



## Microbiome Therapeutics for *Clostridioides difficile* Infection

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### Keywords

*Clostridioides difficile* infection; Fecal microbiota transplant; Fecal microbiota products; Live biotherapeutic products; Recurrent *C difficile*; Microbiome

## INTRODUCTION

*Clostridioides difficile* infection (CDI) is an urgent public health threat and one of the most common health care-associated infections, leading to substantial morbidity, mortality, increased hospital length of stay, and excess health care spending.<sup>1</sup> Up to 30% of patients who develop an episode of CDI suffer disease recurrence after initial antibiotic treatment,<sup>2,3</sup> and the risk of recurrence increases with each subsequent episode.<sup>4</sup> Patients with recurrent CDI (rCDI) suffer repeated episodes of diarrhea and extensive antibiotic exposure that can last years.<sup>5</sup>

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### DISCLOSURES

C.W. Lucky, R.L. Medernach, B.J. Kelly, J.H. Kwon, and M.H. Woodworth do not have any conflicts of interest to disclose. C.W. Lucky and R.L. Medernach were supported by cooperative agreement 6U54CK000607 from the Centers for Disease Control and Prevention, United States (CDC). J.H. Kwon was supported by cooperative agreement 6U54CK000609 from CDC. B.J. Kelly was supported by CDC cooperative agreement FOA#CK16-004-Epicenters for the Prevention of Healthcare Associated Infections. M. H. Woodworth was supported by the Emory Prevention Epicenter Program (PEACH) through CDC (U54CK000601) as well as the National Institute of Allergy and Infectious Diseases, United States (K23AI144036). The contents are solely the responsibility of the authors and do not necessarily represent the official views of CDC or the National Institutes of Health.

The recurrent nature of disease and limited antimicrobial treatments led to the use of adjunct microbiota therapy to interrupt the rCDI cycle by increasing colonic microbial diversity and restoring vital microbial metabolic functions, which promote colonization resistance against *C difficile*.<sup>6</sup> There have been substantial breakthroughs in the development of microbiota-based therapies for prevention and treatment of CDI in addition to antibiotics.

Microbiota-based products include the following.

- Conventional fecal microbiota transplant (FMT) containing donor feces
- Fecal microbiota products (FMPs) manufactured with standardized processes from donor stools
- Live biotherapeutic products (LBPs) comprising well-characterized live bacterial strains or strain consortia

This review highlights the differences between these products and discusses the administration and efficacy data for each method.

## THE MICROBIOTA IN *CLOSTRIDIoidES DIFFICILE* INFECTION AND RATIONALE FOR USE OF MICROBIOME THERAPEUTICS

FMT enriches gut microbiota composition and function, reducing CDI risk through several mechanisms.<sup>7</sup> FMT increases the presence and concentration of microbial-derived metabolites (eg, secondary bile acids and short-chain fatty acids), inhibits growth of *C difficile*, and repairs the intestinal border.<sup>8</sup> Bile salt hydrolases produced by bacteria are an important example of this phenomenon, which consume primary bile acids that stimulate *C difficile* germination, such as taurocholic acid. Microbiota therapies deliver bacterial species (ie, *Bacteroides*) that perform these functions, which together inhibit proliferation and toxin production of *C difficile*.<sup>9</sup>

FMT increases microbial diversity and bacterial competition within the colon. FMT donor bacteria and *C difficile* compete for host dietary substrates (eg, polysaccharides and glycoproteins)<sup>10</sup> and transfer bacteriocins with antibacterial properties. *Bacillus* and *Lactobacillus* species produce thuricin CD<sup>11</sup> and nisin,<sup>12</sup> respectively, which have anti-*C difficile* activity. Finally, FMT conducts signals within the recipient to begin repair of the epithelium and inhibit inflammation caused by *C difficile*<sup>10</sup> by promoting regulatory T-cell growth.<sup>7</sup>

Other fecal microbiota-based products have similar effects, suggesting the use of whole microbiome transfers may not be necessary for clinical improvement in CDI symptoms.<sup>7</sup> Development of FMPs with narrower composition, however, might limit therapeutic potential.<sup>13</sup>

## CLINICAL SPECTRUM OF *CLOSTRIDIODES DIFFICILE* INFECTION AND QUALIFICATION FOR MICROBIOTA-BASED THERAPEUTICS

CDI is defined by clinical symptoms—typically diarrhea (ie, at least 3 unformed stools per 24-hour period)—combined with evidence of toxigenic *C difficile*.<sup>14–18</sup> Microbiota-based therapy has been used for multiple clinical CDI presentations (eg, recurrent, refractory, severe, fulminant/complicated).

Microbiota-based therapies have been most thoroughly studied in their application to rCDI, defined as the recurrence of diarrhea within 8 weeks of treatment of a prior CDI episode.<sup>16,18</sup> Nucleic amplification assay testing for toxigenic *C difficile* or *C difficile* toxin enzyme immunoassay supports this diagnosis.<sup>14,15,17,19</sup> Up to 25% of patients treated for CDI with antimicrobial therapy develop postinfectious irritable bowel syndrome (IBS), mimicking rCDI<sup>20</sup>; the microbiome of patients with *C difficile* postinfectious IBS differs from healthy controls, supporting the use of microbiota-based therapy to restore eubiosis in this cohort.<sup>20</sup>

CDI not responding to standard-of-care antibiotics after 2 to 5 days of treatment is considered refractory CDI,<sup>16–18</sup> particularly in cases of severe or fulminant disease.<sup>19</sup> CDI is considered severe when initial presentation includes poor prognostic features, such as leukocytosis,<sup>14–19</sup> elevated creatinine,<sup>16,18</sup> fever,<sup>16,18</sup> or low albumin.<sup>18</sup> Fulminant or complicated CDI includes toxic megacolon,<sup>14–19</sup> hypotension/shock,<sup>14–19</sup> ileus,<sup>14–17,19</sup> need for surgery or intensive care,<sup>18</sup> or rapid clinical deterioration<sup>16</sup> attributable to CDI. Evidence is more limited in the use of microbiota-based therapies in severe and fulminant cases.

## FECAL MICROBIOTA TRANSPLANT

### Introduction to Fecal Microbiota Transplant

Conventional FMT is the administration of minimally processed stool and distal gut microbiota from healthy donors to restore a healthy gut microbiome in recipients.<sup>7,21</sup> Although microbiota-based therapies have come into vogue in recent years, the use of fresh or processed stool for the treatment of digestive diseases dates to the fourth century CE in China.<sup>22</sup> The first modern case series was published in 1958 by Eiseman and colleagues,<sup>23</sup> demonstrating the use of FMT to treat pseudomembranous enterocolitis.

