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REVIEW

What's New and What's Next in Fecal Microbiota Transplantation?

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Abstract: Fecal microbiota transplantation (FMT) has evolved from a niche therapy to a cornerstone in the treatment of recurrent *Clostridioides difficile* infection (rCDI). Initially introduced in the 1950s, its relevance has surged with the emergence of virulent and antibiotic-resistant *C. difficile* strains. In recent years, the FDA approved two standardized microbiota-based therapeutics—Rebyota™ (fecal microbiota, live-jslm) and Vowst™ (fecal microbiota spores, live-brpk)—for rCDI prevention. Multiple pivotal trials support the efficacy and safety of both traditional FMT and the FDA-approved prescription FMTs, with sustained response rates surpassing 80% in select populations. In parallel, live biotherapeutic products (LBPs)-donor independent, well-defined microbial consortia produced in laboratory setting are under development. Examples include VE303 and NTCD-M3, a single non-toxigenic C. difficile strain (M3). Beyond the FDA approved therapeutics, conventional FMT is gaining traction as a potential treatment for severe or fulminant CDI, especially in patients not responding to antibiotics and ineligible for surgery. Investigational indications include decolonizing multi-drug-resistant organisms and treatment of noninfectious conditions such as inflammatory bowel disease, irritable bowel syndrome, liver disease, and metabolic syndrome. Given the differing pathophysiology of these conditions, a tailored approach supported by rigorous clinical trials is essential. Although there is a growing shift, particularly in the United States, toward the use of FDA-approved FMTs, global practices remain heterogeneous, with conventional FMT still widely employed. Meanwhile, regulatory pathways and clinical guidelines for microbiota-derived biologics and live biotherapeutic products continue to evolve. In this manuscript, we provide an update on the emerging use of FDA-approved prescription microbiota-derived therapeutics for the prevention of rCDI, review data on investigational agents including both donor dependent and donor independent microbial products, and summarize current evidence on the use of conventional FMT for indications beyond prevention of rCDI.

Keywords: fecal microbiota transplant, *Clostridioides difficile* infection, live biotherapeutic products, irritable bowel syndrome, inflammatory bowel disease, metabolic syndrome

Introduction

Clostridioides difficile infection (CDI) affects an estimated 43.5 individuals per 100,000 globally, with the highest burden in North America (66/100,000), and a recurrence rate of up to 60% following multiple episodes.[1] CDI carries a substantial mortality risk, with a pooled 30-day mortality rate of 8.3%, and rates exceeding 16% over longer follow-up periods, underscoring its severity as a healthcare-associated infection.[1]

The critical role of gut microbiota in mediating colonization resistance against potential pathogens was recognized shortly after the introduction of potent antibiotics into clinical practice. As early as 1950s, human stool was introduced as a restorative therapy to repair the gut microbiome in patients suffering from pseudomembranous colitis.[2] This treatment, known as "fecal bacteriotherapy" initially remained a fringe therapy for decades, as antibiotics were generally effective in managing CDI. However, the emergence of increasingly virulent strains – most notably the fluoroquinolone-resistant ribotype 027 identified in Quebec in the early 2000s, marked a turning point. These strains, including those with partial deletion of the tcdC regulatory gene, which normally downregulates toxin production,[3] were associated with higher

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morbidity and mortality. For example, a randomized control trial comparing fidaxomicin with vancomycin, rates of recurrence in patients infected with ribotype 027 were significantly higher than those with non-027 strains (27.4% vs 16.6%, p=0.002).[4] Rates of rCDI began to rise approaching 20–30% after a first episode and up to 60% after two or more episodes.[5]

Over the past decade, the need for restorative options has led to the rapid evolution of crude methods using whole stool from individual donors to standardized, ready-to-use formulations of healthy donor fecal microbiota.[6] A notable player in this field was OpenBiome, a Boston-based non-profit organization that has established itself as a leading "stool bank" and provider of fecal microbiota products throughout the United States. In the absence of approved alternatives, the Food and Drug Administration (FDA) permitted these activities under its policy of enforcement discretion. The situation changed following the approval of the first commercial fecal microbiota transplant (FMT)-based product, fecal microbiota live-jslm (Rebyota™, Ferring Pharmaceuticals), indicated for the *prevention* of *C. difficile* infection recurrence. The new FDA guidance requires "stool banks" to operate under investigational new drug application (IND) toward product commercialization, although individual providers and hospitals are still permitted to locally prepare fecal microbiota for treatment of their own patients.

The clinical success of FMT in treating *C. difficile* infections (CDI) has triggered intense interest in developing new therapeutics targeting the gut microbiome. Besides the donor dependent traditional or conventional FMTs and the FDA approved, prescription FMTs, donor-independent products are under way, classified as "live biotherapeutic products" or LBPs are strictly produced in the laboratory setting. Both types of FMTs and the LBPs are regulated as drugs by the FDA. In this evolving landscape, many commercial efforts are focused on laboratory-produced microbial consortia that avoid the variability and logistical challenges of donor-derived products.

Beyond CDI, interest has grown in exploring FMT for conditions linked to microbiota dysbiosis, including decolonization of multidrug-resistant organisms and management of noninfectious diseases such as inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), liver disease, and metabolic syndrome. These conditions differ markedly in pathogenesis and likely involve the gut microbiota as a disease modifier rather than a primary cause, highlighting the need for tailored strategies and rigorous clinical investigation.

In this manuscript, we provide an update on the current state of therapeutic development, focusing on FDA-approved prescription microbiota-based therapies for rCDI, ongoing investigation into donor-dependent and donor-independent products, and evidence supporting the broader use of FMT.

FDA-Approved Prescription Microbiota-Based Therapeutics for Prevention of Recurrent Clostridioides difficile Infection

Risk factors such as antibiotic use, advanced age and inflammatory bowel disease (IBD) alter the colonic microbiota leading to increased susceptibility to CDI.[7] Antibiotics, used as first-line treatment, paradoxically worsen the dysbiosis. With each treatment of a CDI occurrence, the microbial diversity decreases, hence, patients become increasingly vulnerable to further CDI recurrence.[8] Fecal microbiota transplantation (FMT) was shown to decrease the recurrence of CDI through various mechanisms opening an avenue for microbiome restoration-based therapies.[8] The FDA recently approved two such therapies: fecal microbiota live-jslm and the fecal microbiota spores live-brpk.

