CME

Diagnosis and Management of *Clostridioides difficile*

Colleen R. Kelly, MD, FACG[1,2] and Paul Feuerstadt, MD, FACG[3,4]

***Clostridioides difficile* infection (CDI) is challenging to diagnose and treat. Recently published studies and clinical observations have improved our understanding around diagnostic testing and positioning of antibiotics and microbiota-based therapies. This review synthesizes current evidence and guidelines on CDI diagnosis, highlighting the limitations of individual tests and the value of algorithmic approaches. Treatment paradigms are discussed across the spectrum of disease severity, with vancomycin and fidaxomicin as first-line therapies and the diminishing role of metronidazole. For recurrent CDI, newer fecal microbiota-based therapies, including fecal microbiota, live-jslm (Rebyota), and fecal microbiota spores, live-brpk (Vowst), are reviewed. The role of conventional fecal microbiota transplantation, particularly in fulminant CDI, is also addressed, including challenges resulting from US Food and Drug Administration policies around stool bank material. We aim to clarify diagnostic and therapeutic approaches and optimize care for patients with CDI.**

KEYWORDS: C. difficile; fecal microbiota-based therapies; FMT; microbiota restoration; recurrent CDI; pseudomembranous colitis

ABBREVIATIONS: ACG, American College of Gastroenterology; CCCN, cell culture cytotoxin neutralization assay; CDI, Clostridioides difficile infection; EIA, enzyme immunoassay; FDA, US Food and Drug Administration; FMT, fecal microbiota transplant; GDH, glutamate dehydrogenase; IBD, Inflammatory bowel disease; IBS, irritable bowel syndrome; PCR, polymerase chain reaction; rCDI, recurrent C difficile infection; RCT, randomized controlled trial; SOC, standard of care; VOS, VOWST

Am J Gastroenterol 2026;121:628–634. https://doi.org/10.14309/ajg.0000000000003844

INTRODUCTION

Over the past decade, there has been great progress in our understanding around the pathophysiology of *Clostridioides difficile* infection (CDI) and how factors, such as the high prevalence of colonization in some populations, can present diagnostic challenges. Narrower spectrum antibiotics and the more widespread availability of fecal microbiota-based therapies have shifted the treatment paradigm. While these developments have improved the care of patients suffering from CDI and recurrent CDI (rCDI), they have also created confusion for clinicians around how to most accurately diagnose the infection and where to position these newer, often more expensive, therapies. The status of conventional fecal microbiota transplantation (FMT) raises further uncertainty, particularly in fulminant infections for which there are not yet US Food and Drug Administration (FDA)-approved formulations. We hope this review provides clarity around these diagnostic and treatment issues and facilitates optimal care of patients suffering from CDI.

DIAGNOSTICS

The diagnosis of CDI is not always straightforward. Similar to asymptomatic bacteriuria in elderly patients, this organism can colonize the gut, especially in those who have been recently hospitalized or who are residents of long-term care facilities. Nucleic acid amplification tests, such as *C. difficile* polymerase chain reaction (PCR), detect the presence of a toxigenic (pathogenic) strain but cannot differentiate whether toxin is actually being produced by the organism (1). Their high sensitivity resulted in most laboratories adopting this testing modality, and a subsequent rise in positive test results and "CDI diagnoses" that were not necessarily indicative of a truly active infection. Alternatively, toxin enzyme immunoassays (EIAs), which detect free toxin in the stool, are more specific for actual infection but lack sensitivity, missing up to 15% of true infections, particularly early in the course when there are low levels of free toxin in the stool and if specimens are not processed expeditiously (2). In addition, the glutamate dehydrogenase (GDH) assay may be used as a first-line screening assay, as all strains of *C. difficile* produce this enzyme in abundance. However, it cannot serve as a stand-alone test as even nontoxigenic strains, which do not cause symptoms, produce GDH, so positive results must be followed up with confirmatory testing (3).

Understanding the capabilities of these testing methods is important, but it is also necessary to assess the clinical picture to accurately make the diagnosis. Some situations are straightforward—an elderly patient presenting with new-onset explosive watery diarrhea, leukocytosis, and PCR-positive stool testing shortly after completing a course of antibiotics for pneumonia almost certainly has CDI and requires prompt treatment regardless of EIA results. Conversely, a patient with ongoing loose stools and discomfort after a course of therapy for CDI might

[1]Division of Gastroenterology, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA; [2]Harvard Medical School, Boston, Massachusetts, USA; [3]PACT-Gastroenterology Center, Hamden, Connecticut, USA; [4]Division of Gastroenterology, Yale University School of Medicine, New Haven, Connecticut, USA. **Correspondence:** Colleen R. Kelly, MD. E-mail: ckelly42@bwh.harvard.edu.
Received August 16, 2025; accepted November 12, 2025; published online November 17, 2025