The most compelling indication for FMT is the prevention of CDI recurrences in people with rCDI.<sup>22,24</sup> The evidence for use of FMT in rCDI is longstanding, with the first case report in contemporary medical journals being published in 1983<sup>25</sup> and the first randomized control trial published 30 years later.<sup>26</sup> Meta-analyses have demonstrated FMT is effective for treating rCDI in immunocompetent adults<sup>21</sup> with reported efficacy of 80% to 90%.<sup>22,27–29</sup> The benefits of FMT can be sustained over multiple years.<sup>30–32</sup>

Guidelines recommend consideration of FMT after at least 2 recurrences of CDI (ie, at least 3 episodes; Table 1). The evidence regarding use of FMT after the first or second episode of CDI is mixed.<sup>33,34</sup> The number of FMT doses, timing of FMT after initial CDI treatment, and need for laboratory confirmation differ between studies,<sup>33,34</sup> reflecting the

heterogeneity of FMT trials and the potential requirement of multiple FMT courses for disease resolution.<sup>35</sup>

FMT is also used in the treatment of severe or refractory CDI. Guidelines propose the use of FMT in cases unresponsive to standard-of-care antibiotics, especially for unsuitable surgical candidates, in an interdisciplinary setting with multiple specialists.<sup>16,36</sup>

FMT recipient registries have been created to track real-world efficacy and adverse events. The FMT National Registry, managed by the American Gastrointestinal Association (AGA), plans to follow North American FMT recipients for up to 10 years to compile more long-term safety and efficacy data.<sup>37,38</sup>

### Formulation and Administration

“FMT” is not a singular procedure or product but instead a spectrum of diverse interventions<sup>39</sup> using minimally processed donor stool procured from stool banks or academic medical centers.<sup>6,13</sup> Early FMT programs used donors selected by the recipient; however, with increasingly strict donor screening requirements,<sup>40</sup> among other ethical and practical concerns, the use of anonymous stool donors has proliferated.<sup>6</sup>

FMT comes in several formulations: encapsulated, fresh, or frozen. Oral capsules, frozen or lyophilized, have demonstrated efficacy in preventing rCDI,<sup>27,29,33</sup> although the quantity of capsules ingested varies substantially by study protocol.<sup>29</sup> Oral liquid formulations are an option for patients who cannot swallow capsules.<sup>41</sup> Fresh stool products can be used, but frozen FMT products are equally effective.<sup>24,42</sup> Frozen FMT products offer the convenience of prolonged storage<sup>43</sup> and may increase safety by allowing FMT product destruction if the donor becomes ill in the interval between donation and product use.<sup>24</sup>

Administration of FMT varies by route (eg, upper or lower gastrointestinal [GI] tract) and method of delivery (eg, administration via feeding tube, enema, or instillation during endoscopy). There is insufficient evidence to recommend a specific route of FMT delivery<sup>14,15,17–19,24</sup>; however, there are clinical conditions and patient factors that influence FMT administration. Upper GI administration should be avoided in patients at elevated risk for aspiration or regurgitation.<sup>17–19,24</sup> FMT via enema has lower efficacy but does not require feeding tube placement or the procedural costs and risks of colonoscopy.<sup>19,24</sup> If patients fail initial FMT by oral capsule or enema, subsequent FMT via colonoscopy is recommended<sup>19</sup>; lower GI endoscopy also allows for confirmation of CDI diagnosis and severity.<sup>17</sup>

### Risks of Fecal Microbiota Transplant

The most common side effects of FMT are abdominal discomfort/cramping, flatulence, diarrhea, vomiting, belching, and fever,<sup>44</sup> although rates of diarrhea may be overestimated (Table 2). Serious adverse events can include injury from FMT delivery methods (eg, aspiration of fecal contents, bowel perforation during endoscopy, or anesthesia-related complications). There are rare reports of inflammatory bowel disease exacerbation and development of autoimmune diseases.<sup>44,45</sup> Patients should be followed for a minimum of 8 weeks after FMT to evaluate for adverse events and late treatment failure.<sup>19,24</sup>

The largest safety concern is transmission of infectious pathogens through FMT. Enteric bacteria producing extended-spectrum  $\beta$ -lactamases (ESBL) have been transmitted by FMT<sup>46</sup> as well as viral infections like cytomegalovirus (CMV) and norovirus.<sup>47,48</sup> The Food and Drug Administration (FDA) has also issued safety alerts communicating the risk of potential transmission of SARS-CoV-2 or mpox with FMT.<sup>49,50</sup> Seronegative immunocompromised patients at increased risk of disseminated infection from CMV or Epstein-Barr virus should be informed about the rare possibility of viral transmission through FMT.<sup>19,24</sup>

Donor screening programs mitigate the risk of donor-derived infection through FMT, although there remains a need for standardized screening protocols.<sup>51,52</sup> Generally, donor blood and stool are screened for transmissible diseases, and prospective donors undergo risk assessment of behaviors linked to infectious diseases.<sup>24,45,53</sup> After a donor-derived ESBL *Escherichia coli* strain was linked to invasive infections and one death in 2 immunocompromised FMT recipients,<sup>40,54</sup> the FDA recommended the addition of multidrug-resistant organism screening.<sup>40</sup> Given the possible contribution of recipient neutropenia to the invasive infections and death, FMT is generally avoided in neutropenic patients.<sup>17</sup>

Although serious adverse events have been associated with FMT,<sup>45</sup> these events have been very rare. A review of longitudinal studies found zero FMT-attributable deaths, autoimmune diseases, or GI disorders during a 10-year follow-up period.<sup>30</sup>

### Use in special populations

**Fecal microbiota transplant in pregnancy.** American College of Gastroenterology guidelines recommend avoiding FMT in pregnancy given procedural risks and lack of safety data; maintenance oral vancomycin followed by postpartum FMT is an alternative.<sup>19</sup> CDI during pregnancy is associated with higher rates of venous thromboembolism, delivery complications, and maternal mortality.<sup>19</sup> Patients and specialists may decide the risks of FMT are preferable to morbid CDI recurrence or potential complications of long-term suppressive antibiotic therapy.<sup>55</sup>

**Fecal microbiota transplant in the immunocompromised.** AGA guidelines conditionally recommend avoiding FMT in severely immunocompromised patients.<sup>17</sup> FMT was generally well-tolerated and safe in observational studies of immunocompromised participants, but the certainty of evidence was rated “very low” because of the risk of bias.<sup>17</sup> The decision to pursue FMT in severely immunocompromised patients should be undertaken with careful analysis of risks, benefits, and alternative therapies.<sup>19,56</sup>

### Practical concerns

**Product cost coverage.** FMT is regulated as a medicinal product in the United States.<sup>57</sup> As a result, codes have been assigned for billing private payors and Medicare. Separate codes for donor testing and delivery of FMT have been created for private insurance plans, whereas Medicare recognizes one code for both processes.<sup>58</sup>

**Stool donation.** The cost of creating a fecal donation center can be significant, with many physicians citing the cost and complexity of maintaining a stool donor base and screening fecal products as prohibitive to offering FMT.<sup>59</sup> An FMT program requires identifying and screening donors; collecting, processing, and storing fecal contents; and delivering the appropriate product to the corresponding recipient.<sup>60</sup> Maintenance of a consistent donor population and oversight of the stool bank by specialists in clinical microbiology, infectious diseases, and gastroenterology may be financially infeasible for health care systems.<sup>61</sup> A Canadian study from 2017 reported a total cost of \$15,190 US dollars to screen 46 potential donors, yielding a single suitable donor.<sup>62</sup>

**Stool banking.** Large stool banks have the benefit of scale compared with smaller hospital laboratories but have experienced regulatory hurdles in recent years. In 2022, the FDA announced the end of enforcement discretion for centralized stool banks—notably affecting OpenBiome, a nonprofit providing fecal products to more than 1000 FMT-performing institutions and 10,000 patients yearly at its peak.<sup>13,63</sup> The FDA reinstated an investigational new drug requirement for distributors of FMT in fall 2024, posing challenges to offering FMT as a routine clinical intervention.<sup>64,65</sup> Applying a biological drug regulatory framework to FMT limits the commercial distribution of stool products and restricts patient access to FMT outside of participation in a clinical trial setting for specific indications.<sup>63</sup>

**Storage concerns.** Following collection, FMT products can be stored briefly at 4°C before freezing. Once frozen, stool products are preserved for years at temperatures of –80°C without substantial reductions in potency measured as colony-forming units per milliliter.<sup>43,66</sup> Products can be thawed at room temperature or in a warm bath and then used for FMT within 6 hours of thawing.<sup>61</sup> Use of FMT may be limited by access to deep freezers and locations for dose thawing/preparation.

