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FECAL MICROBIOTA TRANSPLANTATION FOR *CLOSTRIDIOIDES DIFFICILE* INFECTION: WHAT IS NEW?

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Abstract – *Clostridioides difficile* infection (CDI) remains a leading cause of antibiotic-associated diarrhea worldwide, with recurrent episodes representing the most challenging aspect of disease management. Results from randomized controlled trials, multicenter cohorts, and systematic reviews on CDI demonstrate that fecal microbiota transplantation (FMT) achieves cure rates of about 80-90% and markedly reduces recurrence episodes. This review aimed to present an update on the clinical implementation of FMT for CDI treatment, including patient selection, risk stratification, donor screening, recipient preparation, delivery routes, and outcome monitoring. Data obtained from mechanistic studies showed that FMT can cause restoration in gut microbiota structure and diversity, promote butyrate- and secondary bile acid-producing microbial taxa, suppression in *C. difficile* germination, and modulation in mucosal and systemic immune responses. We also summarized other microbiome-based strategies, including defined microbial consortia, engineered live biotherapeutics, postbiotics, and phage therapy, which aim to replicate the ecological and functional benefits of FMT with greater standardization and safety. Ultimately, we investigated outstanding problems, such as donor variability, transmission of multidrug-resistant organisms, long-term ecological concerns, and global inequities in access, while considering potential paths to precision-guided and scalable microbiota-based therapeutics.

Keywords: *Clostridioides difficile* infection, Recurrent CDI, Fecal microbiota transplantation, Gut dysbiosis, FMT.

INTRODUCTION

Clostridioides difficile infection (CDI) represents a major global healthcare burden, with increasing incidence, high rates of recurrence, and substantial impacts on patient morbidity, mortality, and healthcare resources[1]. Once considered a predominantly hospital-associated infection, CDI is now frequently encountered in community settings, with both asymptomatic carriage and active transmission[2,3]. The most established risk factor remains antibiotic exposure, mostly to clindamycin, cephalosporins, fluoroquinolones, and vancomycin, which can disrupt gut microbiota and create favorable conditions for *C. difficile* proliferation[4,5]. Other notable risk factors include advanced age, immunosuppression, proton pump inhibitor (PPI) use, and prolonged hospitalization[2,6]. Of note, PPI-associated risk for

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community-acquired CDI may persist for up to a year after discontinuation[2]. Despite a growing trend to control hospital outbreaks and reduce antibiotic overuse, CDI remains the leading cause of nosocomial diarrhea and a significant contributor to gastrointestinal infections worldwide[7].

CDI severity ranges from mild diarrhea to fulminant colitis, toxic megacolon, and even death. The clinical management of CDI is complicated as approximately 20-30% of patients relapse after initial treatment, with up to 60% experiencing multiple recurrences[7-9]. Recurrence episodes can be more severe and less responsive to standard antibiotics, and in 33-56% of cases, they are caused by new strains rather than relapse from the original infection. Standard treatments, including oral vancomycin or fidaxomicin, help eradicate active infection but further disrupt microbiota structure and enhance the risk of relapse[8-10]. Accordingly, microbiome-based therapeutics that aim to restore intestinal microbial diversity and function rather than suppressing the pathogen have gained prominence in recent CDI studies[11]. Fecal microbiota transplantation (FMT) is the most evidence-based intervention for recurrent CDI (rCDI), in which minimally processed stool from a healthy donor is transferred into the patient's gastrointestinal tract to reestablish microbial homeostasis[12]. By restoring a diverse and resilient microbiota, FMT can enhance colonization resistance through nutrient competition, bile acid metabolism, and modulation of host immune responses[13-15]. A Cochrane meta-analysis of six randomized controlled trials with 320 adult participants showed that FMT significantly increased the likelihood of sustained cure compared with antibiotics alone[16]. The analysis also suggested a possible reduction in all-cause mortality and serious adverse events, though large-scale trials are warranted to clarify long-term safety, especially in immunocompromised populations.

Recent advances are extending beyond traditional FMT toward next-generation microbiota therapeutics, such as defined microbial consortia, synthetic communities, and postbiotics to preserve the ecological advantages of FMT while improving safety, reproducibility, and regulatory compliance[17]. However, FMT remains an indispensable option for patients with rCDI unresponsive to standard treatments until other therapies are broadly available in clinical settings. This review aimed to appraise the existing literature on the new aspects of FMT implementation for CDI treatment, focusing on the mechanistic insights underpinning its efficacy, and emerging strategies to define the next generation of microbiota-directed therapeutics.

Study selection

The studies were selected based on a comprehensive literature search across major databases, including PubMed, Scopus, Embase, Web of Science, and Cochrane, which contained randomized controlled trials, multicenter cohorts, systematic reviews, recent clinical guidelines, and original articles relating to the current landscape of FMT for rCDI.

PATHOPHYSIOLOGY OF RCDI

A healthy human gut harbors a diverse and resilient microbial community that provides colonization resistance against opportunistic pathogens such as *C. difficile*[18]. Gut dysbiosis, a hallmark of CDI, can result from several factors, most importantly antibiotic exposure, but also from chemotherapy, gastrointestinal surgery, dietary deficiencies, and chronic gastrointestinal diseases[19]. Antibiotics, including clindamycin, cephalosporins, fluoroquinolones, and vancomycin, markedly reduce microbial richness and selectively deplete protective taxa within the Firmicutes and Bacteroidetes phyla, while permitting overgrowth of Proteobacteria[19,20]. Gut microbiota imbalance can reduce butyrate-producing organisms, which are crucial for epithelial barrier integrity and normal bile acid metabolism, creating a microenvironment that facilitates spore germination and *C. difficile* overgrowth[21]. Patients with rCDI often fail to restore normal gut microbiota between episodes, allowing persistent dysbiosis that supports the recolonization by toxigenic strains or the reactivation of dormant spores[22]. Furthermore, strains with probiotic properties and commensals capable of competing with *C. difficile* for nutrients or mucosal adhesion sites are frequently absent in rCDI patients[23]. Thus, reinfection with genetically distinct strains has been frequently documented, demonstrating the inability of the disrupted gut ecosystem to regain colonization resistance[24].

The pathogenesis of rCDI is mainly driven by the *C. difficile* exotoxins, namely TcdA and TcdB, which cause epithelial injury, stimulate fluid secretion, and provoke intestinal inflammation[21,25]. These toxins compromise tight junction integrity and cytoskeletal architecture and promote neutrophil and monocyte infiltration, mucosal erosion, and pseudomembrane formation[26]. Chronic toxin exposure can disrupt immune responses, leading to a sustained proinflammatory state, with elevated IL-6 and TNF-α persisting even in remission[27]. Furthermore, barrier breakdown facilitates bacterial and metabolite translocation, fueling systemic inflammation and altering microbial niches[28]. Moreover, following toxin-induced cell death, the release of nutrients such as sialic acids and succinate can selectively support *C. difficile* proliferation within the host[20].