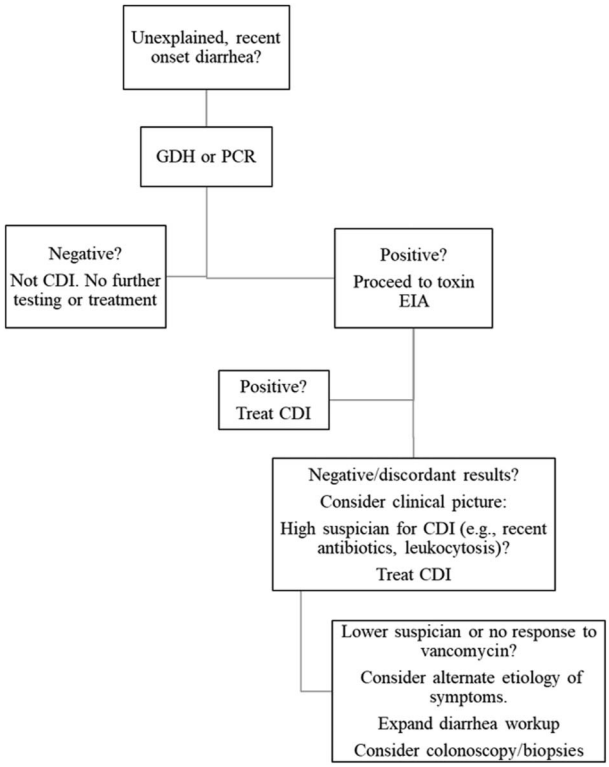

Figure 1. Approach to *C. difficile* diagnosis. CDI, *Clostridioides difficile* infection; GDH, glutamate dehydrogenase assay; EIA, enzyme immunoassay; PCR, polymerase chain reaction.

have a recurrence, or they may have postinfection irritable bowel syndrome (IBS), which is a common occurrence (4). *C. difficile* PCR may remain positive for a period of time after resolution of the actual infection, making it less reliable to confirm or refute recurrence. Patients with chronic diarrhea from an alternative etiology might also be colonized with *C. difficile*, but these patients may also develop CDI, further complicating the picture (5).

Algorithmic testing, starting with a highly sensitive test (PCR or GDH) and, if positive, reflexing to the more specific EIA, has been recommended for best diagnostic accuracy (6) (Figure 1). If the patient tests PCR or GDH negative, no further testing or treatment is warranted. If either are positive along with a positive EIA, true toxin-producing symptomatic CDI is likely. If there are discordant results, that is, positive PCR and negative EIA, then the clinical picture becomes more important. One of the best clinical indicators of true infection is response to vancomycin. If symptoms persist, in a patient with no other signs of severe or fulminant disease (e.g., leukocytosis, megacolon or severe colitis on imaging) and is unabated by treatment with anti-CDI therapy, then the diagnosis should be questioned and other causes of diarrhea explored with a standard workup. Further testing, such as lower endoscopy with biopsies, may help determine whether the patient has CDI, as normal endoscopic/histologic findings exclude CDI and alternate forms of colitis (e.g., microscopic or inflammatory bowel disease [IBD]) might be revealed.

TREATMENT OF CDI

The treatment of CDI involves considering 2 phases of the infection. The vegetative phase, which releases toxins resulting in symptoms, and the spore phase, associated with recurrence and transfer from person to person. The vegetative phase is best controlled with antimicrobials whereas the spore phase requires a healthy diverse microbiota to be eradicated.

ANTIMICROBIALS

There are 3 accepted antimicrobial treatments of CDI: metronidazole, vancomycin, and fidaxomicin (Table 1). Vancomycin and fidaxomicin are FDA approved for this indication.

Initial infection

For initial infection, the American College of Gastroenterology (ACG) Guideline recommended triaging patients based on severity. Those with white blood cell counts less than 15,000/mL^3 and creatinine less than 1.5 mg/dL are considered nonsevere, and metronidazole 500 mg t.i.d. for 10 days, vancomycin 125 mg p.o. q.i.d. for 10 days, or fidaxomicin 200 mg p.o. b.i.d. for 10 days are recommended (6). The Infectious Diseases Society of America/Society for Healthcare Epidemiologists of America took a different approach, agnostic to cost of treatment, recommending a preferred initial approach with fidaxomicin 200 mg p.o. b.i.d. for 10 days. Vancomycin 125 mg p.o. q.i.d. for 10 days was an acceptable alternative, and metronidazole 500 mg p.o. t.i.d. for 10 days was recommended only if fidaxomicin and vancomycin were unavailable in the healthiest of individuals (7).

Metronidazole has a significant side effect profile (e.g., metallic taste in the mouth and nausea) along with a high risk of recurrence. Furthermore, metronidazole was shown to be inferior in older patients, those hospitalized for treatment of CDI, and in those with multiple comorbidities (8). With easier access including lower costs of vancomycin, metronidazole has largely fallen out of favor as a primary treatment of an initial CDI, except for those with fulminant disease where it is used in combination with vancomycin (see below). As metronidazole is associated with recurrence (9,10), it should be used only in those with nonsevere disease and those with no risk factors for rCDI (Table 2).

Vancomycin is the current "go to" treatment of initial CDI. It was the gold standard comparator in the pivotal trial considering fidaxomicin and remains a preferred treatment for initial episode (11). Vancomycin is easily accessible, inexpensive, and effective, with initial treatment response similar to fidaxomicin (12); however, it is associated with modestly increased rate of recurrence in some studies. Within the pivotal fidaxomicin trial, initial treatment responses after 10 days of vancomycin therapy was 85.8%, with recurrence rates of 25.3% within 25 days of completion of this therapy (11). Other trials have shown similar recurrence rates for vancomycin (13,14), though there are some data that vancomycin may be more effective for treatment of severe disease (15) and a recent single-center study of 308 inpatients treated for CDI, did not show difference in 4-week recurrence or 90-day CDI readmission in patients treated with vancomycin compared with fidaxomicin (16). The infectious disease guidelines in the United States and Canada both include vancomycin as a core treatment but give preference to fidaxomicin (7,17).