## FECAL MICROBIOTA PRODUCTS AND LIVE BIOTHERAPEUTIC PRODUCTS

### Introduction to Fecal Microbiota Products

Logistical and regulatory challenges in maintaining safe, consistent supplies of stool from healthy donors to meet clinical demand for microbiota-based therapy led to the commercial development of FMPs.<sup>13</sup> FMPs are manufactured from human donor stool using standardized processes, offering improved ease of distribution and reimbursement over conventional FMT.<sup>4,7,67</sup> Like FMT, these products aim to correct deficiencies in the gut microbiome, mainly by replacing key phyla (ie, *Bacteroidetes* and *Firmicutes*) to prevent *C. difficile* recurrence.<sup>68</sup> FMPs are manufactured using Good Manufacturing Practice<sup>63,69</sup> and undergo sampling before administration to ensure minimum thresholds of bacterial species are met.<sup>68</sup> Two FMPs have received FDA approval for the prevention of rCDI in adults undergoing treatment of rCDI (Tables 3 and 4).

Rebyota (Fecal microbiota, Live-jsIm; Ferring Pharmaceuticals, Parsippany, NJ) was the first FMP to receive FDA approval in 2022. Rebyota is a liquid suspension of fecal microbiota (including  $1 \times 10^5$  colony-forming units of *Bacteroides* spp) administered rectally.<sup>70</sup> Rebyota can be stored in an ultracold freezer (–60°C to –90°C) or refrigerated (2°C to 8°C) for 5 days (Fig. 1).

Vowst (Fecal microbiota spores, Live-brpk; Nestle HealthScience, Hoboken, NJ) was the first oral FMP to receive FDA approval. Vowst is a purified suspension of fecal bacterial spores (*Firmicutes* spp) in oral capsules that can be stored at room temperature (up to 25°C).<sup>71</sup>

Both products should be administered 1 to 3 days after the completion of *C difficile* antibiotics.<sup>70,71</sup> Like conventional FMT, most side effects associated with either drug were mild to moderate GI symptoms.<sup>37</sup> Both products are available by prescription in the United States, generally covered by commercial insurance.

### Special Populations

Given the novelty of FMPs, there are minimal safety data regarding use in pediatrics, pregnancy, and breastfeeding.<sup>70,71</sup> There is insufficient evidence supporting the use of FMPs in immunosuppressed patients,<sup>17</sup> although patients considered immunocompromised were enrolled in trials for both products.<sup>71,73</sup>

## FECAL MICROBIOTA PRODUCTS AND LIVE BIOTHERAPEUTIC PRODUCTS: FUTURE DIRECTIONS

Table 5 includes information about FMPs and LBPs in development. One LBP, VE303, is currently recruiting subjects for a phase III study.<sup>79</sup> LBPs differ from FMPs by their defined composition (ie, consistent proportional abundance of component microbes). For example, VE303 contains 8 strains of commensal *Clostridia* species manufactured from pure clonal cell banks.<sup>60</sup> LBPs may allow better understanding of dose-response effects in the application of microbial therapeutics to the treatment of CDI.<sup>60,76</sup> As selected microbiota formulations and LBPs become more refined in their composition, it remains to be seen if they can provide the same clinical benefits of conventional FMT and FMPs without the full complement of metabolites, viruses, and bacteria delivered by these earlier-generation products.<sup>13,69</sup>

### CHOICE OF MICROBIOTA-BASED THERAPY

The decision to pursue FMT or FMPs depends on patient and provider access to these products, patient comorbidities and preferences, and disease factors. Table 6 compares the use of FMT and FMPs on patient factors, such as indication, age, and patient comorbidities. Cost, insurance coverage, and geography (ie, access to institutions performing FMT) will also influence treatment decisions. Head-to-head comparison of FMT and FMPs for rCDI is lacking,<sup>37</sup> and choosing a product may ultimately depend on patient access.<sup>13</sup>

### SUMMARY

Despite the heterogeneity in study design and products, the clinical benefits of FMT and FMPs in rCDI are well supported. Future directions include the use of precision medicine to design microbiota-based products tailored to specific deficits in an individual microbiome.<sup>7</sup> The rapid expansion of the field will continue as more FMPs and LBPs progress through development. Although the introduction of FMPs has improved standardization of

microbiota products, improving the accessibility of fecal microbiota therapies will be crucial to ensure the wide availability of clinical benefits.

## Abbreviations

|             |                                                     |
|-------------|-----------------------------------------------------|
| <b>AGA</b>  | American Gastrointestinal Association               |
| <b>CDI</b>  | <i>Clostridioides difficile</i> infection           |
| <b>CMV</b>  | Cytomegalovirus                                     |
| <b>ESBL</b> | extended-spectrum $\beta$ -lactamase                |
| <b>FDA</b>  | Food and Drug Administration                        |
| <b>FMP</b>  | fecal microbiota product                            |
| <b>FMT</b>  | fecal microbiota transplant                         |
| <b>GI</b>   | Gastrointestinal                                    |
| <b>IBS</b>  | irritable bowel syndrome                            |
| <b>LBP</b>  | live biotherapeutic product                         |
| <b>rCDI</b> | recurrent <i>Clostridioides difficile</i> infection |

## REFERENCES

1. Marra AR, Perencevich EN, Nelson RE, et al. Incidence and outcomes associated with clostridium difficile infections: a systematic review and meta-analysis. *JAMA Netw Open* 2020;3(1):e1917597. [PubMed: 31913488]
2. Maroo S, Lamont JT. Recurrent clostridium difficile. *Gastroenterology* 2006; 130(4):1311–6. [PubMed: 16618421]
3. Kelly CP. Can we identify patients at high risk of recurrent clostridium difficile infection? *Clin Microbiol Infect* 2012;18:21–7.
4. Morado F, Nanda N. A review of therapies for clostridioides difficile infection. *Antibiotics* 2025;14(1):17.
5. McFarland LV, Elmer GW, Surawicz CM. Breaking the cycle: treatment strategies for 163 cases of recurrent clostridium difficile disease. *Am J Gastroenterol* 2002; 97(7):1769–75. [PubMed: 12135033]
6. Costello SP, Tucker EC, La Brooy J, et al. Establishing a fecal microbiota transplant service for the treatment of clostridium difficile infection. *Clin Infect Dis* 2016;62(7):908–14. [PubMed: 26628567]
7. Bloom PP, Young VB. Microbiome therapeutics for the treatment of recurrent clostridioides difficile infection. *Expert Opin Biol Ther* 2022;23(1):89–101. [PubMed: 36536532]
8. Seekatz AM, Theriot CM, Rao K, et al. Restoration of short chain fatty acid and bile acid metabolism following fecal microbiota transplantation in patients with recurrent clostridium difficile infection. *Anaerobe* 2018;53:64–73. [PubMed: 29654837]
9. Mullish BH, McDonald JAK, Pechlivanis A, et al. Microbial bile salt hydrolases mediate the efficacy of faecal microbiota transplant in the treatment of recurrent clostridioides difficile infection. *Gut* 2019;68(10):1791–800. [PubMed: 30816855]
10. Khoruts A, Sadowsky MJ. Understanding the mechanisms of faecal microbiota transplantation. *Nat Rev Gastroenterol Hepatol* 2016;13(9):508–16. [PubMed: 27329806]