Fecal Microbiota Live-JSLM (Rebyota)

Fecal microbiota, live-jslm (Rebyota™ [RBL]); formerly known as RBX2660, a standardized, donor stool–derived, fecal microbiota-product, was approved on November 30th, 2022,[9] for prevention of recurrent CDI (rCDI), defined as a positive stool test in the setting of symptom recurrence within eight weeks of prior successful treatment with symptom resolution.[9] The product is a single-dose regimen consisting of human stool suspended in 150 cc of 0.9% saline/polyethylene glycol administered rectally. One enema contains between 1×10^8 and 5×10^{10} colony forming units (CFU)/cc of diverse fecal microorganisms with high percentage of Bacteroides (> 1×10^5 CFU/cc).[10] RBL is shipped from the manufacturer frozen and must be thawed prior to administration in either the outpatient or inpatient setting. Post-treatment, avoidance of any unnecessary antibiotics for at least 8 weeks is recommended.[11]

Multiple clinical trials have studied the efficacy of RBL and demonstrated its efficacy in preventing rCDI. Three Phase 2 trials (PUNCH CD,[12] PUNCH CD2[13] and PUNCH CD-OLS[14]) and two Phase 3 trials (PUNCH CD3[15] and PUNCH CD3-OLS[16]) were conducted. Details of these are shown in Table 1. In brief, these trials included patients with >1 rCDI (3 or more occurrences) or >2 severe CDI episodes requiring hospitalization. The last phase 3 trial included a more diverse population with more complex medical disorders (eg IBD, IBS, mild-to-moderate immunocompromised). Overall, these trials have shown that RBL is well tolerated with mild-to-moderate treatment-emergent adverse events (TEAE), primarily gastrointestinal (GI) related including diarrhea, flatulence, abdominal pain and constipation. No serious AE were observed. RBL success rate, defined as lack of recurrence of CDI at 8 weeks, was ~70%, with sustained clinical response, in those who achieved an initial cure, of ~90% at 6 months.[12,13,15,16] Stool studies of responders exhibited increased diversity that was sustained at 24-months.[14] RBL is indicated for the prevention of rCDI in patients 18 years of age and older following completion of treatment with anti-CDI antibiotics (vancomycin or fidaxomicin). Although, the phase 3 open-label trial has demonstrated safety of RBL in patients with more complicated medical history, safety of its use should be discussed case by case, similar to considerations in conventional FMT.

Fecal Microbiota Spores, Live-BRPK

Fecal microbiota spores, live-brpk, also known as SER-109 or VOWST™ (VOS), was the second fecal microbiota product approved by the FDA on April 26th, 2023.[17] It consists of a standardized preparation of donor stool-derived *Firmicutes* spores administered orally. It is approved for the prevention of rCDI in individuals 18 years of age or older after receiving standard of care anti-CDI therapy.[17] The product consists of oral capsules containing *Firmicutes* spores (1×10^6 to 3×10^7 CFU) in 92% of glycerol saline and it is prescribed as 4 capsules daily for 3 days. The product does not need refrigeration. Bowel preparation in the form of either magnesium citrate or polyethylene glycol (in patients with impaired kidney function) is given prior to VOW dosing to flush out any residual antibiotics and improve engraftment.[18] Each administered dose is derived from a single, screened donor; stools are purified using ethanol solvent, which kills vegetative bacterial forms and other microorganisms, and then refined further through filtration and centrifugation.[19]

Multiple clinical trials were conducted to assess the efficacy of VOS in preventing the rCDI. One phase 2 clinical trial (ECOSPOR[20]) and two phase 3 clinical trials (ECOSPOR III[21] and ECOSPOR IV[22]) were completed. Details of these trials are shown in Table 2. ECOSPOR III was a randomized, double-blind, placebo-controlled trial that included patients with ≥3 episodes of CDI within the previous 12 months. Only patients who tested positive with enzyme-linked immunoassay or cell culture were included to avoid enrollment of colonized patients. The primary endpoint was lack of recurrence of CDI at 8 weeks following administration of VOS versus placebo. Recurrence rate was significantly lower in the treatment group (12%) compared to placebo (40%) (RR 0.32, 95% CI 0.18–0.58). Subgroup analyses age by (<65 vs >65 years) and previous initial antibiotic treatments (vancomycin vs fidaxomicin) showed superiority of VOS in all groups. The treatment was well tolerated; most AEs were mild to moderate and GI related. Engraftment, defined as the number of VOS species detected in post-treatment stools that were not present at baseline, was observed as early as 1 week and persisted by week 8. Increase in secondary bile acids, shown to decrease the recurrence of CDI in other studies, was also found in the VOS group post-treatment at week 1 and week 8.[20,21,23,24] The American Gastroenterological Association (AGA) recommends considering VOS in patients after the second recurrence of CDI or in select patients at high risk of CDI recurrence.[25] Notably patients with active IBD, IBS or severe immunodeficiency were excluded from these studies, therefore safety of VOW in these populations cannot be determined.

Future Microbiome Therapeutics for Clostridioides Difficile Infection

Safety concerns and desire for scalability drove efforts to develop live biotherapeutic products (LBPs) as a safer and more reliable option than FMT. In the following section, we will focus on emerging formulations including donor-derived and donor-independent products.

Donor Derived, Full-Spectrum Microbiota

The aim of this therapeutic option, like FMT, is to restore a healthy and balanced gut microbiota composition. A comprehensive collection of bacteria (both known and unknown) is introduced by administering screened stools

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Table 1 Description of Different Clinical Trials of Fecal Microbiota Live-Jslm

