additionally, positive testing may be necessary for insurance to approve coverage of fecal microbiota-based therapies.

Best Practice Advice 7: First CDI recurrence (second episode) within 8 weeks of completing anti-CDI therapy should be treated with either a tapering course of vancomycin or fidaxomicin. Treatment of CDI should include a risk assessment for CDI recurrence and consideration of microbiota restoration therapy to prevent recurrence.

Recurrence, defined as clinically significant diarrhea with positive stool testing within 8 weeks of completing antibiotic therapy for CDI, is common (Figure 2*B*). Although most recurrences (approximately 90%) occur within the first 8 weeks, experts also consider clinically significant diarrhea with positive stool testing occurring within 1 year of completing antibiotic therapy for CDI to represent recurrence or reinfection. Once patients have suffered a recurrence, they are at increased risk for further recurrence.

Experts generally advise treating a first recurrence with an antibiotic different from that used for the initial episode. For patients initially treated with fidaxomicin, a first recurrence should be managed with a vancomycin taper and pulsed regimen (eg, vancomycin 125 mg 4 times per day for 14 days, then vancomycin 125 mg twice daily for 14 days, followed by vancomycin 125 mg once daily for 14 days, then vancomycin every third day for 14 days), or with fidaxomicin using the EXTEND pulsed protocol (200 mg twice daily on days 1–5, then once daily on alternate days on days 7–25).[41,42] For patients initially treated with vancomycin, a first recurrence should be treated with fidaxomicin, either as a standard 10-day course (200 mg orally twice daily) or using the EXTEND pulsed regimen.[20] Dosing and duration of taper/pulsed regimens may differ based on individual practice. Prolonged vancomycin tapers extending beyond 60 days have not been studied and are not likely to provide additional benefit.

Patients should be counseled on the increased risk for further CDI episodes. At this point, it is appropriate to begin discussions around fecal microbiota-based therapies and plans for management should they develop symptoms of further recurrence (eg, lab slip/material for testing, refill for vancomycin or fidaxomicin available at pharmacy). The severity of episodes should be considered and microbiota restoration therapy pursued if infections have been severe, requiring hospitalization, or if the patient is at higher risk for further recurrence based on advanced age or an immunocompromising condition. If patients have risk factors for further recurrence, such as ongoing antibiotic requirements or cytotoxic chemotherapy, continued suppressive vancomycin 125 mg/daily after the initial 10-day treatment course can be undertaken, with plans to taper off or to use a microbiota-based therapy once those treatments have been completed.

Best Practice Advice 8: Fecal microbiota-based therapies (fecal microbiota spores, live-brpk, fecal microbiota, live-jslm or conventional fecal microbiota transplant [FMT]) should be offered after treatment of a second recurrence (third CDI episode). Microbiota restoration therapy may be

considered after treatment of an initial infection or first recurrence in patients who are at high risk for further recurrence or in patients whose initial CDI episode was particularly morbid or difficult to treat.

FMT and other fecal microbiota–based therapies are the most effective options for prevention of further recurrence in patients with multiply recurrent CDI (Figure 2*B*). Either conventional FMT or FDA-approved products (fecal microbiota spores live-brpk or fecal microbiota live-jslm) are advised to prevent recurrence of CDI. Practice guidelines recommend fecal microbiota-based therapies after a second recurrence (or third episode); in our opinion, earlier use may be considered in patients whose prior CDIs were severe, requiring hospitalization, prolonged/difficult treatment, or are high risk for further recurrence (age >65 years, immunocompromised, resident of skilled nursing facility).[17,43] Per product labeling, both fecal microbiota-based products are approved to prevent CDI regardless of the number of recurrences. Prior to fecal microbiota-based therapies, the patient should complete a course of standard CDI antimicrobial treatment and then remain on suppressive oral vancomycin (at least 125 mg daily) until the microbiota restoration therapy is approved and accessible. Generally, antibacterial therapy for CDI should be stopped 1 to 4 days prior to microbiota restoration.