Multiple host-related factors increase the risk of rCDI by weakening immune defenses or sustaining dysbiosis[29]. Immunosenescence in the elderly can reduce the host capacity to mount effective antitoxin antibody responses[30]. In addition, pediatric patients, especially those with comorbidities or frequent healthcare exposure, are at greater risk due to immature immunity and high antibiotic usage[27]. Furthermore, immunosuppressive therapies, including corticosteroids, cytotoxic chemotherapy, and biologics, diminish mucosal immunity and clearance efficiency[31]. PPIs by altering gastric pH and microbial composition further compromise colonization resistance[32]. Hospitalization, particularly in intensive care units (ICUs) or after surgery, increases exposure to nosocomial strains and disrupts the gut microbiota[33]. Malnutrition and inflammatory bowel disease (IBD) impair mucosal integrity and immune competence, while feeding tubes and tracheostomies provide direct routes for pathogen ingress and trigger *C. difficile* colonization[34]. Together, these factors contribute to persistent vulnerability by impeding microbiota restoration and immune recovery.

CLINICAL RESOLUTION AND EFFICACY OF FMT IN CDI

Today, FMT has become a cornerstone of CDI management, and current clinical guidelines recommend it primarily for patients with multiple recurrences despite appropriate antibiotic courses[35,36]. By introducing a complex community of commensal microorganisms from healthy donors, FMT directly addresses the underlying ecological imbalance, promoting colonization resistance and suppressing *C. difficile* germination and toxin production[17,37]. Unlike antibiotics, which perpetuate dysbiosis and fail to eradicate spores, FMT reconstitutes microbial networks that confer durable protection, and long-term follow-up indicates that remission can persist for more than a year in most patients, with durable responses in over 80% after a single treatment[38,39].

FMT is increasingly applied to complex clinical populations, including immunocompromised individuals and those with IBD, where remission rates remain high when careful monitoring and tailored protocols are implemented[40,41]. Across observational studies, randomized controlled trials, and meta-analyses, single-FMT cure rates typically range from 70% to over 90%, with repeat administrations further improving outcomes[42,43]. In a multicenter retrospective cohort of IBD patients, sequential FMT achieved significantly higher sustained cure rates and prolonged symptom-free intervals compared with prolonged antibiotic therapy[40]. Additionally, in cancer patients with advanced disease, retrospective analysis from a tertiary cancer center demonstrated an 84% response rate following FMT for rCDI, with no serious adverse events or 30-day mortality; however, subsequent antibiotic exposure that is often necessitated by chemotherapy-related complications, was associated with reduced efficacy of the treatment[44]. Similarly, a meta-analysis of 1,208 immunocompromised patients across 44 studies, including solid organ transplant recipients, oncology patients on chemotherapy, hematopoietic stem cell transplant recipients, and individuals with advanced HIV, reported a pooled clinical resolution rate of 75.3% (95% CI 71.7–78.6%) after a single FMT, increasing to 87.4% (95% CI 84.8–89.6%) with multiple administrations. Notably, recurrence occurred in 23.9% (95% CI 19.2–29.4%) and serious adverse events presented in 10.1% (95% CI 6.7–14.8%), which were broadly comparable to those observed in immunocompetent cohorts[45].

Patient Selection and Risk Stratification

Effective integration of FMT into practice requires precise patient selection and risk assessment to improve treatment efficacy and ensure patient safety. The explicit indication for patient selection remains multiple CDI episodes unresponsive to standard antibiotic therapy, typically after the second

or third recurrence[46]. Increasingly, early FMT after the first recurrence in high-risk patients has been investigated to reduce repeated antibiotic exposure and stabilize immune function, with evidence suggesting improved outcomes and decreased hospitalization or colectomy rates[47]. Notably, patients with considerable microbiota depletion, including low alpha diversity and Proteobacteria overrepresentation, are typically more responsive to FMT[48]. Studies have shown that patients with higher baseline microbial diversity, or those lacking critical butyrate-producing bacteria such as *Roseburia* and *Fusicatenibacter*, may have reduced response rates[49]. Pre-FMT microbiome profiling to identify deficits in key taxa can refine patient selection and predict response[49].

Age, comorbidities, immune status, and gastrointestinal conditions also influence the risk and benefit balance of FMT in patients[50-52]. While FMT is possibly effective in elderly or immunocompromised patients, including transplant recipients, it requires rigorous donor screening and aseptic preparation to mitigate infectious risks[53,54]. Among CDI patients with concurrent IBD, FMT effectively treats CDI; however, its impact on IBD activity is variable, and flares may occur post-FMT[54,55]. Furthermore, patients who fail multiple vancomycin or fidaxomicin courses and remain toxin-positive are strong FMT candidates, whereas patients with non-infectious diarrhea syndromes should be considered only with supporting evidence[56]. Finally, patients must be informed of potential benefits, uncertainties, and adverse effects/events, especially where data are limited, and informed consent should address the experimental status of FMT outside CDI and detail screening protocols to minimize transmission risk[39,57].

Regulatory and Ethical Challenges

The rapid evolution and clinical success of FMT for rCDI have raised pressing regulatory and ethical challenges, particularly regarding its classification, production, and administration across different regions[39]. Regulatory frameworks in the United States (US) and Europe continue to diverge in their categorization of FMT, which affects its accessibility, safety oversight, and long-term clinical governance[58]. In the United States, FMT is regulated as a biologic drug under the jurisdiction of the FDA[59]. While rCDI was initially permitted under enforcement discretion without an Investigational New Drug (IND), FDA approvals of standardized FMT products like RBX2660 (Rebyota) and SER-109 (Vowst) signal a shift toward more stringent oversight[60,61]. Furthermore, all investigational uses beyond rCDI now require an IND submission, reflecting the importance of quality control, safety, and long-term monitoring[39]. This framework, however, can impede hospital-based or physician-prepared FMT due to logistical and financial barriers[62].

In the European Union (EU), the lack of a unified position from the European Medicines Agency (EMA) has led to fragmented national policies[63,64]. The United Kingdom (UK) treats FMT as a medicinal product under the Medicines and Healthcare Products Regulatory Agency (MHRA). Moreover, France and Germany classify FMT as a drug, while Belgium, the Netherlands, and Italy regulate it as tissues or cells[64,65]. The UK's licensed stool bank operates under Good Manufacturing Practice (GMP) with National Health Service (NHS) access supported by an innovation tariff[66]. Additionally, EU Gastroenterology advocates for harmonized classification of transplant products, with standardized donor screening and safety monitoring[65]. Canada classifies FMT as a biologic drug requiring a full clinical trial application outside compassionate use, whereas Australia applies a Class 1/2 biological classification depending on the preparation and context[67,68]. Uncertainty about the active microbial, metabolic, or immunologic therapeutic components complicates ethical and regulatory frameworks; thus, global harmonization of classification systems and ethical standards is essential to ensure safe, equitable, and evidence-based implementation of FMT in both clinical care and research.