	PUNCH CD	PUNCH CD2	PUNCH CD-OLS	PUNCH CD3	PUNCH CD3-OLS
Design	Prospective OL	Prospective, randomized, double-blind, placebo controlled, three-arm trial	Prospective OL	Randomized, double-blind, placebo controlled	Prospective OL
Study population	I: >2 rCDI or >2 severe CDI episodes requiring hospitalizations E: Refractory CDI, antibiotic use for another condition, vancomycin sensitivity, hx of FMT, IBD, IBS, Chronic diarrhea, Celiac disease, cirrhosis, colostomy, intra-abdominal surgery within 60 days, severe colitis, motility disorders, planned surgery, immunocompromised, breastfeeding	I: >2 rCDI or >2 severe CDI episodes requiring hospitalizations E: Refractory CDI, hx of FMT, IBD, IBS, chronic diarrhea, celiac disease, colostomy, life threatening colitis, planned surgery, severe immunosuppression or other active infections	I: >2 rCDI or >2 severe CDI episodes requiring hospitalizations E: Continued diarrhea, planned surgery requiring antibiotics, immunosuppression, IBD or pregnancy	I: >1 rCDI or >2 severe CDI episodes requiring hospitalizations E: refractory CDI, IBD, IBS, Chronic diarrhea, celiac, colostomy, colitis, continued diarrhea, antibiotic use for another condition or previous FMT	I: >1 rCDI or >2 severe CDI episodes requiring hospitalizations including those with complex medical history E: refractory CDI, antibiotic use for another condition, previous FMT within 6 months, hx of AE related to FMT, Bezlotoxumab within 1 year, CD4<200, ANC< 1000, pregnant or breastfeeding
Dosing protocol	Rebyota dose given 24 to 48 hours after the last dose of antibiotics. Patients with recurrence within 8 weeks were eligible for another dose	Three groups: 1) Two doses Rebyota 2) Two doses placebo 3) Dose of Rebyota followed by one dose of placebo (Second dose 7 ± 2 days after the first dose)	Two doses of the product were given, 7 days apart	One dose of Rebyota or placebo was given	One dose of Rebyota. Patients with recurrence within 8 weeks were eligible for another dose
Total participants	40	150	162	320	793[a]
Follow up period (Months)	6	24	24	6	6
Primary endpoint	TEAE	Absence of CDI related diarrhea at 8 weeks post-treatment	Lack of recurrence of CDI at 8 weeks	Lack of recurrence of CDI at 8 weeks	Safety and tolerability of Rebyota
Secondary endpoint	Absence of CDI related diarrhea at 8 weeks post-treatment	TEAE	TEAE and microbiome analysis of treated patients	Sustained clinical response at 6 months and TEAE	Lack of recurrence of CDI at 8 weeks Sustained clinical response at 6 months
Results (Primary)	Well-tolerated. AE mostly within the first two weeks (GI-related)	- ITT: No statistical difference between the groups. - mITT[b]: No statistical difference between the groups. - Final PP[c]: Group 3 statically significant (p=0.017) vs group 2.	- 8 weeks success rate: 78.9% (treatment group) vs 30.7% (historical control group) - 24 months: sustained response (91%)	- Rebyota success rate: 70.6% - Placebo success rate: 57.5% - Bayesian analysis confirmed superiority (posterior probability: 0.991)	- 47.3% with TEAEs (Mild to moderate GI-related) - 3.9% with serious TEAEs
Results (Secondary)	- First dose success (51.8%; 16/31) - Second dose success (78.6%; 11/14) Combined efficacy (87.1%)	- Safety profile was similar to placebo. TEAE in 82% of all participants. - Most TEAEs were mild to moderate (GI-related).	- 83% reported mild to moderate AEs, with 21% directly attributed to Rebyota. Most AEs were GI-related. - Improved diversity and composition in responders	- Sustained clinical response at 6 months: 90% - AEs were mild to moderate, primarily GI-related, occurring within 2 weeks of administration	- Rebyota success at 8 weeks: 73.8% - Sustained clinical response at 6 months: 91.0%

Notes: [a]submitted 07-12-2024. [b]Participants who received treatment, excluding participants who discontinued prior to outcome evaluation or had eligibility deviations. [c]All randomized participants who successfully received both treatment doses and were evaluable for outcome, excluding participants for predefined reasons.

Abbreviations: OL, open label; I, Inclusion; E, Exclusion; rCDI, recurrent clostridium *difficile* infection; FMT, fecal microbiota transplantation; IBD, inflammatory bowel disease; IBS, inflammatory bowel syndrome; AE, Adverse events; ANC, absolute neutrophil count; GI, gastrointestinal; TEAE, treatment-emergent adverse events; ITT, Intention-to-treat; PP, Per Protocol analysis.

Table 2 Description of Different Clinical Trials of Fecal Microbiota Spore, Live-BRBK

	ECOSPOR	ECOSPOR III	ECOSPOR IV
Design	Prospective, randomized, double-blind, placebo controlled	Prospective, randomized, double-blind, placebo controlled	Prospective, OL, single-arm trial
Study population	I: ≥ 3 episodes of CDI within the previous 9 months E: Pregnant, breastfeeding, toxic megacolon, small bowel ileus, IBS with diarrhea within 12 months, major GI surgery within 3 months, IBD, admitted to acute care facility or ICU, active malignancy with intensive induction chemotherapy, radiotherapy or a biologic	I: ≥ 3 episodes of CDI within the previous 12 months E: Pregnant, breastfeeding, toxic megacolon, small bowel ileus, ANC <500, Major GI surgery within 3 months, hx of total colectomy or bariatric surgery, hx of active IBD with diarrhea, hx of FMT within 3 months, active malignancy with intensive induction chemotherapy, radiotherapy or a biologic	Two Cohorts: Cohort 1: Rollover patients from ECOSPOR III who had a CDI recurrence diagnosed by toxin EIA within 8 weeks after receiving VOS or placebo Cohort 2: De novo patients with ≥ 2 episodes of CDI E: Pregnant, breastfeeding, toxic megacolon, small bowel ileus, ANC <500, Major GI surgery within 3 months, ICU, hx of total colectomy or bariatric surgery, hx of active IBD with diarrhea, hx of FMT within 3 months, active malignancy with intensive induction chemotherapy, radiotherapy or a biologic
Dosing protocol	Two groups: - VOC (4 capsules as a single dose for 3 days) - Placebo	Two groups: - VOC (4 capsules as a single dose for 3 days) - Placebo	VOC (4 capsules as a single dose for 3 days)
Total participants	89	182	263
Follow up period (Months)	6	6	6
Primary endpoint	Lack of recurrence of CDI at 8 weeks	Lack of recurrence of CDI at 8 weeks	TEAEs up to 24 weeks
Secondary endpoint	Treatment-related AE, VOS engraftment with clinical outcomes and secondary bile acids	Treatment-related AE, VOS engraftment, secondary bile acids	CDI recurrence
Results (Primary)	Recurrence within 8 weeks: VOS (44%) vs Placebo (53%) (95% CI, 0.8–1.9). Subgroup analysis: - <65 yo: no difference - >65 yo: VOS (45%) vs Placebo (80%) (95% CI, 1.1–2.8)	Recurrence within 8 weeks: VOS (12%) vs Placebo (40%) (RR 0.32; 95% CI, 0.18–0.58) Subgroup analysis: - <65 yo: VOS (7%) vs Placebo (31%) (RR 0.24; 95% CI, 0.07–0.78) - >65yo: VOS (17%) vs Placebo (46%) (RR 0.36; 95% CI, 0.18–0.72) - Sustained clinical response (8 weeks): VOS (88%) vs Placebo (60%) - Vancomycin as CDI Rx: VOS (16%) vs Placebo (28%) - Fidaxomicin as CDI Rx: VOS (4%) vs Placebo (46%)	VOS was well tolerated. 53.6% of patients experienced TEAEs (mild to moderate and resolved without sequelae), mostly GI related. No AE led to study withdrawal. Invasive infections in 6.5% of patients. Serious AE (12.5% of patients) and fatal outcome (3% of patients): None of these events were deemed by the investigators to be related to VOS)
Results (Secondary)	- Well tolerated; AE mainly mild to moderate (GI related) - Improved engraftment at weeks 1, 4 and 8 ($p<0.001$). Greater engraftment at week 1 associated with better clinical outcomes (non-recurrence of CDI) ($p<0.05$) - At week 1, increased VOS species correlated with increased secondary BAs ($p<0.0001$), however, increase in these secondary BAs did not correlate significantly with rCDI in the treatment group	- Well tolerated; AE mainly mild to moderate (GI related) - Engraftment of VOS dose species was seen by week 1 and persisted through week 8 (higher among VOS recipients). - Greater secondary BAs from baseline observed in the VOS group than in the placebo group through week 8	- Recurrence within 8 weeks: All subjects: 9% Cohort 1: 14% Cohort 2: 8% - Recurrence within 24 weeks: All subjects: 13.7% - Sustained clinical response rates at weeks 8 and 24 were 91.3% (95% CI, 87.2–94.4%) and 86.3% (95% CI, 81.6–90.2%), respectively