11. Rea MC, Sit CS, Clayton E, et al. Thuricin CD, a posttranslationally modified bacteriocin with a narrow spectrum of activity against *Clostridium difficile*. *Proc Natl Acad Sci USA* 2010;107(20):9352–7. [PubMed: 20435915]
12. Le Lay C, Dridi L, Bergeron MG, et al. Nisin is an effective inhibitor of *Clostridium difficile* vegetative cells and spore germination. *J Med Microbiol* 2016;65(2): 169–75. [PubMed: 26555543]
13. Kelly BJ, Kwon JH, Woodworth MH. Escape velocity—the launch of microbiome therapies. *J Infect Dis* 2024;230(1):2–4. [PubMed: 39052747]
14. McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the infectious diseases society of America (IDSA) and society for healthcare epidemiology of America (SHEA). *Clin Infect Dis* 2018;66(7):e1–48. [PubMed: 29462280]
15. Johnson S, Laverne 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):e1029–44. [PubMed: 34164674]
16. 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 Infection* 2021; 27(Suppl 2):S1–21.
17. 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. [PubMed: 38395525]
18. Trubiano JA, Cheng AC, Korman TM, et al. Australasian society of infectious diseases updated guidelines for the management of *Clostridium difficile* infection in adults and children in Australia and New Zealand. *Intern Med J* 2016;46(4): 479–93. [PubMed: 27062204]
19. 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. [PubMed: 34003176]
20. Taghaddos D, Saqib Z, Bai X, et al. Post-infectious IBS following *Clostridioides difficile* infection: role of microbiota and implications for treatment. *Dig Liver Dis* 2024;56(11):1805–9. [PubMed: 38653643]
21. Minkoff NZ, Aslam S, Medina M, et al. Fecal microbiota transplantation for the treatment of recurrent *Clostridioides difficile* (*Clostridium difficile*). *Cochrane Database Syst Rev* 2023;4(4):CD013871. [PubMed: 37096495]
22. Lee JY, Kim Y, Kim J, et al. Fecal microbiota transplantation: indications, methods, and challenges. *J Microbiol* 2024;62(12):1057–74. [PubMed: 39557804]
23. 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. [PubMed: 13592638]
24. Mullish BH, Merrick B, Quraishi MN, et al. The use of faecal microbiota transplant as treatment for recurrent or refractory *Clostridioides difficile* infection and other potential indications: second edition of joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines. *J Hosp Infect* 2024; 148:189–219. [PubMed: 38609760]
25. Schwan A, Sjölin S, Trottestam U, et al. Relapsing *Clostridium difficile* enterocolitis cured by rectal infusion of homologous faeces. *The Lancet (British edition)* 1983; 2(8354):845.
26. 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. [PubMed: 23323867]
27. Du C, Luo Y, Walsh S, et al. Oral fecal microbiota transplant capsules are safe and effective for recurrent *Clostridioides difficile* infection: a systematic review and meta-analysis. *J Clin Gastroenterol* 2021;55(4):300–8. [PubMed: 33471490]
28. Kassam Z, Lee CH, Yuan Y, et al. Fecal microbiota transplantation for *Clostridium difficile* infection: systematic review and meta-analysis. *Am J Gastroenterol* 2013; 108(4):500–8. [PubMed: 23511459]

29. Cold F, Baunwall SMD, Dahlerup JF, et al. Systematic review with meta-analysis: encapsulated faecal microbiota transplantation — evidence for clinical efficacy. *Therap Adv Gastroenterol* 2021;14:17562848211041004.
30. Ooijselaar RE, van Nood E, Goorhuis A, et al. Ten-year follow-up of patients treated with fecal microbiota transplantation for recurrent clostridioides difficile infection from a randomized controlled trial and review of the literature. *Microorganisms* 2021;9(3):548. [PubMed: 33800841]
31. Terveer EM, Vendrik KE, Ooijselaar RE, et al. Faecal microbiota transplantation for clostridioides difficile infection: four years' experience of The Netherlands donor feces bank. *United European Gastroenterol J* 2020;8(10):1236–47.
32. Mamo Y, Woodworth MH, Wang T, et al. Durability and long-term clinical outcomes of fecal microbiota transplant treatment in patients with recurrent clostridium difficile infection. *Clin Infect Dis* 2018;66(11):1705–11. [PubMed: 29272401]
33. Baunwall SMD, Andreasen SE, Hansen MM, et al. Faecal microbiota transplantation for first or second clostridioides difficile infection (EarlyFMT): a randomised, double-blind, placebo-controlled trial. *Lancet Gastroenterol Hepatol* 2022;7(12): 1083–91. [PubMed: 36152636]
34. Drekonja DM, Shaukat A, Huang Y, et al. A randomized controlled trial of efficacy and safety of fecal microbiota transplant for preventing recurrent clostridioides difficile infection. *Clin Infect Dis* 2024;80(1):52–60.
35. Poutanen SM, Hota SS. Déjà vu: unanswered questions about fecal microbiota transplantation for recurrent clostridioides difficile infection. *Clin Infect Dis* 2025;80(1):61–2. [PubMed: 39270730]
36. Kuijper EJ, Garey KW. The new horizon of clostridioides difficile infection treatment. *Gastroenterology* 2025;168(2):219–22. [PubMed: 39505220]
37. Dupont HL, Dupont AW, Tillotson GS. Microbiota restoration therapies for recurrent clostridioides difficile infection reach an important new milestone. *Therap Adv Gastroenterol* 2024;17:17562848241253089.
38. Kelly CR, Yen EF, Grinspan AM, et al. Fecal microbiota transplantation is highly effective in real-world practice: initial results from the FMT national registry. *Gastroenterology* 2021;160(1):183–92.e3. [PubMed: 33011173]
39. Hota SS, Poutanen SM. Is a single fecal microbiota transplant a promising treatment for recurrent clostridium difficile infection? *Open Forum Infect Dis* 2018;5(3): ofy045. [PubMed: 29600252]
40. U.S. Food & Drug Administration. Fecal microbiota for transplantation: safety communication—risk of serious adverse reactions due to transmission of multi-drug resistant organisms. 2019. Available at: <https://www.fda.gov/safety/medical-product-safety-information/fecal-microbiota-transplantation-safety-communication-risk-serious-adverse-reactions-due>. Accessed February 25, 2025.
41. Sadowsky MJ, Matson M, Mathai PP, et al. Successful treatment of recurrent clostridioides difficile infection using a novel, drinkable, oral formulation of fecal microbiota. *Dig Dis Sci* 2024;69(5):1778–84. [PubMed: 38457115]
42. Khan MY, Dirweesh A, Khurshid T, et al. Comparing fecal microbiota transplantation to standard-of-care treatment for recurrent clostridium difficile infection: a systematic review and meta-analysis. *Eur J Gastroenterol Hepatol* 2018;30(11): 1309–17. [PubMed: 30138161]
43. Facchin S, Cardin R, Patuzzi I, et al. Long-term stability and efficacy of frozen fecal microbiota transplant (FMT) product at 24 months. *Dig Liver Dis* 2025; 57(3):702–6. [PubMed: 39672770]
44. Wang S, Xu M, Wang W, et al. Systematic review: adverse events of fecal microbiota transplantation. *PLoS One* 2016;11(8):e0161174. [PubMed: 27529553]
45. Cammarota G, Ianiro G, Tilg H, et al. European consensus conference on faecal microbiota transplantation in clinical practice. *Gut* 2017;66(4):569–80. [PubMed: 28087657]
46. 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. [PubMed: 31665575]
47. Vandenplas Y, Veereman G, van der Werff Ten Bosch J, et al. Fecal microbial transplantation in early-onset colitis: caution advised. *J Pediatr Gastroenterol Nutr* 2015;61(3):e12–4. [PubMed: 24399213]