FMT STANDARDIZATION AND OPTIMIZATION

Donor Screening, Preparation, and Safety

The safety and efficacy of FMT rest on rigorous donor selection and carefully standardized stool processing to avoid transmission of infectious agents, undesirable microbial traits, or pro-inflammatory components[69]. Preferred donors are healthy young adults without recent antibiotic exposure, meta-

bolic syndrome, or gastrointestinal disorders, which can significantly influence microbial diversity, metabolic potential, and stability[70,71]. Diet, travel history, and behavioral risk factors are also assessed to avoid the introduction of pathogens or unfavorable microbiome profiles to recipients[72,73]. Comprehensive health questionnaires, detailed medical histories, and laboratory testing for blood-borne and enteric pathogens are the core of standardized protocols[74]. These efforts include serological screening for HIV, hepatitis A–C, and syphilis, alongside stool assays for enteric bacteria, parasites, viruses, and *C. difficile* toxins[62,75,76]. Importantly, the growing recognition of multidrug-resistant organisms (MDROs) as potential contaminants has required culture and PCR-based evaluations for carbapenem-resistant Enterobacterales, vancomycin-resistant Enterococci, and extended-spectrum β-lactamase–producing bacteria[71,77,78]. Once approved, donors provide fresh stool under controlled conditions to limit environmental contamination. Processing uses sterile techniques to homogenize stool in isotonic or buffered saline, or glycerol-containing cryoprotectants for frozen storage, which should be completed within six hours[79]. Furthermore, particulate matter is removed *via* filtration while preserving viable microbial communities[80]. It is worth noting that centralized stool banks operating under GMP standards enhance quality control, traceability, and batch testing, enabling rapid donor recall and providing standardized preparations for both research and clinical use[81].

Recipient Preparation and Exclusion Criteria

Optimizing recipient readiness is essential for maximizing engraftment success and minimizing adverse outcomes. Most protocols recommend ceasing CDI-directed antibiotics 24-48 hours before FMT to reduce antimicrobial suppression of the donor microbiota[82]. Bowel lavage, akin to colonoscopy preparation, is often performed to reduce residual pathogen burden, though a previous study suggested that its utility may vary by delivery route[35]. While exclusion criteria may differ to protect patients from procedure-related risks, absolute contraindications include severe sepsis, bowel perforation, and hemodynamic instability[83-85]. Additionally, relative contraindications can consist of pregnancy, severe neutropenia, recent gastrointestinal surgery, or inability to provide informed consent[81]. Immunocompromised patients are not uniformly excluded but require enhanced screening and post-procedure surveillance[71]. In some centers, risk stratification combines clinical variables with microbiome biomarkers, such as baseline alpha diversity and the abundance of butyrateproducing taxa, to predict FMT success, which plays a role in maintaining epithelial integrity and modulating immune responses[82]. Finally, high-risk individuals may be offered intensified regimens, such as multi-dose protocols or adjunctive therapies.

Routes of Delivery

The delivery route can considerably influence therapeutic efficacy and patient experience during and after FMT procedure[86]. Administration methods include the lower gastrointestinal route (*via* colonoscopy or retention enema), upper gastrointestinal route (*via* esophagogastroduodenoscopy, nasogastric, nasojejunal, or nasoduodenal tube), and oral capsules[87]. Colonoscopy is the most extensively studied procedure, which allows for the deposition of a high microbial load throughout the colon and permits mucosal inspection[88]. However, bowel preparation, sedation, and procedural requirements limit the use of colonoscopy in unstable or frail patients[89]. Retention enemas are more affordable and less invasive for delivering microbiota to the distal colon and have demonstrated improved outcomes, especially with multi-dose regimens[90,91].

Upper gastrointestinal delivery may be considered in patients with colonic inflammation or altered anatomy, but discomfort during tube placement, aspiration risk, and inability to inspect colonic mucosa are drawbacks of these methods[92]. Notably, comparative studies have shown that FMT delivered *via* lower gastrointestinal routes may represent the most effective response against recurrence or relapse of CDI[92]. Importantly, oral capsule formulations, containing freeze-dried or frozen microbiota in enteric-coated form, offer a non-invasive and sedation-free option with high cure rates comparable to colonoscopy[93]. However, oral capsules require GMP-compliant manufacturing and may involve a substantial capsule burden[94]. Ultimately, route selection should be individualized, considering comorbidities, procedural risk, urgency, patient preference, and local resources. Shared decision-making ensures alignment between clinical considerations and patient priorities.

Follow-up and Outcome Measures

A structured, well-timed follow-up protocol is essential to promptly detect recurrence and assess the therapeutic efficacy of FMT, identifying delayed or rare adverse events that patients may encounter. In clinical practice, primary cure is defined as complete resolution of diarrhea that is accompanied by a negative test for *C. difficile* within eight weeks of FMT and without the need for additional antibiotic therapy[95]. Sustained cure, however, is typically assessed at ≥12 weeks, with recurrence defined as the return of characteristic symptoms and laboratory confirmation of toxigenic *C. difficile* following an initial resolution[96]. Standard follow-up schedules often include evaluations at 1-2 weeks, 1 month, and 3 months post-procedure, supplemented by additional visits or remote contact when clinically indicated[97]. Diagnostic testing is generally performed for symptomatic patients to lessen the risk of misclassifying asymptomatic carriage as CDI recurrence[98]. In research settings, longitudinal microbiome sequencing may also be incorporated to monitor donor strain engraftment and the progressive restoration of microbial diversity[77,99,100].

Long-term patient assessments provide a reliable framework for detecting uncommon or delayed outcomes, including potential metabolic or immune sequelae. Increasingly, patient-reported outcome measures, such as stool form, urgency, abdominal pain, and overall quality of life, are recognized as valuable endpoints in both clinical care and research trials[101]. For patients at high risk of relapse or those with incomplete recovery, repeat FMT or adjunctive strategies, such as bezlotoxumab, probiotics, or tailored dietary interventions, may be considered to maintain remission[102].

MECHANISMS OF ACTION OF FMT IN RCDI

FMT delivers a diverse consortium of commensal microorganisms that re-establish ecological stability in the gut, markedly increase alpha diversity, and restore keystone taxa that provide colonization resistance against *C. difficile*[103,104]. The therapeutic effect of FMT consists of compositional and functional recovery, which includes the restoration of short-chain fatty acid (SCFA) biosynthesis, normalization of redox potential, and reactivation of metabolic pathways disrupted during dysbiosis[105]. Successful FMT rapidly induces a donor-like microbial profile within days that persists for months to years and establishes a resilient network that resists re-emergence of *C. difficile*[106].

When it comes to pathogen exclusion, the occupation of nutrient niche, which can be the depletion of amino acids and simple carbohydrates preferentially utilized by *C. difficile*, can restrict pathogen proliferation[107]. Commensal anaerobes contribute to this effect by producing SCFAs and bacteriocins that directly inhibit *C. difficile* growth, while metabolic cross-feeding stabilizes community function[108]. Restoration of butyrate-producing Firmicutes, such as *Roseburia* spp. and *Faecalibacterium prausnitzii*, can elevate colonic butyrate concentrations and lead to promotion of regulatory T cells (Tregs) and attenuation of pro-inflammatory cytokines[103]. The immunomodulatory changes reduce mucosal inflammation, facilitating epithelial repair and regulating CDI-associated Th17 responses[105]. Innate immunity is likewise regulated, with enhanced tolerance at pattern recognition receptors (PRRs), reduced neutrophil infiltration, and increased secretion of protective mucins[109]. Notably, upregulation of *Bacteroides fragilis* and other polysaccharide A-producing taxa results in elevated levels of IL-10, which can establish an anti-inflammatory milieu in the gut[110]. Thus, FMT would reinforce innate and adaptive immune responses and strengthen gut barrier integrity against *C. difficile*-mediated pathology.