The AGA guidelines recommended conventional FMT in mildly or moderately immunocompromised adults. There is limited data supporting the efficacy and safety of commercial fecal microbiota-based products in immunocompromised patients, but as both are derived from the stool of extensively screened human donors, they are presumed to have a safety profile comparable to conventional FMT.[44,45] A single post-hoc clinical trial data suggests that commercial products may have similar safety and efficacy for preventing CDI in patients who are mildly or moderately immunocompromised as those who are not immunocompromised.[45] Severely immunocompromised patients are at higher risk of poor outcomes, such as infection. This includes patients receiving cytotoxic chemotherapy, recent stem cell transplant, or with severe neutropenia (absolute neutrophil count <500 cells per microliter) or advanced or untreated HIV infection (CD4 counts <200/mm). For these patients, the AGA guideline recommended against any type of fecal microbiota-based therapies (fecal microbiota spores, live-brpk, fecal microbiota, live-jslm or conventional FMT).[17] As the state of being severely immunocompromised is transient in most of these patients, deferring fecal microbiota-based therapies in favor of continued antibiotic therapy (ie, suppressive course of vancomycin) is preferred.

Access to microbiota restoration therapy in any form can be challenging. Conventional FMT may be limited by institutional and practical barriers, and the FDA prohibits use of donor material from stool banks outside of an investigational new drug application. Cost and stringent insurance criteria may impact access to FDA-approved therapies, particularly in financially vulnerable patients.

Best Practice Advice 9: Prolonged, low-dose, suppressive vancomycin regimen (125 mg daily) for secondary prophylaxis may be considered in patients with multiple recurrent episodes who are not candidates for fecal microbiota-based therapies due to ongoing comorbidities, limited life expectancy, or ongoing/frequent systemic antibiotics or who have failed multiple courses of fecal microbiota-based therapy.

In patients with multiple CDI recurrences, the risk of further recurrence without intervention exceeds 40%.[46] Fecal microbiota-based therapies remain the most effective therapeutic option and should be pursued when feasible. However, some patients may fail to achieve sustained cure despite multiple therapies, whereas others may not be appropriate candidates due to safety or futility concerns, including severe immunosuppression, ongoing chemotherapy, pregnancy, the need for frequent systemic antibiotics, or extreme frailty with limited life expectancy. In addition, lack of access to fecal microbiota-based therapies can limit its use. Bezlotoxumab is no longer commercially available, and probiotics have not shown benefit in this clinical setting.

For patients in whom fecal microbiota-based therapies are not feasible or have failed, long-term, low-dose oral vancomycin (eg, 125 mg once daily) is a safe and effective suppressive strategy, with no observed emergence of vancomycin-resistant enterococci.[47,48] This approach can prevent infection in these patients at high risk for recurrence. Importantly however, the likelihood of recurrent CDI exceeds 30% following discontinuation of vancomycin prophylaxis.[47] Therefore, ongoing suppressive oral vancomycin therapy may be required to prevent recurrence in selected individuals. Systemic absorption of oral vancomycin is extremely limited. In a prospective study, oral vancomycin produced no detectable serum levels in 98% of patients, even with renal insufficiency, suggesting negligible risk of ototoxicity.[49]

Best Practice Advice 10: Fulminant CDI should be managed by a multidisciplinary team (gastroenterology/infectious disease, surgery, medicine/critical care) and treated with high-dose vancomycin 500 mg every 6 hours (oral or enteral), with metronidazole 500 mg intravenously every 8 hours, and, if ileus is present, rectal vancomycin 500 mg every 6 hours should be added.

Multidisciplinary management is essential including gastroenterology, infectious disease, critical care, and surgery (Figure 2*C*).[19,20,32] We advise use of high-dose vancomycin, defined as 500 mg every 6 hours (oral or enteral), for at least the first 48 hours after treatment initiation.[19,20] Although observational data does not suggest a clinical benefit, the rationale for higher dosing is to ensure adequate drug delivery and colonic

exposure.[50] Treatment should also include intravenously metronidazole 500 mg intravenously every 8 hours. Intravenously, metronidazole is secreted into the colon, ensuring some intracolonic antibiotic exposure. If an ileus is present, rectal vancomycin should be added, as oral vancomycin delivery to the colon is impaired.[51,52] Following a clinical response, typically after 3 to 5 days, treatment can be narrowed to vancomycin 125 mg 4 times a day monotherapy. Fulminant CDI should be treated for a minimum of 10 days, although we favor 14 days. Patients recovered from fulminant CDI are high risk for recurrent CDI, and a plan for microbiota-based therapies to prevent recurrent CDI should be strongly considered. Patients who have not responded or worsened after 48 hours of aggressive medical therapy should be considered for FMT or colectomy.