Fidaxomicin differs from vancomycin in its targeted spectrum of activity. This antibiotic targets *C. difficile* having much less effect on the surrounding microorganisms, preserving beneficial anaerobic microbiota during treatment, which may explain significantly lower rates of recurrence observed in the phase 3 trial of fidaxomicin—15.4% within 25 days of completing therapy, and

Table 1. Recommended treatment strategies for CDI

Clinical scenario	Criteria	Recommended treatment(s)	Notes
Initial infection	No other episodes within 3 mo in the past	Vancomycin 125 mg p.o. q.i.d. × 10 d OR Fidaxomicin 200 mg p.o. b.i.d. × 10 d OR Metronidazole 500 mg p.o. t.i.d. × 10 d (*limited use*)	Fidaxomicin should be considered in those with multiple risk factors for recurrence but cost must be considered Vancomycin often used in hospitalized patients with severe infection Metronidazole is not recommended in older patients, in those with comorbidities, risk factors for recurrence, or those with WBC <15,000/mm^3 and creatinine <1.5 mg/dL
Fulminant infection	Hypotension, shock, ileus, or megacolon	Vancomycin 500 mg p.o. q.i.d. AND Metronidazole 500 mg i.v. t.i.d. *If ileus*: add vancomycin enema 500 mg q.i.d.	Treat in ICU with multidisciplinary team including surgical consultation Consider imaging to assess for ileus, megacolon or perforation Consider FMT if no response after 48 hr of standard therapy Colectomy if preferred option or if FMT unavailable
First recurrence	Second episode within 2–3 mo	Vancomycin taper-pulse dosed regimen: 125 mg q.i.d. × 14 d → b.i.d. × 7 d → daily × 7 d → every other day × 8 d → every third day × 15 d (7 wk total) OR Fidaxomicin 200 mg b.i.d. × 10 d OR Fidaxomicin EXTEND regimen: 200 mg b.i.d. × 5 d → 1 tablet every other day on days 7–25	Recommend fidaxomicin if not used to treat initial infection Recommend consideration for addition of microbiota restoration therapy (e.g., FMT, Rebyota or VOWST) in those at greatest risk for future recurrence
Second or further recurrence	3rd episode or beyond	Vancomycin or fidaxomicin FOLLOWED BY Microbiota restoration therapy (e.g., FMT, Rebyota, or Vowst)	Consider earlier microbiota restoration if initial infection severe or in patients at high risk for further rCDI

CTI, *Clostridioides difficile* infection; FMT, fecal microbiota transplantation; ICU, intensive care unit; rCDI, recurrent CDI; WBC, white blood cell.

these lower rates of recurrence after treatment of nonsevere CDI have been observed in several other studies over the last 15 years (15). The challenge with fidaxomicin has remained consistent: cost. This challenge was considered in the decision to position it equally to vancomycin within the ACG guidelines. With a generic version of fidaxomicin recently approved by the FDA (18), which will hopefully be less expensive, it may become a clear first-line choice for initial infection and in those with risk factors of future recurrence.

Table 2. Risk factors for recurrence

Age >65 yr
Chronic proton-pump inhibitor usage
Immunocompromised (e.g., chronic kidney disease, diabetes mellitus, active chemotherapy)
Likely future concomitant antimicrobial usage
Lives in skilled nursing facility
Severe underlying illness
Spend significant amount of time as an inpatient at the hospital

For those with fulminant disease, defined by hypotension, shock, ileus, and/or megacolon, treatment should be in the intensive care unit, with general or colorectal surgery following. Antimicrobial treatments should include metronidazole 500 mg i.v. t.i.d. and vancomycin 500 mg p.o. q.i.d. If there is an ileus, vancomycin 500 mg q.i.d. in the form of an enema should be added (6,7,17).

Recurrent infection

Treatment of first recurrence (second episode within 2–3 months) has evolved. The most recent ACG guideline recommended fidaxomicin in patients who initially received 10-day courses of either vancomycin or metronidazole and that we consider vancomycin in a taper-pulse treatment (e.g., 125 mg 4 times a day for 14 days, twice a day for 7 days, daily for 7 days, every second day for 8 days and every third day for 15 days [7 weeks total]), if a patient received vancomycin, fidaxomicin, or metronidazole for an initial infection (6). The Infectious Diseases Society of America/Society for Healthcare Epidemiologists of America guidelines preferentially recommended fidaxomicin as either standard dosing (i.e., 200 mg b.i.d. for 10 days) or part of the EXTEND regimen (i.e., 200 mg twice daily for 5 days, followed by 1 tablet every other day for days 7–25), relegating a vancomycin

taper as an acceptable alternative. Vancomycin 125 mg p.o. q.i.d. for 10 days was indicated for patients who did not have a sustained response to a standard course of metronidazole (7). The EXTEND fidaxomicin regimen includes the full treatment course of 20 tablets but gives "standard" b.i.d. dosing initially for 5 days, followed by a pulse with the remaining tablets and reduced 90-day recurrence rates by 11% over standard dose vancomycin in 1 open-label randomized controlled trial (RCT) (14).

Patients with second recurrence (third episode) and beyond typically warrant adjunctive therapy that targets both the vegetative phase of infection (e.g., antimicrobials) but also the spore phase (microbiota restoration therapy). Bezlotoxumab, a monoclonal antibody directed against *C. difficile* toxin B, was once an adjunctive agent used to reduce recurrence and positioned within treatment guidelines, but it is no longer available so will not be addressed further.