Abbreviations: OL, open label; CDI, Clostridium *Difficile* infection; AE, adverse events; TEAEs, Treatment-emergent adverse events; GI, gastrointestinal; BAs, bile acids; rCDI, recurrent Clostridium *Difficile* infection; CI, confidence interval.

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from healthy donors. However, this strategy comes with challenges including being donor-depending, standardizing the manufacturing process, refining dosing strategies, and resolving safety issues.[26]

RBX7455

RBX7455, manufactured by Rebiotix and derived from RBL, is a standardized, lyophilized, non-frozen, orally administered biologic drug.[27] This product was tested on patients with at least 1 recurrence of CDI who had completed at least two rounds of antibiotics. The safety and efficacy of the product was evaluated in a Phase 1, open label, single arm, dose-ranging study. Thirty patients were assigned to 3 treatment groups: Group 1 received 4 capsules twice daily for 4 days, group 2 received 4 capsules twice daily for 2 days, and group 3 received 2 capsules twice daily for 2 days.[27] The primary outcome was lack of recurrence of CDI at 8 weeks. In addition, safety profile was assessed, and fecal microbiome profile of the patients were studied prior to and up to 6 months following therapy. Eight weeks success rate was 100% for group 3, 90% for group 1 and 80% for group 2. No significant treatment emergent adverse events (TEAE) were noted.[27] An increase in Bacteroidetes and Clostridia class was shown which correlates with increased resistance to C. *difficile* colonization.[28] More trials are needed to evaluate this therapeutic option.

CP101

CP101 (Finch Therapeutics) is an oral, lyophilized LBP drug.[29] It consists of a single administration of 10 capsules without any bowel preparation. This product was tested on patients with rCDI (3 or more episodes of CDI with 2 episodes within 12 months or 1 CDI recurrence in patients >65 years old) after completing the standard CDI treatment. The safety and efficacy of the product was evaluated in a multicenter, double-blind, parallel-arm, placebo-controlled, Phase 2 clinical trial (PRISM-3) and phase 2 open-lab trial. The trials showed positive results in decreasing recurrence rates of CDI.[29] However, in January 2023, PRISM4 (phase 3 trial) was discontinued for financial reasons.

LBP with Well-Defined Composition (Donor Independent)

In contrast to full-spectrum microbiota, defined biotherapeutic interventions are based on specific bacterial strains that have shown to combat C. *difficile* activity and effectively colonize the gut. They are manufactured from clonal cell banks which serve as a repository of well-characterized bacterial strains derived from a healthy human stool-derived microbiome library,[30] ensuring consistency, reproducibility, and independence from ongoing stool donations.

VE303

VE303 (Vedanta Biosciences) is an encapsulated oral formulation composed of 8 Clostridia strains that are non-pathogenic and non-toxigenic.[31] It does not require any bowel preparation prior to administration. This drug was tested in adult patients with rCDI or with primary CDI at high risk of recurrence (defined as 75 year or older or 65 years or older with at least 1 risk factor for recurrence [creatinine clearance <60 mL/min/1.73 m^2 at the time of the current CDI episode, regular use of a proton pump inhibitor within the past 2 months, or a history of CDI >6 months previously]).[32] A phase 2, randomized, double-blind, placebo-controlled, dose-ranging study was conducted to assess safety and efficacy of the product. Seventy-nine participants were randomized into three groups: high-dose VE303 (8.0×10^9 colony-forming units [CFU], 10 capsules), low-dose VE303 (1.6×10^9 CFU, 2 capsules), or placebo orally once daily for 14 days. The primary outcome was lack of recurrence of CDI at 8 weeks. In addition, CDI recurrence at 24 weeks, safety, and changes in fecal microbiome composition were assessed. High dose VE303 was associated with significantly lower CDI recurrence rates (12.8%) compared to placebo (36.4%) or low dose VE303 (33.3%). Based on clinical efficacy analyses that included those who received treatment for recurrent CDI without confirmatory tests, high-dose VE303 demonstrated significantly lower recurrent rates (13.8%) compared to placebo (45.5%) or low-dose VE303 (37%). Results were sustained through 24 weeks with a single patient in the high-dose group having CDI recurrence. VE303 was well tolerated with mild-to-moderate TEAE (mostly GI related). Colonization of VE303 strains was higher in the treatment group and correlated with dosing. Higher colonization rates were associated with a lower probability of CDI recurrence. A phase 3 trial is currently under way and is expected to be completed by October 2027.