Empiric antibiotics not directed at CDI should be avoided as they can worsen gut dysbiosis. Of note, critically ill patients may develop coinfections (pneumonia, intra-abdominal infection, bacteremia) that require antibiotic treatment. Coinfection treatment should be guided by infectious disease consultation. We suggest continuing low dose suppressive vancomycin (125 mg daily or twice daily) while on concomitant non-CDI antibiotics.

Best Practice Advice 11: Multi-dose FMT (fresh-directed donors or institutional stool banks), delivered via lower endoscopy, should be considered in individuals with fulminant CDI. Fecal microbiota, live-jslm (Rebyota) and fecal microbiota spores, live-brpk (Vowst) have not been studied and are not approved for treatment of severe and/or fulminant CDI. Due to high risk of CDI recurrence, patients who recover from severe or fulminant CDI should be maintained on a suppressive vancomycin regimen until a final FMT can be administered as an outpatient.

Although no randomized controlled trials (RCTs) exist for FMT in the treatment of fulminant CDI, observational data suggest benefit, as well as in those with severe, hospitalized treatment-refractory CDI. In individuals with fulminant disease, we advise assessing for nonresponse after 48 hours (as discussed in BPA 10). There is no standard definition of severe disease refractory to CDI therapy. In our experience, this is typically hospitalized individuals with ongoing diarrhea and persistent leukocytosis after 5 to 7 days of appropriate medical therapy, generally oral vancomycin 125 mg every 6 hours. These patients should also be considered for FMT.

An AGA guideline suggests use of conventional FMT over no FMT in adults hospitalized with severe or fulminant CDI not responding to antimicrobial therapy.[17] The recommendation was based on data from 5 observational studies in 647 patients with severe or fulminant CDI. Specifically, patients hospitalized with severe or fulminant CDI treated with conventional FMT had a reduced risk of mortality compared to standard of care (relative risk, 0.37; 95% confidence interval, 0.23–0.59), and a number needed to treat of 4 to prevent 1 death, with no difference between groups in serious adverse events.

Use of FMT in treatment-refractory severe or fulminant CDI is distinct from its role in preventing recurrent CDI. In severe and fulminant cases, FMT may have direct antimicrobial effects, potentially altering disease trajectory. FMT is not advised in patients with a bowel perforation or obstruction/high-grade colonic stricture. Caution should be used in patients who are severely immunocompromised.

Commercial microbiota products, such as fecal microbiota, live-jslm and fecal microbiota spores, live-brpk, have not been studied as treatment severe or fulminant CDI and are not approved for this indication. These formulations may be underdosed or lack microbial diversity required for effective treatment.

FMT procured locally falls under FDA enforcement discretion and requires appropriate risk-benefit discussions with patients.[53] FMT treatment should be guided by clinical and endoscopic markers of disease activity, most notably the presence of pseudomembranes,[54] but also, resolution of diarrhea and leukocytosis. As is the case in flares of IBD/colitis, C-reactive protein is typically elevated in these patients, and downtrends with successful treatment.[55] Figure 2*C* outlines FMT use in patients with fulminant CDI. The authors acknowledge institutional barriers exist to implementing FMT protocols; transfer of patients to a tertiary care center where FMT is available may be necessary. However, any hospital or physician who chooses to offer this potentially life-saving therapy can refer to the provided summary of procedures for performing donor directed FMT for fulminant CDI in Supplementary Table 1. Most individuals will need 2 to 3 administrations of liquid FMT product via lower endoscopy to resolve the acute/severe infection. Standard of care oral vancomycin can be held on the day of FMT but should otherwise be continued after FMT.[56]

Once the patient has experienced resolution of severe/fulminant symptoms, we advise continuing oral vancomycin 125 mg 4 times a day for a total of 14 days and then decreasing the dose to 125 mg once or twice daily until outpatient follow-up and treatment with FDA-approved fecal microbiota-based therapies can be arranged to decrease the risks for recurrent infection.

Best Practice Advice 12: Use of vancomycin is not advised during systemic antibiotic administration to prevent CDI. Probiotics are not advised to prevent an initial or recurrent CDI. To promote restoration of healthy gut microbiota, patients should be instructed to consume a healthy diet including a variety of fruits and vegetables, rich in both soluble and insoluble fiber.