One common challenging scenario involves those patients who have experienced rCDI, and are cured, but subsequently require an antimicrobial for another indication within the subsequent 6 months. Within the ACG guidelines, vancomycin prophylaxis was conditionally recommended with a low level of evidence. They recommended giving oral vancomycin 125 mg once daily for the duration of the other antimicrobial and then for 5 days thereafter (6). A recent double-blind RCT considered vancomycin prophylaxis in those with 1 or more episodes of CDI within the previous 6 months. There were nonsignificant trends for lower rates of recurrence in those who received vancomycin prophylaxis, but the study appeared underpowered (19). Vancomycin is itself broad spectrum and through further disruption of the microbiome might also increase risk of subsequent CDI. Although the data seem mixed, we believe vancomycin prophylaxis is safe and potentially effective for those patients who are at greatest risk of future recurrence (≥2 risk factors for future recurrence) when receiving antimicrobials for other indications within 6 months of completion of most recent therapy.

FECAL MICROBIOTA TRANSPLANTATION

Though initially described in 1958, for treatment of pseudomembranous enterocolitis (20), with a few additional case reports over the years, treating CDI with donor stool was often viewed as a last resort. The rise of more severe and multiply recurrent infections early in this century led to renewed interest in "fecal bacteriotherapy." Between 2010 and 2012, a series of studies, including the first guideline which coined the term "fecal microbiota transplantation," were published, supporting the high efficacy and safety of this therapy (21–23).

In 2013, the first RCT demonstrating the superiority of duodenal infusion of donor stool over standard-of-care (SOC) vancomycin was published in the *New England Journal of Medicine* (24). Shortly thereafter the FDA, together with the National Institutes of Health, convened a public workshop to communicate the scientific and regulatory issues around FMT with the medical community. It was at this meeting that the decision to regulate FMT as a biologic drug was first announced, and since this therapy was yet unapproved, an investigational new drug application would be required to administer FMT or perform clinical trials for any indication. Physicians and patient advocacy groups expressed concern that this was overly burdensome and would lead to decreased availability of FMT to those suffering from rCDI. The FDA subsequently revised the initial guidance to one of "enforcement discretion," permitting FMT for patients with rCDI not responding to standard therapies, provided they were given appropriate informed consent and informed that FMT was considered experimental (25).

Early protocols used volunteer donors, often patients' friends and family members. They were screened to exclude those with risk factors of infection transmission or underlying conditions associated with dysbiosis, such as IBD. Serologic and stool testing for pathogens was also performed on each individual donor. Physicians then processed and administered the donor material using various methodologies. Given the logistical challenges related to using directed donors, OpenBiome, a nonprofit stool bank founded by a team of physicians, microbiologists, and public health experts, was established and began to provide screened donor material for FMT in 2012. OpenBiome centralized the process of donor testing, stool donation, and processing and shipped preparations of frozen donor material to clinicians for use. With extensive donor health screenings, serologic and stool testing, infection transmission risk was minimized and with this convenient source of donor stool, FMT was widely facilitated.

Most FMT was performed using a liquid suspension of donor stool administered colonoscopically, though encapsulated formulations administered orally were also used (26). Enema suspensions had an advantage of lower cost of administration and avoiding procedural risks but were less effective, often requiring repeat dosing (27,28).

The effectiveness of FMT for prevention of further recurrence of CDI is high, with a meta-analysis of 11 RCTs enrolling 1,172 patients, treated using various routes and dosing regimens, showing that those randomized to receive fecal microbiota-based therapies were more likely to have prevention of rCDI compared with controls (overall: 74.2% vs 51.7%; relative risk 1.59; 95% confidence interval 1.27–2.00) (29). For conventional FMT, the number needed to treat to prevent 1 infection was 3, with trivial or no difference in serious adverse events in those treated with FMT compared with placebo. There was no difference in rates of prevention of rCDI in mild to moderately immunocompromised patients compared with immunocompetent patients with rates of severe adverse events also comparable with those seen in immunocompetent patients.

Treatment guidelines recommend fecal microbiota-based therapies after a second recurrence (third episode) or earlier in patients who are at high risk of further recurrence or in whom previous CDI have been particularly severe or difficult to treat (6,17,29). This should be administered after patients have completed a standard 10-day course of anti-CDI therapy, typically using vancomycin, followed by a short "wash-out period" of 48–72 hours when no therapy is given. Colonoscopic administration enables examination of the mucosa and assessment of underlying conditions, such as IBD. Encapsulated formulations are preferred by most patients (30,31) and easier to administer but cannot be used safely in those with dysphagia. Though FMT seems safe and is recommended for patients who are mild to moderately immuncompromised (29,32), studies considering FMT to prevent rCDI have largely excluded severe immunocompromised patients, such as those receiving cytotoxic chemotherapy, given higher risk for life-threatening infection. Experts recommend delaying FMT in favor of extended or suppressive antibiotic therapy (e.g., long term vancomycin at lowest effective dose) until immune recovery in this population (29). Cases of drug-resistant *Escherichia coli* infections transmitted from a donor to 2 severely immunocompromised patients by

FMT (33), highlights the potential risk in this population and lead to an FDA alert in 2019 (34).