NTCD-M3

Nontoxigenic strain C. *difficile*-M3 (NTCD-M3 or VP20621, Destiny Pharma), is an oral suspension that contains C. *difficile* strains that lack toxin coding genes. Historically, patients with *C. difficile* colonization were associated with decreased risk of C. *difficile*- associated diarrhea.[33] Hence, NTCD-D3 was developed to temporarily colonize the human gut without causing any symptoms and prevent proliferation of toxigenic strains of C. *difficile* after antibiotic treatment. A phase 2b, randomized, double-blind, placebo controlled clinical trial was conducted to evaluate the safety and efficacy of this therapy.[34] One hundred seventy-three adult patients with first episode of CDI or first recurrence were enrolled. Participants were assigned to 4 groups: NTCD-M3 10^4 spores/d for 7 days; NTCD-M3 10^7 spores/d for 7 days; NTCD-M3 10^7 spores/d for 14 days; or placebo. The primary outcome was safety and tolerability. The secondary outcome was lack of recurrence of CDI at 6 weeks post-treatment. TEAE was reported in 78% of patients taking the therapy, predominantly GI symptoms and headaches. Overall, the drug was well tolerated compared to placebo. The rate of recurrence with patients taking NTCD-M3 at 10^7 spores/d for 7 days dose was significantly lower (5%) than patients who received placebo (30%) (p=0.01). In patients who received NTCD-M3, CDI recurrence was significantly lower in patients who were colonized (2%) vs patients who were not (31%) (OR, 0.01; 95% CI, 0.00–0.05; $P < .001$). A Phase 3 clinical trial is being planned to further assess the efficacy of this therapy.

MET-2

Microbial Ecosystem Therapeutic 2 (MET-2; NuBiyota), is a lyophilized and encapsulated oral formulation of 40 bacterial strains. These strains were initially isolated from the stool of healthy donors then manufactured independently of donor donation.[35] A phase 1, open-label, single-group, feasibility study was conducted in Alberta, Canada. Nineteen participants with non-severe rCDI in the previous 12 months were enrolled. They received ten capsules orally for 2 days then three capsules for 8 days. If *C. difficile* recurred, patients were re-treated with 20 capsules for 2 days then three capsules for 8 days. The primary outcome was lack of CDI recurrence at day 40 after receiving at least one course of MET-2. Secondary outcomes were mortality and hospitalizations. The results were overall positive; 79% of patients avoided CDI recurrence after the initial treatment and 95% of patients after retreatment at 40 days. However, the company decided to halt the development of MET-2 given the competitive space (*personal communication, Dina Kao*).

ADS024

ADS024 (Adiso Therapeutics) is a lyophilized, encapsulated, single-strain oral LBP consisting of *Bacillus velezensis*. This bacterium was discovered using a culture-based screen of aerobic spore-formers that inhibit *C. difficile. Bacillus velezensis* was shown to kill *C. difficile* directly in vitro by inhibiting translation of proteins and permeabilization of the *Bacillus* cell membrane and by production of proteases that degrade toxins A and B.[36] Another study showed that *Bacillus velezensis* inhibited toxin B-mediated apoptosis in human colonic epithelial cells and colonic explants.[37] A phase 1 clinical trial (NCT04891965) of ADS024 is under way to investigate its role in preventing the recurrence of CDI.

Emerging Infectious Indications for FMT

Severe and Fulminant Clostridioides difficile Infection

The phenotype of severe and fulminant CDI (SFCDI) is characteristically different from recurrent CDI, in that it is often refractory to antibiotic therapy with high morbidity and mortality. The Infectious Diseases Society of America defines severe CDI as leukocytosis with a white blood cell count of >15,000 cells/mL or a serum creatinine level >1.5 mg/dl with fulminant is a CDI contributing to hypotension or shock.[38] These patients must be closely monitored as they can deteriorate rapidly. If severe or fulminant CDI becomes resistant to maximum standard antibiotic therapy, either surgical intervention or FMT should be considered.[8] Post-operative mortality rate remains high regardless of surgical technique, ranging from 17% to 30%.[39] Furthermore, many patients with severe or fulminant CDI are not considered to be surgical candidates.

FMT as a treatment for SFCDI refractory to standard antibiotics theoretically promises certain advantages to surgical treatment in addressing the "too early or too late" dilemma. Performing a colectomy too early unnecessarily exposes patients to high risks of postoperative mortality, whereas delaying surgery until the patient's condition deteriorates may render them unsuitable for surgery, potentially resulting in death from the SFCDI. FMT has been effective in treating this patient population, and even if critically ill patients only partially improve after FMT, it may stabilize them enough to improve their candidacy for subsequent surgery.

Although, no RCTs have been performed on FMT for SFCDI to date, the evidence from large cohorts shows a favorable cure rate and safety profile. A meta-analysis of 676 patients with severe or fulminant CDI in one RCT, four cohort studies, and 11 case series found a 61.3% clinical cure rate after one FMT (95% CI 43.2–78.0%); 15.6% rate of all-cause mortality rate after FMT (95% CI 7.8–25.0%); 10.9% rate of major adverse events defined as death, hospitalization, or colectomy within 12 weeks of FMT (95% CI 0.2–30.2%); and a 8.2% rate of colectomy after FMT (95% CI 0.1–23.7%).[40]

In a single-center retrospective study following implementation of an inpatient FMT program, overall CDI-related mortality decreased significantly from 10.2% to 4.4% (p=0.02), with reductions in fulminant CDI (21.3% to 9.1%, p=0.015) and refractory SFCDI (43.2% to 12.1%, p<0.001).[41] Another retrospective cohort study of 16 patients treated with FMT among 48 SFCDI patients estimated the number needed to be treated to prevent one death was 3 patients.[42] Additionally, CDI-related colectomy rates were significantly reduced across all groups—SFCDI (6.8% to 2.7%, p=0.041), fulminant CDI (15.7% to 5.5%, p=0.017), and refractory SFCDI (31.8% to 7.6%, p=0.001). Patients in this study were treated using a pseudomembrane-driven "sequential FMT" protocol,[43] which identifies a subset of SFCDI patients who have pseudomembranes on colonoscopy as a marker of severe disease. This subset of patients was then treated with oral vancomycin and additional FMT(s) until the pseudomembranes were completely resolved.