In the dysbiotic gut, the dominance of primary bile acids facilitates *C. difficile* spore germination, while secondary bile acids are depleted, which can inhibit germination and vegetative growth of the pathogen[14]. FMT restores bile salt hydrolase-producing bacteria and regulates efficient conversion of primary to secondary bile acids such as deoxycholic acid and lithocholic acid, which suppress spore germination and toxin synthesis[111]. Accordingly, it has been reported that stable reconstitution of *Clostridium scindens* and other 7α-dehydroxylating taxa is significantly associated with durable remission of CDI[106]. Metabolomic studies further illustrated that restoration of indole derivatives and polyamines, which support epithelial function, regulate immune responses, and promote mucosal integrity[17,112]. Secondary metabolites from re-established commensals can directly repress *C. difficile* toxin gene expression and impair biofilm formation[14].

Additional protective effects arise from the re-establishment of mucus-associated microbiota, which function as both a physical and biochemical barrier to pathogen adherence and biofilm

development[113]. In murine models, donor communities with intact metabolic capacity clear *C. difficile* more efficiently than simplified consortia, reflecting the importance of functional breadth in competitive exclusion[107]. The donor virome, namely bacteriophages, is also transferred during FMT and can modulate bacterial community composition by selectively lysing competing taxa or enhancing beneficial strains *via* lysogenic conversion[114]. Furthermore, reductions in *Candida* overgrowth observed post-FMT may alleviate immune activation and epithelial stress[115,116]. Collectively, FMT orchestrates a multistep re-establishment of microbial, metabolic, and immunological homeostasis to achieve durable suppression of rCDI.

EMERGING ALTERNATIVES TO FMT

Defined Consortia and Synthetic Microbiota Therapies

The development of standardized microbial therapeutics aims to overcome the variability and logistical challenges of traditional donor-derived FMT. Products such as SER-109 and RBX2660 contain defined microbial consortia derived from purified spore-forming bacteria, which can ensure batch-to-batch consistency and reduce the risk of transmitting MDROs. SER-109 is an oral formulation of purified spores of Firmicutes, which demonstrated significant reductions in rCDI recurrence compared to placebo in phase III trials, with durable microbiome engraftment and restoration of secondary bile acid metabolism[117]. In addition, administration of RBX2660 *via* enema has been shown to achieve high sustained clinical response rates and regulatory approval as the first FDA-licensed microbiota-based therapy for rCDI[118]. These next-generation therapeutics address key barriers to conventional FMT by eliminating donor-to-donor variability, enabling scalable manufacturing, and aligning with regulatory quality control requirements. In addition to improved safety, defined consortia allow targeted selection of functional taxa critical for colonization resistance, such as Lachnospiraceae and Ruminococcaceae, thereby enhancing mechanistic predictability compared to traditional FMT.

Engineered Microbial Therapeutics

Engineered live biotherapeutics, which involve genetic modification of commensal or probiotic strains, may significantly enhance pathogen suppression, modulate host immunity, or deliver therapeutic agents to the site of infection[119]. For instance, *Bacillus subtilis* and *Lactococcus lactis* can be engineered to secrete antimicrobial peptides or neutralizing antibodies that target *C. difficile* toxins[120]. These biotherapeutics not only provide competitive colonization resistance and direct toxin neutralization but also preserve beneficial host-microbe interactions and affect gut metabolic function. Synthetic biology has also enabled the design of modular therapeutic strains, which are capable of responding to disease-specific signals by releasing bioactives only in the presence of pathogenic metabolites to reduce off-target effects. Interestingly, engineered microbiota can be combined with defined consortia frameworks to create hybrid therapeutics with both predictable composition and programmable functions[108].

Postbiotics and targeted metabolites

Postbiotics are non-viable microbial products such as SCFAs, bacteriocins, and bioactive peptides, which are increasingly recognized as potential independent or adjunctive therapies for rCDI[121]. It has been suggested that delivering key metabolic end-products without introducing live organisms may help avoid safety concerns in immunocompromised patients[122]. Accordingly, studies reported that SCFAs, such as butyrate, can promote epithelial barrier repair and suppress inflammatory signaling cascades, potentially inhibiting *C. difficile* growth[123]. On the other hand, targeted delivery of bile acid derivatives that restore secondary bile acid pools can directly inhibit *C. difficile* spore germination, which represents a critical functional outcome of successful FMT[14,123]. Certain bacteriocins, including thuricin CD and nisin variants, exhibit potent narrow-spectrum activity against *C. difficile* with minimal disruption to the surrounding microbiota[108,124]. Of note, engineered bacterio-

cin-producing strains may deliver these molecules directly into the gut to provide localized sustained activity. Furthermore, bacteriocins may be deployed alongside defined microbial consortia to enhance competitive exclusion and prevent post-treatment recolonization by *C. difficile*.

PHAGE THERAPY

Phage therapy offers a precision antimicrobial strategy by selectively lysing *C. difficile* strains without depleting beneficial taxa. Several lytic phages targeting diverse ribotypes have been identified, with *in vitro* studies demonstrating strain-specific bactericidal activity and potential synergy with antibiotic or microbiota-restoring treatments[125]. Although the majority of naturally isolated *C. difficile* phages are benign and belong to the Myoviridae or Siphoviridae families, advances in isolation techniques and synthetic biology are accelerating the discovery or engineering of strictly lytic candidates[126,127]. A complementary approach involves phage-derived endolysins, which are modular enzymes that degrade the bacterial cell wall with high specificity[128]. For example, endolysins such as CD27L derived from phage phiCD27 can lyse a broad spectrum of *C. difficile* strains, including hypervirulent ribotype 027, while sparing commensal species to avoid gut dysbiosis[126,129]. Interestingly, these enzymes can also disrupt biofilms and retain bacteriolytic activity under physiological conditions. Recent advances in metagenomic technologies can allow the discovery of novel *C. difficile*-specific phages and endolysins directly from human fecal viromes, which can bypass the need to culture the target organism[130]. Furthermore, innovative delivery platforms, such as encapsulation systems to enhance gastrointestinal stability, engineered phages with broader host ranges, and designed endolysin fusion proteins, are under investigation[131,132]. Thus, phage-based therapeutics can be considered a strongly promising addition to the therapeutic arsenal against rCDI.

Challenges, Risks, and Controversies

Despite high efficacy in preventing rCDI, FMT carries important clinical and regulatory challenges that should be considered in clinical practice. Most patients experience transient adverse effects, including abdominal discomfort, bloating, diarrhea, or low-grade fever; yet severe complications such as bacteremia, sepsis, or exacerbation of comorbidities have been reported, particularly in vulnerable hosts[133,134]. Pathogen transmission is a major concern, as documented cases showed transmission of extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* that led to fatal sepsis in an immunocompromised patient[135], ESBL-producing *Klebsiella pneumoniae* in a renal transplant recipient[136], shedding of norovirus gastroenteritis from asymptomatic donor[137], and FDA-reported incidents involving Shiga toxin–producing *E. coli*[138]. In response to transmission events, agencies such as the FDA and EMA have reinforced guidance, mandating MDRO screening, molecular testing for enteric pathogens, and temporary donor exclusion during outbreaks[71]. Therefore, careful assessments are advised for individuals with immunosuppression, recent hospitalization, central venous catheters, or concurrent broad-spectrum antibiotics, conditions in which donor-strain engraftment may be delayed, and susceptibility to translocation increased. While these measures reduce risk, they also increase costs and logistical complexity for stool banks and treatment centers[139].