FMT is also effective in hospitalized patients with severe/fulminant CDI, who are not responding to standard antibiotic therapies and not good candidates for colectomy. Mortality is high in this group, 40%–50% based on historical data (35,36). There are no RCTs in this population, though a meta-analysis of 5 observational studies, enrolling 280 patients showed reduced risk of mortality with conventional FMT compared with SOC, including colectomy (relative risk 0.37; 95% confidence interval 0.23–0.59), giving a number needed to treat of 4 to prevent 1 death (29). Unfortunately, there is not a commercial formulation of donor stool indicated for treatment of severe/fulminant infection and an FDA guidance issued in November 2022, just after the approval of the first FDA-approved microbiota therapeutic, stated that use of material from stool banks was no longer permissible under enforcement discretion (37,38). The timing of this guidance was related to the orphan drug designation of Rebyota (RBL), and that FDA approval of this fecal microbiota formulation entitled the company to 7 years market exclusivity in the United States. Local/institutional or hospital-based stool banks are still permitted to operate under this current guidance to treat their own patients. This FDA policy has greatly affected the use of FMT in the acute/severe and fulminant CDI population, particularly in smaller community hospitals.

It is still permissible and recommended to perform directed donor FMT (29), screening healthy volunteers, as was performed before 2013, in patients who have not responded to SOC antibiotics within 2–5 days. In these emergent situations, clinicians should choose a donor who does not have medical comorbidities thought to be rooted in the microbiota and who has not recently (within 90 days) been treated with antibiotics and conduct expeditious screening for viral or enteric infections (Table 3). Given the urgency of the situation and high mortality of severe/fulminant CDI, the risk/benefit of fresh donor FMT with less stringent screening protocols should be considered. Risks of transmission of metabolic conditions or gastrointestinal disorders are largely theoretical and less of a concern in life-threatening CDI. The patient or their healthcare proxy should undergo adequate informed consent, including counseling that FMT is considered experimental by the FDA for this indication and detailing of risks, such as procedural complications or infection transmission, and alternatives (e.g., colectomy). The cost of donor laboratory screening adds logistical complexity, though screening diagnostic codes for screening may be used when testing for viral hepatitis and HIV, and the potential costs to the donor for bloodwork and stool testing should be acknowledged. FMT is not advised in patients with bowel perforation, obstruction, or those who are severely immunocompromised. The upper gastrointestinal route of administration should be avoided given aspiration risk, with at least the initial dose given by unprepped colonoscopy or sigmoidoscopy. Antibiotics (e.g., vancomycin) are typically continued around FMT in this scenario and repeated FMTs (2 or 3) are typically needed and should be continued until clinical recovery and the resolution of pseudomembranes, as described in the Fischer protocol (39,40).

FDA-APPROVED MICROBIOTA RESTORATION THERAPY

Fecal microbiota, live-jslm (Rebyota)

RBL contains a broad consortium of microorganisms, including both spore- and nonspore-forming bacteria. Having a minimum of 1.5×10^7 *Bacteroides*, RBL is administered as a single 150 mL enema after SOC antimicrobial (e.g., at least 10 days of vancomycin or fidaxomicin) and a 1–3 day washout period (e.g., time between completion of antimicrobial and microbial restoration for the antimicrobial to be passed by the patient) (41).

The PUNCH-CD3 study, a prospective double-blinded, randomized, placebo-controlled trial including patients with first recurrence and beyond was the pivotal trial for this product. With FDA input, a Bayesian statistical analysis was set a priori to the trial, ultimately revealing 8-week responses of 70.6% for RBL and 57.5% for placebo, after SOC antimicrobials (posterior probability of superiority of 0.991) (41). Of those who responded to RBL initially, 92.1% remained responsive 6 months later (41). The most common adverse events were abdominal pain, diarrhea, distension, fatigue, and constipation; most of which were short lived and mild-moderate in nature.

A large open-label study (OLS) considering RBL included 676 patients with first recurrence and beyond, who also could have common gastrointestinal comorbidities, including IBS, IBD, and mild-moderate immunocompromised status. 8-week efficacy was

Table 3. Suggested evaluation for directed donor FMT

Category	Test/screening	Notes
Serologic testing	Hepatitis panel (HBsAg, HBsAb, HBcAb IgM/IgG, Hep A IgM, HBc IgM, HCV Ab) RPR/VDRL HIV, type 1 and 2	
Stool testing	*C. difficile* PCR Viral PCR and bacterial culture or PCR for pathogens	May need to inform lab not to discard solid specimen—donor screening for FMT Extended gastrointestinal pathogen panel if available (e.g., BioFire PCR, Mayo Clinic Labs)
Other screening	Nasal swab for COVID-19 AABB DHQ—available for download at aabb.org MDRO screening (e.g., VRE, MRSA)	No recent (90 d) antibiotics; limited comorbidities; no high risk behaviors Consider if readily available locally

AABB, American Association of Blood Banks; CTI, *Clostridioides difficile* infection; DHQ, Donor History Questionnaire; FMT, fecal microbiota transplantation; HBCAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HCV Ab, hepatitis C antibody; Hep A IgM, hepatitis A IgM; MDRO, multi-drug resistant organisms; MRSA, methacillin-resistant Staphylococcus aureus; PCR, polymerase chain reaction; RPR/VDRL, rapid plasma reagin/venereal disease research laboratory; VRE, vancomycin-resistant enterococci.

73.8%; of those who responded initially, 91.0% remained responsive 6 months after administration (42). This OLS showed consistent safety and efficacy in those who were immunocompromised and those with IBS and IBD (43,44). A prospective trial administering RBL by colonoscopy (i.e., SCOPE Study) showed a 95% 8-week response rate, consistent with effectiveness seen in previous studies of colonoscopic FMT (45). With the departure of OpenBiome and some providers being hesitant to perform local screening and transplants, the various subgroup analyses for this product help provide data support for its usage in those with IBD, IBS, and those who are immunocompromised. The AGA guideline, stating that there were insufficient data to justify FDA-approved treatments in those who were mild-moderately immunocompromised (29), predated the analysis from the OLS for RBL showing a consistent safety and efficacy profile for this subgroup. RBL should be considered in patients at greatest risk of recurrence who are immunocompetent or mild-moderate immunocompromised (≥2 risk factors for recurrence with initial recurrence or anyone with second recurrence and beyond).