The most recent guidelines generally agree that there is a role for FMT in SFCDI refractory to standard antibiotics. The 2024 AGA guideline on FMT provides a conditional recommendation, based on very low certainty evidence, suggesting conventional FMT over no FMT in adults hospitalized with severe or fulminant CDI who do not respond within 2–5 days of starting standard antibiotic therapy.[25] The ACG 2021 guideline put forth a strong recommendation based on low quality of evidence, that FMT be considered in severe or fulminant not responding to antibiotics, especially in poor surgical candidates.[44] The 2017/2021 IDSA guidelines do not discuss FMT for severe or fulminant CDI.[38,45] The most recent 2024 British Society of Gastroenterology and Healthcare Infection Society guidelines notes that there is weak evidence that FMT is beneficial in severe or fulminant CDI, and offers expert consensus guidance to consider FMT earlier than the second recurrence for patients with severe or fulminant CDI not responding to antibiotics.[46] The 2021 European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines give a weak recommendation based on very low-quality evidence that FMT may be a rescue therapy in severe refractory CDI, while emphasizing that this must be discussed on a case-by-case basis by the multidisciplinary team and surgical consultation should be sought immediately when CDI is deemed to be refractory to medical therapy.[47]

In alignment with shared decision-making, if FMT is pursued, conventional FMT using screened donor stool should be the preferred approach. No evidence supporting the use of FDA-approved fecal microbiota spores live-BRPK or fecal microbiota live-JSLM for severe or fulminant CDI exists, as the microbial content per dose of fecal microbiota live-JSLM is significantly lower than that found in 1 gram of stool, far below the stool weight used in conventional FMT studies.[25] Most data support lower administration route in SFCDI either via colonoscopy or flexible sigmoidoscopy. The evidence is insufficient for the delivery of conventional FMT via enema or capsule in SFCDI.[25] Nasoenteric tube is not recommended due to risk of aspiration. Clinical response after FMT can be gauged by monitoring stool frequency and consistency, leukocyte count and C-reactive protein levels, or presence of pseudomembrane on colonoscopy. Most SFCDI patients will require repeat FMT in combination with an anti-CDI antibiotic to achieve sustained clinical resolution due to the severity of the dysbiosis.[25] As previously discussed, a sequential protocol is useful for determining which patients require additional FMTs. If a pseudomembrane is present, FMT is generally repeated every 3–5 days and oral vancomycin (125mg every 6 hours) or fidaxomicin (200mg every 12 hours) are continued until the pseudomembrane is completely resolved.[44]

Decolonization of Multidrug-Resistant Organisms

Although FMT was initially studied for prevention of recurrent CDI, there was also interest growing in its potential to decolonizing the gut of other organisms, specifically multidrug-resistant organisms (MDROs) which are associated with significant mortality and healthcare costs. Examples of MDROs include vancomycin-resistant enterococci (VRE), carbapenemase-producing Enterobacteriaceae (CPE), carbapenemase-producing Acinetobacter (CPA), extended-spectrum β-lactamase (ESBL)–producing Enterobacterales, and multidrug-resistant Pseudomonas aeruginosa (MDRP). In addition, emerging evidence suggest that FMT may modulate or down regulate antibiotic resistance genes. In a single-center prospective study of 29 patients with VRE and/or CPE, significant decrease in expression of antibiotic resistance genes as measured by real-time reverse-transcription polymerase-chain reaction was observed.[48] A randomized, placebo-controlled trial found that while FMT initially lead to a low-level transfer of antibiotic resistance genes from commensal bacteria, it was ultimately followed by long-term protection against new antibiotic resistance genes as stable microbial communities formed.[49] Another recent randomized controlled trial using whole-genome sequencing, antimicrobial susceptibility testing, and metagenomic analysis found evidence of antibiotic-susceptible strains replacing antibiotic-resistant strains of bacteria of the same species following FMT.[50] This mechanistic evidence provides some insight into the rationale of FMT for MRDO decolonization.

At this time, the evidence for FMT in MRDO decolonization is much more heterogeneous and limited compared to the evidence for FMT in recurrent CDI. A 2021 meta-analysis could not draw any definitive conclusions about the efficacy of FMT for MRDO decolonization based on the limited and heterogeneous evidence.[51] A 2019 meta-analysis including 20 studies (one RCT) and 121 patients found that the efficacy of FMT for the eradication of each MDRO was 70.3%.[52] However, these results warrant cautious interpretation. A crucial consideration when interpreting data on FMT for MDROs is the inclusion of a control group to account for the natural occurrence of spontaneous decolonization. A meta-analysis of 37 studies performed on patients in healthcare settings showed colonization of ESBL–producing Enterobacterales spontaneously decreased (ie without decolonization antibiotic therapy) over time from 80.2% at 1 month to 35.7% at 12 months, and spontaneous decrease for CPE from 73.9% at 1 month to 34.6% at 12 months.[53] A retrospective multicenter study of 125 patients with CRE and/or VRE found that spontaneous decolonization occurred in 16.4% of cases within the first 30 days and 48.2% of cases at 90 days.[54]

To date, two RCTs and a small number of studies that have control groups studying the use of FMT for MRDO decolonization. The PREMIX trial was a single-center, phase 1 RCT of 11 renal transplant recipients who had at least one initial MDRO infection (CPE, VRE, ESBL–producing Enterobacterales, and MDRP).[50] Six patients received FMT and five patients were in the observation group. The patients in the observation period were then given FMT if they remained MDRO-positive after 36 days, to serve as their own controls. Of the 11 total participants in the RCT, seven received one FMT and three received two FMTs; one patient in the observation group ultimately did not receive any FMT due to the COVID-19 pandemic. FMT was delivered via retention enema. FMT was found to be as safe with no increase in alloimmunity, renal allograft rejection, or HLA antibodies. In terms of efficacy, FMT accelerated MDRO decolonization. At day 36, only 33% of the FMT group were MDRO positive compared to 100% of the observation group. None of the patients in the observation group exhibited spontaneous decolonization. At the end of the study, eight of nine patients completing all FMT treatment(s) achieved MDRO-negative stool cultures. Furthermore, a post-hoc analysis showed that the time to negative stool culture was significantly shorter in the FMT group compared to the observation group, with a median time of 35 days versus 88 days, respectively.