The success of FMT depends on both donor microbiome composition and the recipient's factors, including diet, medications, and underlying health conditions. In some patient groups, the transplanted microbiome remains functionally stable over time, while in others, diversity and resilience gradually decline[140]. Differences between donors remain a serious obstacle to reproducibility, as they affect how quickly and effectively donor microbes establish themselves and restore key metabolic pathways. When it comes to treatment failure, mounting evidence suggests that pre-treatment with low microbial diversity and a marked loss of butyrate-producing Firmicutes, like *Roseburia*, *Oscillospira*, and *Fusicatenibacter*, can be related to limited outcomes, characterized by weak donor colonization and persistently low alpha diversity post-FMT[49]. Similarly, donors with low microbial diversity have been associated with reduced patient response rates[37]. Additionally, procedural variables, which include homogenization, cryopreservation, and delivery route, can influence microbial viability and community structure post-FMT[140]. Multi-donor pooling may help overcome the shortcomings of an individual donor's microbiome, but it also increases the risk of exposing recipients to a wider range of potential pathogens during regulatory efforts[140]. The ab-

sence of universally accepted standards for screening, microbiome characterization, product formulation, and quality control continues to complicate multicenter trials and harmonized regulation.

Finally, as the long-term safety of FMT is not well characterized, open questions exist about ecological stability, metabolic and immune remodeling, and possible neoplastic risk. Studies have shown that the transferred microbial communities *via* FMT can remain in the gut for extended periods and influence the host's metabolic and immune functions beyond preventing CDI[140]. Furthermore, the potential transfer of latent traits that encompass antibiotic resistance genes or virulence factors remains a serious unresolved concern, which may be activated by future host or environmental pressures[133]. The uncertainties highlight the need for long-term surveillance of FMT recipients and systematic monitoring of microbiome composition, functional capacity, and host health outcomes to define the durability of therapeutic benefits and to identify potential late adverse effects.

CONCLUSIONS

Access to standardized microbiome FMT procedures remains uneven worldwide due to regulatory heterogeneity, the scarcity of accredited stool banks, high donor-screening costs, and limited cold-chain and processing infrastructure. While current FMT practice favors universal high-diversity donors, inter-individual differences in microbial composition, metabolic capacity, and immunomodulatory potential may result in an effective donor for one recipient while causing a suboptimal outcome in another. In this case, defined microbial consortia offer scalable alternatives to donor-derived FMT, potentially reducing reliance on large donor programs. On the other hand, targeted donor-recipient matching to address specific deficiencies, such as low butyrate-producing Firmicutes or depleted secondary bile-acid producers, could accelerate engraftment and functional recovery. Foundational parameters, including optimal donor criteria, dosing frequency, and delivery routes for certain patient subgroups, remain to be determined. In addition, high-resolution profiling techniques such as shotgun metagenomics, targeted metabolomics, and microbial transcriptomics enable detailed characterization of both taxonomic and functional microbiota landscapes, guiding therapy choice and timing. Profiles showing severe diversity loss, opportunist dominance, or depletion of keystone taxa may warrant earlier FMT rather than prolonged antibiotic use. Also, post-FMT surveillance can identify engraftment failure or instability; for instance, persistent Enterobacteriaceae dominance or incomplete restoration of secondary bile-acid metabolism may represent recurrence and prompt retreatment or adjunctive therapy. Integrating multi-omics data that includes host genetics and immune profiling, with artificial intelligence (AI) can result in designing predictive patterns and *in silico* networks, which inform patient stratification, forecast microbiome stability, and guide the design of synthetic microbial consortia that replicate beneficial functions while reducing transmission risks. In addition, critical research priorities include identifying validated biomarkers for patient selection and response prediction, conducting large, multicenter, longitudinal studies to determine long-term safety and ecological stability, and systematically evaluating combination strategies, such as FMT with bacteriophages, targeted metabolites, or engineered probiotics, to improve the durability of remission in CDI patients. Further, robust cost-effectiveness analyses will be essential to inform reimbursement frameworks and ensure equitable global access to microbiome-based therapeutics.

Conflicts of Interest

The authors declare no conflicts of interest.

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Authors' Contributions

MA contributed to the literature review and drafted the manuscript. MRZ critically edited the manuscript. AY designed the study, conceptualized the research, administered the project, and critically edited the manuscript. All authors read and approved the final version.

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REFERENCES

1. Dop D, Marcu IR, Padureanu V, Caragea DC, Padureanu R, Niculescu S-A, Niculescu CE. Clostridium difficile infection in pediatric patients. Biomed Rep 2024; 20: 1-8.
2. Inghammar M, Svanström H, Voldstedlund M, Melbye M, Hviid A, Mølbak K, Pasternak B. Proton-Pump Inhibitor Use and the Risk of Community-Associated Clostridium difficile Infection. Clin Infect Dis 2021; 72: e1084-e1089.
3. Álvarez-Villalobos NA, Ruiz-Hernandez FG, Méndez-Arellano AC, Azamar-Márquez JM, Camacho-Ortiz A. Epidemiologic profile of community-acquired Clostridioides difficile infections: a systematic review and meta-analysis. Epidemiol Infect 2025; 153: e46.
4. Liu Y, Dai M, Zhang K, Zhang L, Lin B, Chen K, Wang H, Gu Z, Yu Y, Wang Y. Risk of Clostridioides difficile infection following different antibiotics: insights from multi-source medical data. Int J Antimicrob Agents 2024; 64: 107288.
5. Beom JS, Park MS, Seol DG, Moon MK, Ahn HC. Analysis of Risk Factors and Evaluation of Medication Use Affecting Clostridioides Difficile Infections (CDIs) in Adults in a Single Tertiary Hospital. Journal of Korean Society of Health-System Pharmacists 2024; 41: 237-252.
6. Ghioldiş AC, Sârbu V, Pundiche M, Dan C, Butelchin C, Olteanu C, Popescu RC. Clostridium Difficile Infection in Rectal Cancer Patients after Diverted Loop Ileostomy Closure. Chirurgia (Bucur) 2024; 119: 36-43.
7. Chitapanarux T, Wiracha U, Winichakoon P, Salee P, Traisathit P. Efficacy and safety of Saccharomyces boulardii as adjunct therapy with Vancomycin in treating Clostridioides difficile infection: A randomized controlled trial. Sci Rep 2025; 15: 19326.
8. Figueroa I, Johnson S, Sambol SP, Goldstein EJ, Citron DM, Gerding DN. Relapse versus reinfection: recurrent Clostridium difficile infection following treatment with fidaxomicin or vancomycin. Clin Infect Dis 2012; 55 Suppl 2: S104-S109.
9. Sulaiman JE, Thompson J, Qian Y, Vivas EI, Diener C, Gibbons SM, Safdar N, Venturelli OS. Elucidating human gut microbiota interactions that robustly inhibit diverse Clostridioides difficile strains across different nutrient landscapes. Nat Commun 2024; 15: 7416.
10. Giacobbe DR, Vena A, Falcone M, Menichetti F, Bassetti M. Fidaxomicin for the treatment of Clostridioides difficile infection in adult patients: an update on results from randomized controlled trials. Antibiotics 2022; 11: 1365.
11. Orenstein R. The Role of Microbiome-Based Therapeutics in Clostridioides difficile Infection: Durable, Long-Term Results of RBX2660. Infect Dis Ther 2023; 12: 1-7.
12. Oneto C, Khanna S. Prescription Microbiome Therapeutic for Recurrent Clostridioides difficile Infection: Fecal Microbiota Live-jslm. Am J Gastroenterol 2024; 119: S16-S21.
13. Mehta N, Little K, Woodworth MH, Goodenough D, Dhonau R, Fridkin SK. Evaluating Disparities in Recurrent Clostridioides difficile Infection and Fecal Microbiota Transplant Treatment Using Geospatial and Social Vulnerability Analytic Tools. Gastroenterology 2025; 169: 771-775.e1.
14. McMillan AS, Theriot CM. Bile acids impact the microbiota, host, and C. difficile dynamics providing insight into mechanisms of efficacy of FMTs and microbiota-focused therapeutics. Gut Microbes 2024; 16: 2393766.
15. Azimirad M, Jo Y, Kim MS, et al. Alterations and Prediction of Functional Profiles of Gut Microbiota After Fecal Microbiota Transplantation for Iranian Recurrent Clostridioides difficile Infection with Underlying Inflammatory Bowel Disease: A Pilot Study. J Inflamm Res 2022; 15: 105-116.
16. Minkoff NZ, Aslam S, Medina M, Tanner-Smith EE, Zackular JP, Acra S, Nicholson MR, Imdad A. Fecal microbiota transplantation for the treatment of recurrent Clostridioides difficile (Clostridium difficile). Cochrane Database Syst Rev 2023; 4: CD013871.
17. Khoruts A, Staley C, Sadowsky MJ. Faecal microbiota transplantation for Clostridioides difficile: mechanisms and pharmacology. Nat Rev Gastroenterol Hepatol 2021; 18: 67-80.
18. Seekatz AM, Safdar N, Khanna S. The role of the gut microbiome in colonization resistance and recurrent Clostridioides difficile infection. Ther Adv Gastroenterol 2022; 15: 17562848221134396.
19. Vasilescu IM, Chifiriuc MC, Pircalabioru GG, Filip R, Bolocan A, Lazăr V, Diţu LM, Bleotu C. Gut Dysbiosis and Clostridioides difficile Infection in Neonates and Adults. Front Microbiol 2022; 12: 651081.
20. Nibbering B, Gerding DN, Kuijper EJ, Zwittink RD, Smits WK. Host Immune Responses to Clostridioides difficile: Toxins and Beyond. Front Microbiol 2021; 12: 804949.
21. Peritore-Galve FC, Shupe JA, Cave RJ, Childress KO, Washington MK, Kuehne SA, Lacy DB. Glucosyltransferase-dependent and independent effects of Clostridioides difficile toxins during infection. PLoS Pathog 2022; 18: e1010323.