48. Schwartz M, Gluck M, Koon S. Norovirus gastroenteritis after fecal microbiota transplantation for treatment of clostridium difficile infection despite asymptomatic donors and lack of sick contacts. *Am J Gastroenterol* 2013;108(8):1367.
49. U.S. Food & Drug Administration. Safety alert regarding use of fecal microbiota for transplantation and additional safety protections pertaining to SARS-CoV-2 and COVID-19. 2020. Available at: <https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/safety-alert-regarding-use-fecal-microbiota-transplantation-and-additional-safety-protections>. Accessed June 16, 2025.
50. U.S. Food & Drug Administration. Safety alert regarding use of fecal microbiota for transplantation and additional safety protections pertaining to monkeypox virus. 2022. Available at: <https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/safety-alert-regarding-use-fecal-microbiota-transplantation-and-additional-safety-protections-0>. Accessed June 16, 2025.
51. Mehta N, Wang T, Friedman-Moraco RJ, et al. Fecal microbiota transplantation donor screening updates and research gaps for solid organ transplant recipients. *J Clin Microbiol* 2022;60(2):e0016121. [PubMed: 34133889]
52. Woodworth MH, Carpentieri C, Sitchenko KL, et al. Challenges in fecal donor selection and screening for fecal microbiota transplantation: a review. *Gut Microbes* 2017;8(3):225–37. [PubMed: 28129018]
53. Terveer EM, van Beurden YH, Goorhuis A, et al. How to: establish and run a stool bank. *Clin Microbiol Infect* 2017;23(12):924–30. [PubMed: 28529025]
54. Revolinski S, Munoz-Price LS. Fecal microbiota transplantation for clostridioides difficile infection in immunocompromised hosts. *Clin Infect Dis* 2021;72(12):2247.
55. Saeedi BJ, Morison DG, Kraft CS, et al. Fecal microbiota transplant for clostridium difficile infection in a pregnant patient. *Obstet Gynecol* 2017;129(3):507–9. [PubMed: 28178052]
56. Lee MSL, Ramakrishna B, Moss AC, et al. Successful treatment of fulminant clostridioides difficile infection with emergent fecal microbiota transplantation in a patient with acute myeloid leukemia and prolonged, severe neutropenia. *Transpl Infect Dis* 2020;22(1):e13216. [PubMed: 31769569]
57. Cammarota G, Gallo A, Ianiro G, et al. Emerging drugs for the treatment of clostridium difficile. *Expert Opin Emerg Drugs* 2019;24(1):17–28.
58. American Gastroenterological Association. Coding: fecal microbiota transplant (FMT) guidance. Available at: <https://gastro.org/practice-resources/reimbursement/coding/coding-fecal-microbiota-transplant-fmt-guidance/>. Accessed January 24, 2025.
59. Bakken JS, Polgreen PM, Beekmann SE, et al. Treatment approaches including fecal microbiota transplantation for recurrent clostridium difficile infection (RCDI) among infectious disease physicians. *Anaerobe* 2013;24:20–4. [PubMed: 24012687]
60. Dsouza M, Menon R, Crossette E, et al. Colonization of the live biotherapeutic product VE303 and modulation of the microbiota and metabolites in healthy volunteers. *Cell Host Microbe* 2022;30(4):583–98.e8. [PubMed: 35421353]
61. Cammarota G, Ianiro G, Kelly CR, et al. International consensus conference on stool banking for faecal microbiota transplantation in clinical practice. *Gut* 2019;68(12):2111–21. [PubMed: 31563878]
62. Laura JC, Nair Parvathy S, Tat-Ko J, et al. Extended screening costs associated with selecting donors for fecal microbiota transplantation for treatment of metabolic syndrome-associated diseases. *Open Forum Infect Dis* 2017;4(4):ofx243. [PubMed: 29255739]
63. Hoffmann DE, Javitt GH, Kelly CR, et al. Fecal microbiota transplantation: a tale of two regulatory pathways. *Gut Microbes* 2025;17(1):2493901. [PubMed: 40302307]
64. Webb J The state of fecal transplants. Peggy Lillis Foundation Web site. 2024. Available at: <https://cdiff.org/the-state-of-fmt/>. Accessed March 27, 2025.
65. Abreu MT, Schmitt SK, Lightdale J, et al. American Gastroenterological Association. Re: retention of access to conventional fecal microbiota transplantation for complicated and vulnerable patients with *C. difficile* infection. 2024. Available at: <https://gastro.org/news/aga-calls-on-fda-to-retain-access-to-conventional-fmt/>.

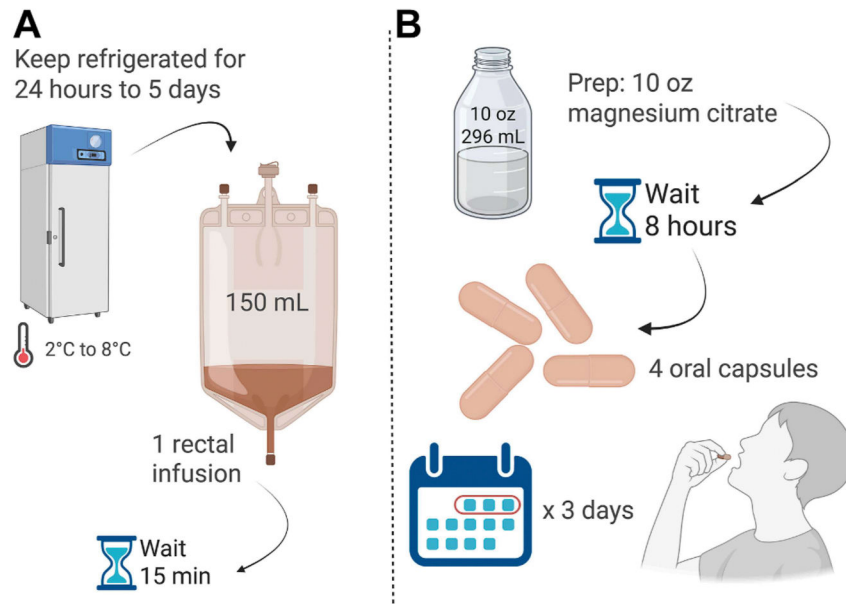
66. Soukupova H, Rehorova V, Cibulkova I, et al. Assessment of faecal microbiota transplant stability in Deep-Freeze conditions: a 12-Month Ex Vivo viability analysis. *J Clin Lab Anal* 2024;38(7):e25023. [PubMed: 38544348]
67. Ott SJ, Waetzig GH, Rehman A, et al. Efficacy of sterile fecal filtrate transfer for treating patients with clostridium difficile infection. *Gastroenterology* 2017; 152(4):799–811.e7. [PubMed: 27866880]
68. Sehgal K, Feuerstadt P. Live biotherapeutic products: a capstone for prevention of recurrent clostridioides difficile infection. *Front Microbiomes* 2024;3. 10.3389/frmbi.2024.1399440.
69. Kim D, Lee S, Lee J, et al. Gut microbiome therapy: fecal microbiota transplantation vs live biotherapeutic products. *Gut Microbes* 2024;16(1):2412376. [PubMed: 39377231]
70. REBYOTA (fecal microbiota, live-jslm). [package insert]. Roseville, MN: Ferring pharmaceuticals; 2022. Available at: file:///C:/Users/20572/Downloads/Ref70-Rebyota.pdf.
71. Vowst (fecal microbiota spores, live-brpk). [package insert]. Cambridge, MA: Seres Therapeutics, Inc; 2024. Available at: file:///C:/Users/20572/Downloads/Ref71-Vowst.pdf.
72. 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. [PubMed: 36287379]
73. 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-jsIm (REBYOTA) in adults with recurrent clostridioides difficile infection. *Clin Infect Dis* 2025;80(1):43–51. [PubMed: 39180326]
74. 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. [PubMed: 35045228]
75. 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. [PubMed: 36780159]
76. Louie T, Golan Y, Khanna S, et al. VE303, a defined bacterial consortium, for prevention of recurrent clostridioides difficile infection. *JAMA* 2023;329(16):1356. [PubMed: 37060545]
77. Kao D, Wong K, Franz R, et al. The effect of a microbial ecosystem therapeutic (MET-2) on recurrent clostridioides difficile infection: a phase 1, open-label, sin-gle-group trial. *Lancet Gastroenterol Hepatol* 2021;6(4):282–91. [PubMed: 33631102]
78. Gerding DN, Meyer T, Lee C, et al. Administration of spores of nontoxigenic clostridium difficile strain M3 for prevention of recurrent C difficile infection: a randomized clinical trial. *JAMA* 2015;313(17):1719–27. [PubMed: 25942722]
79. Vedanta Biosciences I VE303 for prevention of recurrent clostridioides difficile infection (RESTORATiVE303). ClinicalTrials.gov Web site. 2025. Available at: <https://clinicaltrials.gov/study/NCT06237452>. Accessed June 4, 2025.