The limitations of no longer having access to donor material from stool banks, such as OpenBiome, have presented challenges around management of fulminant disease. There are no published data to support the off-label usage of RBL in this population, though anecdotal reports of use in this setting suggest that this product could be considered following the Fischer protocol outlined earlier. However, though there are concerns around dilution, which at 10^7 *Bacteriodes*/mL is several orders of magnitude lower than the material previously supplied by OpenBiome (10^{12} cells) (46) and the high costs of multidose treatment using this product.

Fecal microbiota spores, live-brpk (Vowst)

Vowst (VOS) is a defined consortium of bacteria. Sourced from human stool, this product undergoes an ethanol purification process, whereby *Firmicutes* spores are isolated and encapsulated in a heat stable formulation. This fecal microbiota-based therapy is administered as 4 capsules daily for 3 days after SOC antimicrobial, a 2–4 day washout, and then a bowel lavage with magnesium citrate (47).

The ECOSPOR III study was the pivotal trial considering VOS; a prospective, multicenter, double-blinded, randomized, placebo-controlled trial including those patients with second recurrence (e.g., third episode) and beyond who were diagnosed with either EIA or cell culture cytotoxin neutralization assay (CCCN). Eight weeks after administration, 88% of those patients who received VOS remained responsive, compared with 60% in those who received placebo after SOC antimicrobial (47). Patients were followed for 6 months for safety and efficacy with no concerning safety signals. The 6-month sustained response was 79% in those receiving VOS vs 53% receiving placebo. The most common side effects included distension, fatigue, constipation, chills, and diarrhea. These were mostly mild-moderate in severity and short lived. The OLS considering VOS expanded its inclusion to allow for those with first recurrence and utilization of the PCR assay for diagnosis, both exclusionary in the ECOSPOR III. Eight weeks after administration of SOC antimicrobial plus VOS, 91% of the patients remained responsive. In those with first recurrence, 94% were responsive at 8 weeks. After 6 months, 86% of the overall cohort receiving VOS were without recurrence (48).

VOS has an excellent safety and efficacy profile when used in clinical practice. Patients with IBS, IBD, and who were immunocompromised were excluded from the phase 3 trials (49), though these are not contraindications to its use and VOS should be considered in patients at greatest risk of recurrence (≥2 risk factors for recurrence [Table 2] with initial recurrence or anyone with second recurrence and beyond) who are not severely immunocompromised and who can swallow pills.

CONCLUSION

The world of *C. difficile* continues to evolve. There is no ideal stand-alone diagnostic test, so testing algorithms, with an initial screen using GDH or PCR followed by confirmatory EIA, have become the preferred approach. Vancomycin and fidaxomicin remain the mainstays of antibiotic therapy for treatment of CDI. Microbiota restoration therapy to prevent recurrence in those at greatest risk is also essential. With OpenBiome not currently available, clinicians should consider either RBL or VOS to prevent rCDI in those patients who are at risk. There is a pipeline of an antibiotic and microbiota-based therapies currently in clinical trials, so the future remains bright for our ability to further treat this challenging infection more effectively.

CONFLICTS OF INTEREST

Guarantor of the article: Colleen R. Kelly, MD, FACG.

Specific author contributions: C.R.K.: drafting, review, and editing the manuscript. P.F.: drafting, review, and editing the manuscript.

Financial support: None to report.

Potential competing interests: P.F.: speakers bureau of Nestle Health Science, Ferring Pharmaceuticals Sanofi and Regeneron Pharmaceuticals; advisory boards for Vedanta Biosciences, Probiotech, Nestle Health Science, Ferring Pharmaceuticals, Sanofi and Takeda Pharmaceuticals. C.R.K.: is a principal investigator for the NIH-funded FMT National Patient registry, serves on the clinical advisory board for OpenBiome (unpaid) and has served on an advisory board for Eli Lilly and Company.

REFERENCES

1. O'Horo JC, Jones A, Sternke M, et al. Molecular techniques for diagnosis of *Clostridium difficile* infection: Systematic review and meta-analysis. Mayo Clinic Proc 2012;87(7):643–51.
2. Planche T, Aghaizu A, Holliman R, et al. Diagnosis of *Clostridium difficile* infection by toxin detection kits: A systematic review. Lancet Infect Dis 2008;8(12):777–84.
3. Arimoto J, Horita N, Kato S, et al. Diagnostic test accuracy of glutamate dehydrogenase for *Clostridium difficile*: Systematic review and meta-analysis. Sci Rep 2016;6:29754.
4. Polage CR, Gyorke CE, Kennedy MA, et al. Overdiagnosis of *Clostridium difficile* infection in the molecular test era. JAMA Intern Med 2015; 175(11):1792–801.
5. Jackson M, Olefson S, Machan JT, et al. A high rate of alternative diagnoses in patients referred for presumed *Clostridium difficile* infection. J Clin Gastroenterol 2016;50(9):742–6.
6. Kelly CR, Fischer M, Allegretti JR, et al. ACG clinical guidelines: Prevention, diagnosis, and treatment of *Clostridioides difficile* infections. Am J Gastroenterol. 2021;116(6):1124–47.
7. Johnson S, Lavergne V, Skinner AM, et al. Clinical practice guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 focused update guidelines on management of *Clostridioides difficile* infection in adults. Clin Infect Dis. 2021;73(5):755–7.
8. Appaneal HJ, Caffrey AR, LaPlante KL. What is the role for metronidazole in the treatment of *Clostridium difficile* infection? Results from a national cohort study of veterans with initial mild disease. Clin Infect Dis 2019; 69(8):1288–95.
9. Zhang K, Beckett P, Abouanaser S, et al. Initial vancomycin versus metronidazole for the treatment of first-episode non-severe *Clostridioides difficile* infection. Antimicrob Steward Healthc Epidemiol. 2021;1(1):e27.