Another RCT evaluated a 5-day course of oral colistin and neomycin followed by FMT to decolonize 39 patients who were carriers of either ESBL-Enterobacteriaceae or CPE.[55] The study found no statistically significant benefit: the intention-to-treat decolonization rates were 41% in the intervention group versus 29% in controls (OR 1.7, 95% CI 0.4–6.4). A per-protocol analysis, which excluded patients who did not fully adhere to the study protocol or received non-study antibiotics, showed a higher decolonization rate of 50% in the intervention group, compared to 23% in the control group, with an OR of 3.3 (95% CI 0.7–16.8), however, this was also not statistically significant. Diarrhea was a common side effect, leading three patients to stop antibiotics early, and no colistin-resistant strains emerged in the intervention

group. The study did not reach its planned sample size: only 39 patients were enrolled instead of 64. The findings from this RCT do not support FMT for decolonization.

While the pathophysiologic rationale for using of FMT for MDRO decolonization is promising, its use remains investigational due to the small sample sizes and heterogeneity of current evidence. It is possible that FMT could offer benefit in certain patient subgroups even without achieving complete MDRO decolonization. However, larger, randomized controlled trials with more substantial sample sizes are necessary to fully understand its potential and efficacy.

Emerging Noninfectious Indications of FMT

Irritable Bowel Syndrome

Irritable Bowel Syndrome (IBS) is a highly prevalent and chronic disorder that significantly impacts the quality of life for many patients. Affecting approximately 4.4–4.8% of the population in the United States, United Kingdom, and Canada, IBS most common in women and individuals under the age of fifty.[56] Despite its prevalence, effective treatments remain elusive for many sufferers, and patients often face persistent, debilitating symptoms. As research into the gut microbiota advanced, data supporting the role of the intestinal microbiome in the pathophysiology of IBS emerged. One key discovery was the finding that transplanting fecal microbiota from IBS patients into germ-free rats provoked IBS-like symptoms.[57] However, no consistent microbial signature for IBS has been identified, making it difficult to definitively establish the gut microbiome as the root cause of the disorder. Nevertheless, these studies raised the possibility that microbiome modulation might be a therapeutic target for IBS.

Several randomized controlled trials (RCTs) studied FMT as a potential treatment for IBS. One such study, conducted by Holvoet et al, focused on patients with refractory IBS—defined as failure of three or more conventional therapies. In this double-blind trial, participants were randomly assigned to receive either a single-dose fecal transplant via nasojejunal tube (NJ) from a healthy donor or autologous stool.[57] The primary outcomes were improvement in IBS symptoms, including abdominal discomfort, bloating, pain, flatulence, and bowel movement frequency, as well as quality of life. At 12-weeks, 56% of patients receiving donor stool reported significant improvement in both primary outcomes, compared to just 26% of patients in the placebo group. A striking finding was that 21% of patients who received donor stool reported sustained benefits lasting longer than one year, compared to only 5% in the placebo group. In case of symptomatic relapse, a second FMT was beneficial in 67% of those who initially responded, but it had no impact on those who had shown no prior response.[57]

Another double-blind, RCT conducted by Salhy et al included 165 participants who were randomized into three groups: placebo (autologous stool), 30g FMT, or 60g FMT.[58] Donor stools were obtained from healthy individuals, frozen, and administered via a gastroscope. The primary outcome was a reduction in IBS symptoms at three months after FMT, with a 50-point reduction in the total IBS symptom score (IBS-SSS) considered a response. Secondary outcomes included a reduction in the dysbiosis index and a change in the intestinal bacterial profile as analyzed by gene sequencing one-month post-treatment. Participants in this study underwent a thorough work-up, including CBC, CMP, TSH, calprotectin testing, and duodenal biopsy/colonoscopy to rule out other gastrointestinal disorders. They also followed a diet consistent with guidelines from the National Institute for Health and Care Excellence (NICE) for at least three months before enrollment. The study found that the concentration of specific microbiota species, such as Lactobacillus and Alistipes, was inversely correlated with IBS-SSS scores. Following FMT, higher concentrations of these species were observed in both the 30g and 60g FMT groups, while a lower concentration of Bacteroides species was noted. Additionally, women responded better to donor stool compared to men, and patients who responded to FMT had higher baseline microbiome diversity compared to nonresponders.[58]

However, results have been inconsistent. A randomized double-blinded placebo-controlled study compared FMT to placebo capsules and followed patients for 6 months.[59] Although fecal microbial biodiversity increased following FMT, patients in the placebo group experienced greater symptom relief based on IBS-SSS ($p=0.012$) and IBS-specific quality of life ($p=0.003$) after 3 months.

The American College of Gastroenterology (ACG) recommends against the widespread use of FMT for treating global IBS symptoms.[56] In the systematic review and meta-analysis by Ianiro et al,[60] data from 5 RCTs[57,59,61–63] showed

no significant improvement in IBS symptoms with FMT versus placebo. Similarly, the AGA panel made a conditional recommendation against the use of FMT in adults with IBS except in the context of clinical trials.[25] This guideline was based on a 2019 meta-analysis of RCTs of FMT for IBS which found no significant change in overall IBS symptoms at 12 weeks (RR=0.93, 95% CI 0.48–1.79). However, they found significant heterogeneity between studies (I^2 = 79%) and overall low quality of evidence.[64] In addition, a 2023 systematic review, pairwise meta-analysis and network meta analysis of RTC showed similar findings. Pooled results showed no significant improvement in IBS symptoms with FMT versus placebo. However, subgroup analysis showed that FMT delivered through duodenoscopy or nasojejunal tube reduces the severity of symptoms and quality of life of IBS patients.[65] The ACG also emphasizes the lack of large, multicenter, double-blind, placebo-controlled studies, which are necessary to fully assess the potential role of FMT in IBS treatment.[56]

Inflammatory Bowel Disease

Fecal microbiota transplantation showed promise for the treatment of inflammatory bowel disease (IBD), in particular for ulcerative colitis (UC). While research studies initially focused on FMT as an induction therapy, more recent trials examined its potential as maintenance therapy. Notably, these studies have used conventional donor-derived FMT, not defined live biotherapeutic products (LBPs). Certain microbial taxa were linked to response, but the optimal microbiota composition and donor type to boost efficacy requires further exploration. Some studies suggested that shorter disease duration and milder disease severity predict better response, implying that FMT might have more benefit earlier in the clinical course and for milder disease activity. The AGA made a conditional recommendation against the use of conventional FMT for the treatment of UC or Crohn's disease (CD), except in the context of clinical trials.