**KEY POINTS**

- Fecal microbiota transplant (FMT) has been used to treat recurrent *Clostridioides difficile* infection (rCDI), severe or fulminant/complicated *Clostridioides difficile* infection (CDI), and refractory CDI.
- The need for regulated, standardized microbiota-based therapy has led to the development of fecal microbiota products (FMPs) and live biotherapeutic products (LBPs).
- FMT, FMPs, and LBPs are used in cases of rCDI to prevent further recurrences of CDI.

**CLINICS CARE POINTS**

- Fecal microbiota transplant encompasses a spectrum of interventions used to enhance a recipient's gut microbiome by the instillation of donor stool, and guidelines for use in recurrent *Clostridioides difficile* infection are published by several medical societies including IDSA and AGA.
- Fecal microbiota products are produced from donor stool and formulated to contain a certain amount of beneficial bacteria in each dose.
- Fecal microbiota products have been approved for patients with recurrent *Clostridioides difficile* infection and can be administered rectally (Rebyota) or taken orally (Vowst).
- Individual comorbidities should be evaluated when considering use of fecal microbiota transplant or fecal microbiota products.



**Fig. 1.** Method of fecal microbiota production administration. (A) Fecal microbiota, live-jslm. (B) Fecal microbiota spores, Live-brpk. (BioRender.com).

**Table 1**  
Society guidelines for the use of fecal microbiota transplant in the prevention and treatment of *Clostridioides difficile* infection

| Society (Year)                    | FMT for rCDI <sup>a</sup>                                                                                               | FMT for Severe or Complicated CDI                                                                                                                                                                                                                                                                                                         | Administration Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|-----------------------------------|-------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ASID (2016) <sup>18</sup>         | After the failure of less-invasive therapy (as alternative therapy)                                                     | After failure of the standard of care                                                                                                                                                                                                                                                                                                     | <i>Pre-FMT:</i><br>Give vancomycin or fidaxomicin for 3–5 d<br>Stop CDI antibiotics 1–2 d before FMT<br>Consider low-dose bowel prep<br><i>FMT delivery:</i><br>No optimal route defined<br>Avoid upper GI modality in elevated risk of aspiration<br>Avoid colonoscopy in severe disease or toxic megacolon                                                                                                                                                                                                                                                          |
| IDSA/SHEA (2021) <sup>14,15</sup> | After the failure of appropriate antibiotic therapy for at least 2 recurrences                                          | No further recommendations                                                                                                                                                                                                                                                                                                                | <i>Pre-FMT:</i><br>Consider induction vancomycin for 3–4 d if not on active CDI therapy<br><i>FMT delivery:</i><br>Optimal route based on individual preferences                                                                                                                                                                                                                                                                                                                                                                                                      |
| ESCMID (2021) <sup>16</sup>       | After second or greater recurrence of CDI following standard-of-care antibiotic treatment                               | Rescue therapy in severe-complicated CDI with clinical deterioration despite antibiotic therapy, especially in poor surgical candidates<br>Consider multiple FMTs                                                                                                                                                                         | No further recommendations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| ACG (2021) <sup>19</sup>          | After 2 or more CDI recurrences to prevent further episodes<br>After recurrence of CDI within 8 wk of prior FMT         | In severe or fulminant CDI refractory to antibiotic therapy, especially in poor surgical candidates                                                                                                                                                                                                                                       | <i>FMT delivery:</i><br>Colonoscopy or oral capsules preferred<br>Enema acceptable if all other routes unavailable<br>Avoid nasogastric administration in severe/fulminant CDI<br><i>Post-FMT:</i><br>Evaluate patients (1) within 1 wk and (2) 4–8 wk after FMT to assess for adverse events and recurrence<br>Repeat FMT if rCDI occurs after initial FMT<br>Colonoscopy preferred for subsequent FMT if initial FMT delivery by capsule or enema has failed                                                                                                        |
| BSG/HIS (2024) <sup>24</sup>      | After first recurrence of CDI<br>After 2 or more recurrences of CDI in all patients without severe food allergies       | Adjunct to antibiotics therapy in refractory CDI<br>Before a second CDI recurrence in cases of severe, fulminant, or complicated CDI not responding to antibiotic therapy                                                                                                                                                                 | <i>Pre-FMT:</i><br>Treat with CDI antibiotic therapy for minimum 10 d<br>Stop CDI antibiotics ≥1 d before FMT<br>Bowel preparation with polyethylene glycol<br>Avoid unnecessary antisecretory or antimotility agents<br><i>FMT delivery:</i><br>Frozen products preferred<br>Enema acceptable only if no alternative routes available<br>Avoid upper GI administration in elevated risk for regurgitation or swallowing disorders<br><i>Post-FMT:</i><br>Avoid non-CDI antibiotics for ≥8 wk<br>Monitor patients for ≥8 wk to assess FMT efficacy and adverse events |
| AGA (2024) <sup>17</sup>          | After second recurrence of CDI<br>Before the second recurrence in those at high risk of rCDI or a morbid CDI recurrence | Insufficient evidence to recommend FMT by oral capsule or enema<br>Consider FMT in hospitalized patients not responding to standard-of-care antibiotics (eg, 2–5 d after initiation of treatment)<br>Most patients with severe or fulminant CDI who receive FMT will need repeat FMT<br>After resolution of colitis, continue suppressive | <i>Pre-FMT:</i><br>Use suppressive antibiotics to bridge CDI treatment and FMT<br>Stop CDI antibiotics 1–3 d before FMT, if possible<br>Perform bowel preparation, if feasible and safe<br><i>FMT delivery:</i><br>No optimal route of administration defined<br>Lower GI endoscopic delivery of first dose is preferred in severe/fulminant CDI to                                                                                                                                                                                                                   |

| Society (Year) | FMT for rCDI <sup>a</sup> | FMT for Severe or Complicated CDI                                                   | Administration Considerations                                                                     |
|----------------|---------------------------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|
|                |                           | vancomycin therapy at discharge with final outpatient FMT to prevent CDI recurrence | confirm diagnosis and severity<br>Avoid nasogastric administration given risk of fecal aspiration |

*Abbreviations:* ACG, American College of Gastroenterology; ASID, Australasian Society for Infectious Diseases; BSG, British Society of Gastroenterology; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; HIS, Healthcare Infection Society; IDSA, Infectious Diseases Society of America; SHEA, Society for Healthcare Epidemiology of America.