There is limited and conflicting evidence on use of oral vancomycin prophylaxis (OVP) to prevent CDI. The only RCT did not show a statistically significant

difference in recurrent CDI in patients who received OVP. Although OVP was associated with a 13.5% absolute reduction in CDI, the study was not powered to detect that difference.[57] Additional research is needed to understand if this is an effective strategy. Although some guidelines suggest OVP in high-risk patients, these recommendations were conditional and based on low-quality evidence.[20]

In general, we do not use OVP for secondary CDI prophylaxis. We advise close observation for diarrhea on or after antibiotic use and prompt testing and treatment if recurrent CDI develops. A standing order for *C difficile* testing can help to expedite the diagnostic workup.

Patients recovering from CDI frequently ask about probiotics and dietary recommendations to optimize recovery and avoid further recurrences. Probiotics are ineffective for primary or secondary prevention of CDI and are not recommended in guidelines.[20] Instead of probiotics, we focus on prebiotics and nutrition as a preventative strategy. Although there is a lack of clinical evidence to support dietary changes preventing recurrent CDI, it is reasonable to assume that a diet that nurtures a healthy and diverse intestinal microbiota resilient to CDI would be beneficial. A diet varied in fruits and vegetables as fiber sources is important to promote microbial diversity.[58] And certain compounds in fruits and vegetables may have anti–*C difficile* effects.[59,60] The amino acid citrulline, found in high concentrations in watermelon, exerts anti-inflammatory effects against *C difficile* toxins and inhibits CDI recurrence in mice, with human trials underway.[60] Consumption of a low-fiber diet after antibiotics has been shown to contribute to prolonged susceptibility to CDI that corresponds to a perturbation in both microbiota and bile acid composition.[35] Ultra-processed foods should also be avoided as they are detrimental to the microbiome.[61] Patients should not be instructed to eat "bland" or "clear liquid diets" while suffering from CDI, but rather eat a healthy, high-fiber (as tolerated) diverse diet.[35,58–61]

Best Practice Advice 13: During the treatment of CDI or the prevention of its recurrence, the use of proton pump inhibitors (PPIs) should be evaluated. If a legitimate indication exists for their use, PPI discontinuation is not necessary.

PPIs may increase the risk of CDI; however, the absolute magnitude of risk is low. The likely mechanism is enhanced spore survival in a less acidic stomach. Additionally, suppression of gastric acid can alter the gut microbiome, diminishing colonization resistance against pathogens like *C difficile*.[62] Pooled analysis of observational data suggests an increased risk of recurrent CDI (24% in PPI users vs 18% in nonusers),[63] although the largest RCT to date involving >17,000 patients followed for 3 years found no significant increase in number of CDI case with PPI use (11 cases among PPI users vs 4 cases in nonusers; number needed to harm = 1800 with daily pantoprazole).[63] In addition, more recent meta-analyses found no significant difference in CDI risk among PPI users compared with placebo, H2 blocker, or potassium-competitive acid blocker users.[64,65]

In individuals with a clear PPI indication, such as ulcer prevention or severe gastroesophageal reflux disease, the benefits of PPI therapy likely outweigh the potential risk of CDI recurrence. In the absence of an indication, PPI cessation should be discussed. There is no evidence to support recommending a dose reduction.

Best Practice Advice 14: Individuals with a history of CDI should be specifically counseled to avoid unnecessary antibiotic therapy.

Antibiotic stewardship should always be practiced. In individuals with a history of CDI, specific counseling to the patient should occur to inform other health care providers that they have recovered from CDI, and any antibiotic therapy should have an indication. Guidelines are clear that providers should avoid using antibiotics when bacterial infection is unlikely, and prophylactic antibiotics are no longer routinely recommended before dental procedures for most patients with prosthetic joint implants or certain heart conditions.[66] Patients should take antibiotics if they have an appropriate indication and should not fear antibiotic use. As described in BPA 12, concomitant vancomycin or probiotics are not advised.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2026.05.007.

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Conflicts of interest
These authors disclose the following: Monika Fischer reports advisory board for Ferring and Seres; advisory board and teaching for Johnson and Johnson, Eli Lilly, and Bristol Myers Squibb; and serves as an unpaid adviser to Openbiome. Colleen R. Kelly reports advisory board for Eli Lilly; and serves as a paid consultant to Openbiome. Byron P. Vaughn received personal income/renumeration from Health Delegates; and reports grant support from Openbiome. The remaining author discloses no conflict.