A 2023 Cochrane meta-analysis evaluated the benefits and safety profile of FMT for treatment of UC.[66] They included twelve RTCs[67–78] with 550 participants. Nine studies focusing on adults with UC showed that FMT increases rates of induction of clinical remission in compared to control at 6–12 weeks (RR 1.79, 95% CI 1.13–2.84). However, it was low certainty evidence. Five studies evaluated the induction of endoscopic remission in UC. At 8–12 weeks, RR was 1.45 with wide CIs around the summary estimate and including a possible null effect (0.64–3.29). Also, the evidence was very uncertain for assessing maintenance of clinical remission at 48 to 56 weeks using two studies (RR 2.97, 95% CI 0.26–34.42) and endoscopic remission (RR 3.28, 95% CI 0.73–14.74). A recent systemic review and meta-analysis of 29 RCTs on FMT for UC focused on the role of microbiota composition. High α-diversity in both donors and recipients was strongly associated with a positive clinical response, while interestingly engraftment did not appear to play a significant role. Butyrate-producing species from the Lachnospiraceae and Oscillospiraceae families were often associated with response, whereas abundance of *Fusobacteria*, many *Proteobacteria*, and *Ruminococcus gnavus* were disadvantages.[79]

For therapy of Crohn's disease, the results on FMT's efficacy and safety mostly based on cohort studies and case-series. No RCTs of FMT were identified in the 2023 Cochrane meta-anlaysis for induction in CD with FMT and only one was reported for the maintenance of remission.[66,77] This RTC included 21 patients who achieved clinical remission with systemic corticosteroids. They were randomized to receive FMT (n=11) or allocated to Sham-transplantation (n=10). FMT was not significantly associated with clinical remission at 24 weeks compared to placebo (50% versus 33.3%). The role of FMT in CD treatment is still unclear and more studies are needed to assess its role in achieving and maintaining remission.

Metabolic Syndrome

Outside of IBD and IBS, FMT transplantation showed some success in the management of metabolic syndrome. A meta-analysis conducted by Qiu et al included nine studies comprising 303 participants in where short-term outcomes were assessed within 6 weeks after FMT compared with the placebo group. The FMT group had lower fasting blood glucose, hemoglobin A1c, and insulin levels, along with higher HDL levels. On the contrary, there was no significant difference between the FMT group and the placebo group in terms of weight reduction.[80] It is unclear how the transplanted microbiota achieve improvements in these parameters. One hypothesis focuses on decreased levels of inflammatory cytokines, another one claims positive impact on the gut-brain axis.

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Liver Disease

FMT has emerged as a potential therapeutic option for individuals with liver disease; primarily focusing on the management of hepatic encephalopathy (HE) in patients with cirrhosis. The THEMATIC trial, a phase-2 RCT tested capsule and enema FMT compared to placebo. The 60 enrolled patients were randomized into four groups receiving between 0 and 3 active treatments (two capsule and one enema) and followed up for 6 months.[81] The primary outcome was safety, focusing on FMT-related hospitalizations or ER visits. The secondary outcome was HE recurrence, all-cause hospitalization, death, donor microbiota engraftment and quality of life. Results showed no FMT-related SAEs/AEs and no difference in all-cause hospitalization or death in patients with any FMT group vs placebo. In the post-hoc analysis, HE recurrences were lower in any FMT (1–3 doses) recipient compared to placebo, regardless of FMT doses, route, or donor type.

Treatment of alcoholic hepatitis (AH) with FMT is another focus of research. A pilot study offering FMT to 8 subjects with AH and contraindication to steroid therapy showed promising results.[82] An RCT measuring the effectiveness of prednisolone therapy vs FMT in patients with severe AH (SAH) randomized steroid-eligible SAH patients to prednisolone 40mg/day for 28 days or healthy donor FMT daily for seven days. The primary outcome of the study was 90-day survival which was achieved by 56.6% of patients in the prednisolone group and 75% in the FMT group. Infectious complications occurred in 11 and 2 individuals in the prednisolone and FMT groups, respectively, suggesting that FMT is and an alternative to prednisolone therapy.[83]

Summary

Over the last 15 years, FMT has gained wide acceptance and changed the treatment paradigm for recurrent CDI, as it is now recommended by practice guidelines after the second or third episode of CDI. It has an emerging role for the treatment of severe or fulminant CDI non-responsive to maximum medical therapy after 48 hours, particularly in patients with multiple comorbidities who are poor candidates for colectomy. Multiple clinical trials are exploring the potential of FMTs beyond CDI, including for the treatment of IBD, IBS, metabolic disorders, liver disease, decolonization of MDROs, and others. However, it is important to acknowledge the mechanistic differences between all these indications. Whereas the objective of FMT in CDI is a simple repair of the gut microbiome severely damaged by antibiotics, most other indications aim to introduce certain microbiome functionalities that are beneficial to the host metabolism or immune function. The regimens to achieve the latter are more likely to require personalized formulations of donor microbiota and more intensive dosing protocols. The ideal microbiota composition for therapeutic success has yet to be identified, and further large-scale, multicenter, placebo-controlled studies are essential to evaluate its efficacy and safety. Until more robust data is available, FMT remains an experimental therapy for all indications outside of CDI, primarily restricted to clinical trials and specialized settings.

Recently, two FDA approved prescription therapies for the prevention of rCDI became available, branded Rebyota™ for enema delivery at a healthcare facility and Vowst™ for oral administration at home. This has expanded patient access to fecal microbiota-based therapies, though prior authorization is required for both agents with variable insurance coverage. Locally prepared FMT can still be utilized for CDI indications, ie, prevention of rCDI or treatment of severe and fulminant CDI without submission of an IND application. For any alternative clinical indication, FMT must be administered strictly within the limits of a clinical trial with an active IND.

However, the field is now evolving beyond traditional FMT approaches to include the development of defined, donor-independent microbiome therapeutics. These include LBPs such as VE303 and NTCD-M3. Unlike FMT or donor-derived products, these LBPs are produced from cultured, well-characterized organisms and are designed to offer greater consistency. These advances aim to not only restore microbiota diversity and prevent recurrence of CDI but also to exert promising effects on variety of other diseases. However, considerable research work is yet to be done before these next-generation FMT preparations or alternative live biotherapeutic products can be expected to enter clinical practice.

Disclosure

CK reports advisory board for Eli Lilly and Company (paid) and Open Biome (unpaid). MF participated on advisory boards for Abbvie, Johnson and Johnson, BMS, Eli Lilly, Seres, Ferring, Pfizer; Non-branded lecturer for Johnson and Johnson. Data safety monitoring board chair for Criscot. The authors report no other conflicts of interest in this work.

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