<sup>a</sup> rCDI is the recurrence of diarrhea or other CDI symptoms within 8 wk of appropriate treatment of a prior episode of CDI.

**Table 2**  
Reported adverse events after fecal microbiota transplant

|                  |                                                                                                                                                                                                                                                                     |
|------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Gastrointestinal | <ul style="list-style-type: none"> <li>• Belching</li> <li>• Vomiting</li> <li>• Abdominal discomfort</li> <li>• Abdominal cramping</li> <li>• Diarrhea</li> <li>• Constipation</li> <li>• Flatulence</li> <li>• Inflammatory bowel disease exacerbation</li> </ul> |
| Systemic         | <ul style="list-style-type: none"> <li>• Transient fever</li> <li>• Malaise</li> <li>• Dizziness</li> <li>• Headache</li> <li>• Night sweats</li> </ul>                                                                                                             |
| Infectious       | <ul style="list-style-type: none"> <li>• Donor-derived infections<sup>a</sup></li> <li>• Colonization with multidrug-resistant organisms (MDROs)<sup>a</sup></li> </ul>                                                                                             |
| Autoimmune       | <ul style="list-style-type: none"> <li>• Development of autoimmune disease</li> </ul>                                                                                                                                                                               |
| Metabolic        | <ul style="list-style-type: none"> <li>• Weight gain</li> </ul>                                                                                                                                                                                                     |
| Procedural       | <ul style="list-style-type: none"> <li>• Endoscopic injury or bowel perforation</li> <li>• Aspiration of fecal contents<sup>a</sup></li> <li>• Complications of anesthesia<sup>a</sup></li> </ul>                                                                   |

<sup>a</sup>Reported cause of FMT-related fatalities.<sup>40,45</sup>

**Table 3**

Commercially available fecal microbiota products for the prevention of recurrent *Clostridioides difficile* infection after antibiotic therapy

| Product Name                                             | Product Administration                                                                                                                                                                                                                                                                                                                              |
|----------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Rebyota (Fecal microbiota, Live-jslm) <sup>70</sup>      | <i>Pretreatment:</i> None<br><i>Administration:</i> <ul style="list-style-type: none"> <li>• Administer 150 mL liquid suspension rectally</li> <li>• Remain in the left-side recumbent or knee-chest position for up to 15 min after administration</li> </ul>                                                                                      |
| Vowst (Fecal microbiota spores, Live-brpk) <sup>71</sup> | <i>Pretreatment:</i> <ul style="list-style-type: none"> <li>• Drink 296 mL (10 oz) of magnesium citrate solution ≥8 h before initiation of therapy</li> </ul> <i>Administration:</i> <ul style="list-style-type: none"> <li>• Take 4 capsules by mouth once daily for 3 consecutive days</li> <li>• Fast for ≥8 h before each daily dose</li> </ul> |

**Table 4**  
Efficacy data for US Food and Drug Administration-approved fecal microbiota products for recurrent *Clostridioides difficile* infection

| Product and Trial Design                                                                                                                                                                                                             | Inclusion Criteria                                                                                                                                                       | Demographics                                                                                                                                                                                                                              | Endpoint                                                                                                                                                                                       | Results                                                                                                                                                                                                                                                 | Adverse Events                                                                                                                                                                                                                                                |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Trial:</b><br>PUNCH CD3 (Khanna et al. <sup>72</sup> 2022)<br><b>Product:</b><br>Rebyota (Fecal microbiota, Live-Jslm)<br><b>Design:</b><br>Phase III randomized, double-blind, placebo-controlled trial with mITT analysis       | Age ≥18 y with<br>a. ≥1 recurrence of CDI and completion of ≥1 round of antibiotic therapy<br>b. ≥2 episodes of severe CDI resulting in hospitalization in the past year | <b>Median age:</b> 63.0 y<br><b>Race:</b> White (92.1%)<br><b>Sex:</b> Female (68.5%)<br><b>Diagnostics:</b><br>• PCR test (73.0%)<br>• Toxin A/B EIA (24.7%)<br>• GDH Ag (17.2%)<br><b>Anti-CDI antibiotic:</b><br>• Vancomycin (88.0%)  | <b>a. Treatment success:</b><br>Absence of CDI diarrhea within 8 wk of study treatment<br><b>b. Sustained response:</b><br>Treatment success at 8 wk, free of CDI recurrence at 6 mo follow-up | <b>a. mITT:</b><br>• Drug (70.4%)<br>• Placebo (58.1 %) <sup>a</sup><br><b>b. mITT:</b><br>• Drug (92.1%)<br>• Placebo (90.6%)                                                                                                                          | <b>AEs:</b><br>At 6 mo<br>• Drug (55.6%)<br>• Placebo (44.8%)<br><b>SAEs:</b><br>• Drug (3.9%)<br>• Placebo (2.3%)<br><b>Colectomy:</b> (n = 2)<br><b>Death:</b> (n = 2)<br><b>Common AEs:</b><br>• GI symptoms (≥5% of participants in all treatment groups) |
| <b>Trial:</b><br>PUNCH CD3-OLS (Feuerstadt et al., <sup>73</sup> 2024)<br><b>Product:</b><br>Rebyota (Fecal microbiota, Live-Jslm)<br><b>Design:</b><br>Phase III, open-label, single-arm with mITT analysis                         | Age ≥18 y with<br>a. ≥1 recurrence of CDI<br>b. ≥2 episodes of severe CDI resulting in hospitalization                                                                   | <b>Age:</b> ≥65 y (48.5%)<br><b>Race:</b> White (93.8%)<br><b>Sex:</b> Female (69.9%)<br><b>Diagnostics:</b><br>• PCR test (62.0%)<br>• Toxin A/B EIA (10.8%)<br>• GDH Ag (7.2%)<br><b>Anti-CDI antibiotic:</b><br>• Vancomycin (84.6%)   | <b>a. Treatment success:</b><br>Absence of CDI diarrhea within 8 wk of study treatment<br><b>b. Sustained response:</b><br>Treatment success at 8 wk, free of CDI recurrence at 6 mo follow-up | <b>a. mITT:</b><br>• Drug (73.8%)<br><b>b. mITT:</b><br>• Drug (91.0%)                                                                                                                                                                                  | <b>AEs:</b><br>• Drug (57.1%)<br><b>SAEs:</b><br>At ≤8 wk<br>• Drug (3.9%)<br>At >8 wk and <6 mo<br>• Drug (3.6%)<br><b>Colectomy:</b> (n = 0)<br><b>Death:</b> (n = 1)<br><b>Common AEs:</b><br>• GI symptoms (29.4% in ≤8 wk)                               |
| <b>Trial:</b><br>ECOSPOR III (Feuerstadt et al., <sup>74</sup> 2022)<br><b>Product:</b><br>Vowst (Fecal microbiota spores, Live-brpk)<br><b>Design:</b><br>Phase III randomized, double-blind, placebo-controlled with mITT analysis | Age ≥18 y with ≥3 episodes of CDI within 12 mo                                                                                                                           | <b>Mean age:</b> 65.5 y<br><b>Race:</b> White (93.0%)<br><b>Sex:</b> Female (59.9%)<br><b>Diagnostics:</b><br>• <i>C. difficile</i> toxin test (EIA or CCNA)<br><b>Anti-CDI antibiotic:</b><br>• Vancomycin (73.1%)                       | <b>a. Risk of CDI recurrence within 8 wk of treatment</b><br><b>b. Sustained clinical response:</b> No recurrence of CDI treated with antibiotics within 8 wk                                  | <b>a. mITT:</b><br>• Drug (12%)<br>• Placebo (40%) <sup>a</sup><br><b>b. mITT:</b><br>• Drug (88%)<br>• Placebo (60%)                                                                                                                                   | <b>AEs:</b><br>At 8 wk<br>• Drug (93%)<br>• Placebo (91%)<br><b>SAEs:</b><br>At 8 wk<br>• Drug (8%)<br>• Placebo (16%)<br><b>Colectomy:</b> NR<br><b>Death:</b> (n = 3)<br><b>Common AEs:</b><br>• GI symptoms                                                |
| <b>Trial:</b><br>ECOSPOR IV (Sims et al., <sup>75</sup> 2023)<br><b>Product:</b><br>Vowst (Fecal microbiota spores, Live-brpk)<br><b>Design:</b><br>Phase III, open-label, single-arm with mITT analysis                             | Age ≥18 y with<br>a. Treatment failure (any arm) from ECOSPOR III (CDI recurrence within 8 wk), rollover subjects<br>b. ≥1 recurrence of CDI, de novo subjects           | <b>Mean age:</b> 64.0 y<br><b>Race:</b> White (92.4%)<br><b>Sex:</b> Female (68.4%)<br><b>Diagnostics:</b><br>• <i>C. difficile</i> toxin test (EIA or CCNA)<br>• PCR only (26.4%)<br><b>Anti-CDI antibiotic:</b><br>• Vancomycin (72.6%) | <b>a. Treatment failure:</b> CDI recurrence within 8 wk of treatment                                                                                                                           | <b>ITT:</b><br>• Drug (8.7%)<br>• Rollover cohort (13.8%)<br>• De novo cohort (8.1%)<br><b>Recurrence at 8 wk:</b><br>• Confirmed (n = 16)<br>• Imputed (ie, LTFU) (n = 7)<br><b>Recurrence at 24 wk:</b><br>• Confirmed (n = 22)<br>• Imputed (n = 14) | <b>AEs:</b><br>Drug (53.6%)<br><b>SAEs:</b><br>Drug (12.5%)<br><b>Colectomy:</b> NR<br><b>Death:</b> (n = 8)<br><b>Common AEs:</b><br>• GI symptoms<br>• Fatigue<br>• UTI                                                                                     |