10. Allegretti JR, Marcus J, Storm M, et al. Clinical predictors of recurrence after primary *Clostridioides difficile* infection: A prospective cohort study. Dig Dis Sci. 2020;65(6):1761–6.
11. Louie TJ, Miller MA, Mullane KM, et al. Fidaxomicin versus vancomycin for *Clostridium difficile* infection. N Engl J Med 2011;364(5):422–31.
12. Cornely OA, Crook DW, Esposito R, et al. Fidaxomicin versus vancomycin for infection with *Clostridium difficile* in Europe, Canada, and the USA: A double-blind, non-inferiority, randomised controlled trial. Lancet Infect Dis 2012;12(4):281–9.
13. Wilcox MH, Gerding DN, Poxton IR, et al. Bezlotoxumab for prevention of recurrent *Clostridium difficile* infection. N Engl J Med 2017;376(4): 305–17.
14. Guery B, Menichetti F, Anttila VJ, et al. Extended-pulsed fidaxomicin versus vancomycin for *Clostridium difficile* infection in patients 60 years and older (EXTEND): A randomised, controlled, open-label, phase 3b/4 trial. Lancet Infect Dis 2018;18(3):296–307.
15. Zhao Z, Wu Y, Geng X, et al. Efficacy of fidaxomicin versus vancomycin in the treatment of *Clostridium difficile* infection: A systematic meta-analysis. Medicine (Baltimore) 2024;103(32):e39213.
16. Colwell B, Aguilar J, Hughes F, et al. Real-world effectiveness of fidaxomicin in patients at high risk of *Clostridioides difficile* recurrence. Antimicrob Steward Healthc Epidemiol. 2024;4(1):e127.
17. van Prehn J, Reigadas E, Vogelzang EH, et al. European Society of Clinical Microbiology and Infectious Diseases: 2021 update on the treatment guidance document for *Clostridioides difficile* infection in adults. Clin Microbiol Infect. 2021;27(Suppl 2):S1–S21.
18. ANDA 208443 FDA Approval Letter. https://www.tevausa.com/globalassets/us/teva-generics/catalog-pdfs/fda/Fida_208443.pdf Accessed August 4, 2025.
19. Keating JA, Xu T, Graham MB, et al. Oral vancomycin for prevention of recurrent *Clostridioides difficile* infection: A randomized clinical trial. JAMA Netw Open. 2025;8(7):e2517834.
20. Eiseman B, Silen W, Bascom GS, et al. Fecal enema as an adjunct in the treatment of pseudomembranous enterocolitis. Surgery 1958;44(5):854–9.
21. Yoon SS, Brandt LJ. Treatment of refractory/recurrent *C. difficile*-associated disease by donated stool transplanted via colonoscopy: A case series of 12 patients. J Clin Gastroenterol. 2010;44(8):562–6.
22. Brandt LJ, Aroniadis OC, Mellow M, et al. Long-term follow-up of colonoscopic fecal microbiota transplant for recurrent *Clostridium difficile* infection. Am J Gastroenterol 2012;107(7):1079–87.
23. Bakken JS, Borody T, Brandt LJ, et al. Treating *Clostridium difficile* infection with fecal microbiota transplantation. Clin Gastroenterol Hepatol 2011;9(12):1044–9.
24. van Nood E, Vrieze A, Nieuwdorp M, et al. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. N Engl J Med 2013;368(5):407–15.
25. Hoffmann DE, Javitt GH, Kelly CR, et al. Fecal microbiota transplantation: A tale of two regulatory pathways. Gut Microbes 2025; 17(1):2493901.
26. Vaughn BP, Fischer M, Kelly CR, et al. Effectiveness and safety of colonic and capsule fecal microbiota transplantation for recurrent *Clostridioides difficile* infection. Clin Gastroenterol Hepatol. 2023;21(5):1330–7.e2.
27. Hota SS, Sales V, Tomlinson G, et al. Oral vancomycin followed by fecal transplantation versus tapering oral vancomycin treatment for recurrent *Clostridium difficile* infection: An open-label, randomized controlled trial. Clin Infect Dis 2017;64(3):265–71.
28. Lee CH, Steiner T, Petrof EO, et al. Frozen vs fresh fecal microbiota transplantation and clinical resolution of diarrhea in patients with recurrent *Clostridium difficile* infection: A randomized clinical trial. JAMA 2016;315(2):142–9.
29. Peery AF, Kelly CR, Kao D, et al. AGA clinical practice guideline on fecal microbiota-based therapies for select gastrointestinal diseases. Gastroenterology 2024;166(3):409–34.
30. Zipursky JS, Sidorsky TI, Freedman CA, et al. Patient attitudes toward the use of fecal microbiota transplantation in the treatment of recurrent *Clostridium difficile* infection. Clin Infect Dis 2012;55(12):1652–8.
31. Kao D, Roach B, Silva M, et al. Effect of oral capsule- vs colonoscopy-delivered fecal microbiota transplantation on recurrent *Clostridium difficile* infection: A randomized clinical trial. JAMA 2017;318(20):1985–93.
32. Kelly CR, Ihunnah C, Fischer M, et al. Fecal microbiota transplant for treatment of *Clostridium difficile* infection in immunocompromised patients. Am J Gastroenterol 2014;109(7):1065–71.