22. Spigaglia P. Clostridioides difficile and gut microbiota: from colonization to infection and treatment. Pathogens 2024; 13: 646.
23. Wu Z, Xu Q, Gu S, Chen Y, Lv L, Zheng B, Wang Q, Wang K, Wang S, Xia J, Yang L, Bian X, Jiang X, Zheng L, Li L. Akkermansia muciniphila Ameliorates Clostridioides difficile Infection in Mice by Modulating the Intestinal Microbiome and Metabolites. Front Microbiol 2022; 13: 841920.
24. Dicks LM. Biofilm formation of Clostridioides difficile, Toxin Production and Alternatives to Conventional Antibiotics in the Treatment of CDI. Microorganisms 2023; 11: 2161.
25. Feuerstadt P, Theriault N, Tillotson G. The burden of CDI in the United States: a multifactorial challenge. BMC Infect Dis 2023; 23: 132.
26. Qutub M, Tatode A, Hussain UM, Premchandani T, Taksande J, Umekar M, Thakre D. Deciphering the Structural and Functional Paradigms of Clostridioides difficile Toxins TcdA and TcdB. Bacteria 2025; 4: 21.
27. Huang JY, Wang N, Wang JY, Zuo HC, Li J, Zhao Y. Analysis of clinical characteristics and risk factors of recurrent Clostridioides difficile infection in children. Front Pediatr 2025; 13: 1571199.
28. Guh AY, Li R, Korhonen L, Winston LG, Parker E, Czaja CA, Johnston H, Basiliere E, Meek J, Olson D, Fridkin SK, Wilson LE, Perlmutter R, Holzbauer SM, D'Heilly P, Phipps EC, Flores KG, Dumyati GK, Pierce R, Ocampo VLS, Wilson CD, Watkins JJ, Gerding DN, McDonald LC. Characteristics of Patients With Initial Clostridioides difficile Infection (CDI) That Are Associated With Increased Risk of Multiple CDI Recurrences. Open Forum Infect Dis 2024; 11: ofae127.
29. Gazzola A, Panelli S, Corbella M, Merla C, Comandatore F, De Silvestri A, Piralla A, Zuccaro V, Bandi C, Marone P, Cambieri P. Microbiota in Clostridioides difficile-Associated Diarrhea: Comparison in Recurrent and Non-Recurrent Infections. Biomedicines 2020; 8: 335.
30. Eeuwijk J, Ferreira G, Yarzabal JP, Robert-Du Ry van Beest Holle M. A systematic literature review on risk factors for and timing of Clostridioides difficile infection in the United States. Infectious Diseases and Therapy 2024; 13: 273-298.
31. Tricotel A, Antunes A, Wilk A, Dombrowski S, Rinta-Kokko H, Andersson FL, Ghosh S. Epidemiological and clinical burden of Clostridioides difficile infections and recurrences between 2015– 2019: the RECUR Germany study. BMC Infectious Diseases 2024; 24: 357.
32. Finn E, Andersson FL, Madin-Warburton M. Burden of Clostridioides difficile infection (CDI) - a systematic review of the epidemiology of primary and recurrent CDI. BMC Infect Dis 2021; 21: 456.
33. Wang D, Dong D, Wang C, Cui Y, Jiang C, Ni Q, Su T, Wang G, Mao E, Peng Y. Risk factors and intestinal microbiota: Clostridioides difficile infection in patients receiving enteral nutrition at Intensive Care Units. Crit Care 2020; 24: 426.
34. Massironi S, Viganò C, Palermo A, Pirola L, Mulinacci G, Allocca M, Peyrin-Biroulet L, Danese S. Inflammation and malnutrition in inflammatory bowel disease. Lancet Gastroenterol Hepatol 2023; 8: 579-590.
35. Yadegar A, Bar-Yoseph H, Monaghan TM, Pakpour S, Severino A, Kuijper EJ, Smits WK, Terveer EM, Neupane S, Nabavi-Rad A, Sadeghi J, Cammarota G, Ianiro G, Nap-Hill E, Leung D, Wong K, Kao D. Fecal microbiota transplantation: current challenges and future landscapes. Clin Microbiol Rev 2024; 37: e0006022.
36. Fitzpatrick F, Brennan R, van Prehn J, Skally M, Brady M, Burns K, Rooney C, Wilcox MH. European Practice for CDI Treatment. Adv Exp Med Biol 2024; 1435: 57-84.
37. Hou S, Yu J, Li Y, Zhao D, Zhang Z. Advances in Fecal Microbiota Transplantation for Gut Dysbiosis-Related Diseases. Adv Sci (Weinh) 2025; 12: e2413197.
38. Koppenol E, Terveer EM, Vendrik KE, et al. Fecal microbiota transplantation is associated with improved aspects of mental health of patients with recurrent Clostridioides difficile infections: effect of FMT on affect in rCDI patients. J Affect Disord Rep 2022; 9: 100355.
39. Deepti I, Chettri B, Mehra A, Pinheiro AM, Ravi R. Faecal microbiota transplantation for recurrent Clostridiodes difficile infection & its global regulatory landscape. Indian J Med Res 2025; 161: 113-119.
40. Ianiro G, Bibbò S, Porcari S, Settanni CR, Giambò F, Curta AR, Quaranta G, Scaldaferri F, Masucci L, Sanguinetti M, Gasbarrini A, Cammarota G. Fecal microbiota transplantation for recurrent C. difficile infection in patients with inflammatory bowel disease: experience of a large-volume European FMT center. Gut Microbes 2021; 13: 1994834.
41. Porcari S, Severino A, Rondinella D, Bibbò S, Quaranta G, Masucci L, Maida M, Scaldaferri F, Sanguinetti M, Gasbarrini A, Cammarota G, Ianiro G. Fecal microbiota transplantation for recurrent Clostridioides difficile infection in patients with concurrent ulcerative colitis. J Autoimmun 2023; 141: 103033.
42. Porcari S, Baunwall SMD, Occhionero AS, Ingrosso MR, Ford AC, Hvas CL, Gasbarrini A, Cammarota G, Ianiro G. Fecal microbiota transplantation for recurrent C. difficile infection in patients with inflammatory bowel disease: A systematic review and meta-analysis. J Autoimmun 2023; 141: 103036.
43. Urbonas T, Petrauskas D, Kiudelis V, Jonaitis L, Skieceviciene J, Gedgaudas R, Kiudeliene E, Valantiene I, Zykus R, Varkalaite G, Inciuraite R, Trapenske E, Kulokiene U, Jonaitis P, Ramonaite R, Velickiene J, Zvirbliene A, Morkunas E, Kuliaviene I, Sumskiene J, Adamonis K, Macas A, Kupcinskiene K, Lukosiene L, Janciauskas D, Poskiene L, Vitkauskiene A, Ianiro G, Gasbarrini A, Kiudelis G, Kupcinskas J. Fecal Microbiome Transplantation for Recurrent CDI: Treatment Efficacy and Safety with Oral Capsules. J Gastrointestin Liver Dis 2025; 34: 199-204.
44. Ali H, Khurana S, Ma W, Peng Y, Jiang ZD, DuPont H, Zhang HC, Thomas AS, Okhuysen P, Wang Y. Safety and efficacy of fecal microbiota transplantation to treat and prevent recurrent Clostridioides difficile in cancer patients. J Cancer 2021; 12: 6498-6506.
45. Berry P, Tariq R, Pardi DS, Khanna S. Effectiveness and Safety of Fecal Microbiota Transplantation for Recurrent Clostridioides difficile Infection in Immunocompromised Patients. Clin Gastroenterol Hepatol 2026; 24: 949-973.