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*Abbreviations:* AE, adverse event; Ag, antigen; CCNA, cell cytotoxicity neutralization assay; EIA, enzyme immunoassay; GDH, glutamate dehydrogenase; ITT, intention-to-treat; LTFU, lost to follow-up; mITT, modified intention-to-treat (analysis); NR, not reported; PCR, polymerase chain reaction; SAE, serious adverse event; UTI, urinary tract infection.

<sup>a</sup>Exceeded threshold for demonstrating drug superiority over placebo.

**Table 5**

Fecal microbiota products and live biotherapeutic products in development for prevention of recurrent *Clostridioides difficile* infection

| Product                                                   | Type of Product                                                                                     | Route of Administration                                                                                                                                    | Phase of Development                                                       | Published Data                                                                                                                                                                                  |
|-----------------------------------------------------------|-----------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| VE303<br>Louie et al, <sup>76</sup><br>2023               | <i>LBP</i> : Oral capsules containing 8 strains of commensal <i>Clostridia</i> bacteria             | High dose: 10 capsules po daily × 14 d<br>Low dose: 2 capsules po daily × 14 d                                                                             | Phase II randomized, double-blind, placebo-controlled, dose-ranging trial  | <i>Recurrence of CDI</i> :<br>rCDI diagnosed by toxin assay:<br>Adjusted ARR = 11<br>• High dose vs placebo<br><i>rCDI diagnosed by PCR</i> :<br>Adjusted ARR = 21.1*<br>• High dose vs placebo |
| MET-2<br>Kao et al, <sup>77</sup><br>2021                 | <i>FMP</i> : Lyophilized, oral capsules containing 40 bacterial species isolated from healthy stool | 10 capsules po daily × 1 d, then 3 capsules po daily × 8 d<br>Nonresponders undergo dose escalation                                                        | Phase I open-label, single-group trial                                     | <i>Recurrence-free at 40 d</i> :<br>79% (one course of therapy)                                                                                                                                 |
| VP20621 (NTCD-M3)<br>Gerding et al, <sup>78</sup><br>2015 | <i>FMP</i> : Oral liquid suspension containing non-toxigenic <i>C. difficile</i> spores (M3 strain) | High dose: 10 <sup>7</sup> spores po daily × 14 d<br>Medium dose: 10 <sup>7</sup> spores po daily × 7 d<br>Low dose: 10 <sup>4</sup> spores po daily × 7 d | Phase II, randomized, double-blind, placebo-controlled, dose-ranging trial | <i>Recurrence at 6 wk</i> :<br>OR = 0.28**<br>• Drug (11%)<br>• Placebo (30%)                                                                                                                   |

Statistical significance:

\*  $P < .05$ ,

\*\*  $P < .01$ .

Abbreviations: ARR, absolute risk reduction; OR, odds ratio; po, orally.

**Table 6**

Patient factors influencing choice of fecal microbiota transplant or use of fecal microbiota products for *Clostridioides difficile* infection

|                      | Patient Factors                                                   | FMT | FMPs | Comments                                                                                                                                                                                                                                                                                                             |
|----------------------|-------------------------------------------------------------------|-----|------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Indication</i>    | Recurrent CDI (rCDI)                                              | ✓   | ✓    |                                                                                                                                                                                                                                                                                                                      |
|                      | Initial CDI episode, at high risk of morbid recurrence            | ✓   | ×    | Vowst and Rebyota are currently approved only for adults with rCDI                                                                                                                                                                                                                                                   |
|                      | Severe/fu I minant CDI refractory to standard-of-care antibiotics | ✓   | ×    | Vowst and Rebyota are not currently indicated for treatment of CDI                                                                                                                                                                                                                                                   |
| <i>Age</i>           | Adults                                                            | ✓   | ✓    |                                                                                                                                                                                                                                                                                                                      |
|                      | Pediatric (age <18 y)                                             | ✓   | ×    | Vowst and Rebyota are currently approved only for use in adults                                                                                                                                                                                                                                                      |
|                      | Geriatric (age ≥65 y)                                             |     |      | Insufficient data to determine differences in FMP treatment response based on age. About half of adults receiving Vowst or Rebyota in clinical trials were 65 y of age or older                                                                                                                                      |
| <i>Comorbidities</i> | Pregnancy                                                         | ?   | ?    | Limited data regarding use of FMT or FMPs during pregnancy or lactation. Rebyota is rectally administered and not expected to be systemically absorbed                                                                                                                                                               |
|                      | Severe food allergies (anaphylaxis)                               | ×   | ?    | Avoid use of FMT; use FMPs with caution. Do not administer FMPs in cases of severe allergy to any components                                                                                                                                                                                                         |
|                      | Immunocompromise                                                  | ?   | ×    | FMT is generally avoided in severe immunocompromise and used with caution in mild to moderate immunocompromise. Limited data regarding use of FMPs in immunocompromised patients                                                                                                                                     |
|                      | Dysphagia or elevated aspiration risk                             | ?   | ?    | Use with caution in patients at risk of aspiration or regurgitation; avoid upper GI instillations if possible                                                                                                                                                                                                        |
|                      | Frequent antibiotic use                                           | ?   | ?    | Concurrent antibiotic use, particularly with drugs with anaerobic activity, may reduce efficacy of FMT or FMPs. Patients with long-term or frequent antibiotic use (eg, recurrent UTIs) may benefit from careful planning of administration timing after antibiotics with careful monitoring for recurrent infection |

✓, use recommended; ?, use with caution; ×, avoid use.