33. DeFilipp Z, Bloom PP, Torres Soto M, et al. Drug-resistant *E. coli* bacteremia transmitted by fecal microbiota transplant. N Engl J Med. 2019;381(21):2043–50.
34. Food and Drug Administration. Information Pertaining to Additional Safety Protections Regarding Use of Fecal Microbiota for Transplantation: Screening and Testing of Stool Donors for Multi-drug Resistant Organisms. https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/information-pertaining-additional-safety-protections-regarding-use-fecal-microbiota-transplantation Accessed September 26, 2019.
35. Poylin V, Hawkins AT, Bhama AR, et al. The American Society of Colon and Rectal Surgeons clinical practice guidelines for the management of *Clostridioides difficile* infection. Dis Colon Rectum. 2021;64(6):650–68.
36. Felsenreich DM, Gachabayov M, Rojas A, et al. Meta-analysis of postoperative mortality and morbidity after total abdominal colectomy versus loop ileostomy with colonic lavage for fulminant *Clostridium difficile* colitis. Dis Colon Rectum 2020;63(9):1317–26.
37. Ferring receives U.S. FDA approval for REBYOTA (fecal microbiota, live-jslm): A novel first-in-class microbiota-based live biotherapeutic. https://www.ferring.com/ferring-receives-u-s-fda-approval-for-rebyota-fecal-microbiota-live-jslm-a-novel-first-in-class-microbiota-based-live-biotherapeutic/#:~:text=Saint-Prex%2C%20Switzerland%20and%20Parsippany%2C%20NJ%2C%20USA%20%E2%80%93%2030,and%20older%2C%20following%20antibiotic%20treatment%20for%20recurrent%20CDI Accessed July 20, 2023.
38. US Food & Drug Administration. Enforcement policy regarding investigational new drug requirements for use of fecal microbiota for transplantation to treat clostridioides difficile infection not responsive to standard therapies. https://www.fda.gov/media/86440/download Accessed October 17, 2025.
39. Fischer M, Sipe BW, Rogers NA, et al. Faecal microbiota transplantation plus selected use of vancomycin for severe-complicated *Clostridium difficile* infection: Description of a protocol with high success rate. Aliment Pharmacol Ther 2015;42(4):470–6.
40. Ianiro G, Masucci L, Quaranta G, et al. Randomised clinical trial: Faecal microbiota transplantation by colonoscopy plus vancomycin for the treatment of severe refractory *Clostridium difficile* infection-single versus multiple infusions. Aliment Pharmacol Ther 2018;48(2):152–9.
41. Khanna S, Assi M, Lee C, et al. Efficacy and safety of RBX2660 in PUNCH CD3, a phase III, randomized, double-blind, placebo-controlled trial with a bayesian primary analysis for the prevention of recurrent *Clostridioides difficile* infection. Drugs. 2022;82(15):1527–38.
42. Feuerstadt P, Chopra T, Knapple W, et al. PUNCH CD3-OLS: A phase 3 prospective observational cohort study to evaluate the safety and efficacy of fecal microbiota, live-jslm (REBYOTA) in adults with recurrent *Clostridioides difficile* infection. Clin Infect Dis. 2025;80(1): 43–51.
43. Alonso CD, Tillotson GS, Bidell MR, et al. Safety and efficacy of fecal microbiota, live-jslm, in preventing recurrent *Clostridioides difficile* infection in participants who were mildly to moderately immunocompromised in the phase 3 PUNCH CD3-OLS study. Open Forum Infect Dis. 2025;12(4):ofaf117.
44. Allegretti JR, Feuerstadt P, Knapple WL, et al. Safety and efficacy of fecal microbiota, live-jslm (REBYOTA), for the prevention of recurrent *Clostridioides difficile* infection in participants with inflammatory bowel disease in PUNCH CD3-OLS. Inflamm Bowel Dis. 2025;31(8):2112–22.
45. Khanna S, Yoho D, Van Handel D, et al. Safety and effectiveness of fecal microbiota, live-jslm (REBYOTA) administered by colonoscopy for prevention of recurrent *Clostridioides difficile* infection: 8-week results from CDI-SCOPE, a single-arm, phase IIIb trial. Therap Adv Gastroenterol. 2025;18:17562848251339697.
46. Chen J, Zaman A, Ramakrishna B, et al. Stool banking for fecal microbiota transplantation: Methods and operations at a large stool bank. Front Cell Infect Microbiol 2021;11:622949.
47. Feuerstadt P, Louie TJ, Lashner B, et al. SER-109, an oral microbiome therapy for recurrent *Clostridioides difficile* infection. N Engl J Med. 2022;386(3):220–9.
48. Sims MD, Khanna S, Feuerstadt P, et al. Safety and tolerability of SER-109 as an investigational microbiome therapeutic in adults with recurrent *Clostridioides difficile* infection: A phase 3, open-label, single-arm trial. JAMA Netw Open. 2023;6(2):e2255758.
49. Kelly CR, Fischer M, Grinspan A, et al. Patients eligible for trials of microbe-based therapeutics do not represent the population with recurrent *Clostridioides difficile* infection. Clin Gastroenterol Hepatol. 2020;18(5):1099–101.