46. Popa D, Neamtu B, Mihalache M, Boicean A, Banciu A, Banciu DD, Moga DFC, Birlutiu V. Fecal Microbiota Transplant in Severe and Non-Severe Clostridioides difficile Infection. Is There a Role of FMT in Primary Severe CDI? J Clin Med 2021; 10: 5822.
47. Paaske SE, Baumwall SMD, Rubak T, Birn FH, Rågård N, Kelsen J, Hansen MM, Svenningsen L, Krarup AL, Fernis CMC, Neumann A, Lødrup AB, Glerup H, Vinter-Jensen L, Helms M, Erikstrup LT, Grosen AK, Mikkelsen S, Erikstrup C, Dahlerup JF, Hvas CL. Real-world Effectiveness of Fecal Microbiota Transplantation for First or Second Clostridioides difficile Infection. Clin Gastroenterol Hepatol 2025; 23: 602-611.e8.
48. Bibbò S, Settanni CR, Porcari S, Bocchino E, Ianiro G, Cammarota G, Gasbarrini A. Fecal Microbiota Transplantation: Screening and Selection to Choose the Optimal Donor. J Clin Med 2020; 9: 1757.
49. Tian H, Cui J, Ye C, Zhao J, Yang B, Xu Y, Ji S, Wang L, Lv X, Ma C, Zhou S, Li N, Wang X, Qin H, Chen Q. Depletion of butyrate-producing microbes of the Firmicutes predicts nonresponse to FMT therapy in patients with recurrent Clostridium difficile infection. Gut Microbes 2023; 15: 2236362.
50. Agrawal M, Aroniadis OC, Brandt LJ, Kelly C, Freeman S, Surawicz C, Broussard E, Stollman N, Giovanelli A, Smith B, Yen E, Trivedi A, Hubble L, Kao D, Borody T, Finlayson S, Ray A, Smith R. The Long-term Efficacy and Safety of Fecal Microbiota Transplant for Recurrent, Severe, and Complicated Clostridium difficile Infection in 146 Elderly Individuals. J Clin Gastroenterol 2016; 50: 403-407.
51. Kachlíková M, Sabaka P, Koščálová A, Bendžala M, Dovalová Z, Stankovič I. Comorbid status and the faecal microbial transplantation failure in treatment of recurrent Clostridioides difficile infection - pilot prospective observational cohort study. BMC Infect Dis 2020; 20: 52.
52. Luo Y, Tixier EN, Grinspan AM. Fecal Microbiota Transplantation for Clostridioides difficile in High-Risk Older Adults Is Associated with Early Recurrence. Dig Dis Sci 2020; 65: 3647-3651.
53. Baunwall SMD, Andreasen SE, Hansen MM, Kelsen J, Høyer KL, Rågård N, Eriksen LL, Støy S, Rubak T, Damsgaard EMS, Mikkelsen S, Erikstrup C, Dahlerup JF, Hvas CL. Faecal microbiota transplantation for first or second Clostridioides difficile infection (EarlyFMT): a randomised, double-blind, placebo-controlled trial. Lancet Gastroenterol Hepatol 2022; 7: 1083-1091.
54. Hocking L, Ianiro G, Leong RW, Iqbal T, Kao D, Cabling M, Stockwell S, Romanelli RJ, Marjanovic S. Faecal microbiota transplantation for recurrent C. difficile infections: challenges and improvement opportunities for clinical practice and healthcare systems. Aliment Pharmacol Ther 2023; 57: 549-564.
55. Rajpal RD. The Role of Fecal Microbiota Transplantation in Treating Clostridium difficile Infection and Beyond. Scholar's Digest: Journal of Gastroenterology 2025; 1: 132-145.
56. Allegretti JR, Kassam Z, Osman M, Budree S, Fischer M, Kelly CR. The 5D framework: a clinical primer for fecal microbiota transplantation to treat Clostridium difficile infection. Gastrointest Endosc 2018; 87: 18-29.
57. Liu H, Wei Y, Jiang P, Fan S, Zhao Y, Li Z, Wang S, Zhang N, Zhi J, Wei Q, Gu Y, Yang B, Feng N, Wu Y, Liu F. Navigating the decision landscape: understanding interstitial cystitis/bladder pain syndrome patients' motivations and medical support needs for fecal microbiota transplantation: a qualitative research. BMC Complement Med Ther 2025; 25: 268.
58. Hoffmann DE, Javitt GH, Kelly CR, Keller JJ, Baunwall SMD, Hvas CL. Fecal microbiota transplantation: a tale of two regulatory pathways. Gut Microbes 2025; 17: 2493901.
59. Scheeler A. Where Stool is a Drug: International Approaches to Regulating the use of Fecal Microbiota for Transplantation. J Law Med Ethics 2019; 47: 524-540.
60. Jain N, Umar TP, Fahner AF, Gibietis V. Advancing therapeutics for recurrent clostridioides difficile infections: an overview of vowst's FDA approval and implications. Gut Microbes 2023; 15: 2232137.
61. Kelly CR, Schoenfeld P. Donor Stool Product for FMT Decreases Recurrent Clostridioides difficile Infection: RBX2660 Is the First FDA-Approved Live Biotherapeutic Product. Evidence-Based GI 2022. Available from: https://gi.org/journals-publications/ebgi/kelly_schoenfeld_dec2022/.
62. Elendu C, Omeludike EK, Aregbesola ET, Mordi P, Blewusi GS, Ogidan AO, Okeke NG, Obidigbo BT, Asini AO, Ubi ES, Etakewen PO, Amahalu CA, Foncham RF, Gana LT, Onwe CJ, Ojeabuo OF, Ojo AO, Ikeaba CS, Opara NC. Fecal microbiota transplantation as a therapeutic modality for recurrent Clostridioides difficile infection: reviewing efficacy, safety, mechanisms of action, and outcomes. Ann Med Surg (Lond) 2025; 87: 5829-5850.
63. Steube A, Stallhofer J, Stallmach A. Fecal microbiota transfer to treat ulcerative colitis: Medical and legal challenges. Front Gastroenterol (Lausanne) 2023; 2: 1161610.
64. Hvas CL, Keller J, Baunwall SD, Edwards LA, Ianiro G, Kupcinskas J, Link A, Mullish BH, Satokari R, Terveer E, Vehreshild MJG. European academic faecal microbiota transplantation (EURFMT) network: improving the safety and quality of microbiome therapies in Europe. Microb Health Dis 2023; 5: e954.
65. Baunwall SMD, Terveer EM, Dahlerup JF, Erikstrup C, Arkkila P, Vehreschild MJ, Ianiro G, Gasbarrini A, Sokol H, Kump PK, Satokari R, De Looze D, Vermeire S, Nakov R, Brezina J, Helms M, Kjeldsen J, Rode AA, Kousgaard SJ, Alric L, Trang-Poisson C, Scanzi J, Link A, Stallmach A, Kupcinskas J, Johnsen PH, Garborg K, Rodríguez ES, Serrander L, Brummer RJ, Galpérine KT, Goldenberg SD, Mullish BH, Williams HR, Iqbal TH, Ponsioen C, Kuijper EJ, Cammarota G, Keller JJ, Hvas CL. The use of Faecal Microbiota Transplantation (FMT) in Europe: A Europe-wide survey. Lancet Reg Health Eur 2021; 9: 100181.
66. McCune VL, Quraishi MN, Manzoor S, Moran CE, Banavathi K, Steed H, Massey DCO, Trafford GR, Iqbal TH, Hawkey PM. Results from the first English stool bank using faecal microbiota transplant as a medicinal product for the treatment of Clostridioides difficile infection. EClinicalMedicine 2020; 20: 100301.
67. Edelstein CA, Kassam Z, Daw J, Smith MB, Kelly CR. The regulation of fecal microbiota for transplantation: An international perspective for policy and public health. Clinical Research and Regulatory Affairs 2015; 32: 99-107.
68. Haifer C, Kelly CR, Paramsothy S, Andresen D, Papanicolas LE, McKew GL, Borody TJ, Kamm M, Costello SP, An-

drews JM, Begun J, Chan HT, Connor S, Ghaly S, Johnson PD, Lemberg DA, Paramsothy R, Redmond A, Sheorey H, van der Poorten D, Leong RW. Australian consensus statements for the regulation, production and use of faecal microbiota transplantation in clinical practice. Gut 2020; 69: 801-810.
69. Zou B, Liu SX, Li XS, He JY, Dong C, Ruan ML, Xu L, Bai T, Huang ZH, Shu SN. Long-term safety and efficacy of fecal microbiota transplantation in 74 children: A single-center retrospective study. Front Pediatr 2022; 10: 964154.
70. Wilson BC, Vatanen T, Cutfield WS, O'Sullivan JM. The Super-Donor Phenomenon in Fecal Microbiota Transplantation. Front Cell Infect Microbiol 2019; 9: 2.
71. Ng RW, Dharmaratne P, Wong S, Hawkey P, Chan P, Ip M. Revisiting the donor screening protocol of faecal microbiota transplantation (FMT): a systematic review. Gut 2024; 73: 1029-1031.
72. Mikail M, O'Doherty KC, Poutanen SM, Hota SS. Ethical implications of recruiting universal stool donors for faecal microbiota transplantation. Lancet Infect Dis 2020; 20: e44-e49.
73. Silva R, Dinis L, Peris A, Novais L, Calhau C, Pestana D, Marques C. Fecal microbiota transplantation-could stool donors' and receptors' diet be the key to future success? Front Gastroenterol (Lausanne) 2023; 2: 1270899.
74. Tariq R, Weatherly R, Kammer P, Pardi DS, Khanna S. Donor Screening Experience for Fecal Microbiota Transplantation in Patients With Recurrent C. difficile Infection. J Clin Gastroenterol 2018; 52: 146-150.
75. Woodworth MH, Carpentieri C, Sitchenko KL, Kraft CS. Challenges in fecal donor selection and screening for fecal microbiota transplantation: A review. Gut Microbes 2017; 8: 225-237.
76. Karimi M, Shirsalimi N, Hashempour Z, Salehi Omran H, Sedighi E, Beigi F, Mortezazadeh M. Safety and efficacy of fecal microbiota transplantation (FMT) as a modern adjuvant therapy in various diseases and disorders: a comprehensive literature review. Front Immunol 2024; 15: 1439176.
77. Liu Q, Zuo T, Lu W, Yeoh YK, Su Q, Xu Z, Tang W, Yang K, Zhang F, Lau LHS, Lui RNS, Chin ML, Wong R, Cheung CP, Zhu W, Chan PKS, Chan FKL, Lui GC, Ng SC. Longitudinal Evaluation of Gut Bacteriomes and Viromes after Fecal Microbiota Transplantation for Eradication of Carbapenem-Resistant Enterobacteriaceae. mSystems 2022; 7: e0151021.
78. Sadek M, Poirel L, Nordmann P. Optimal detection of extended-spectrum β-lactamase producers, carbapenemase producers, polymyxin-resistant Enterobacterales, and vancomycin-resistant enterococci from stools. Diagn Microbiol Infect Dis 2020; 96: 114919.
79. Gibbons SJ. Development of a high-throughput approach for testing optimal fecal microbiota transplant material [thesis]. London (ON): Western University; 2023. Available from: https://ir.lib.uwo.ca/etd/9509/.
80. Reigadas E, Olmedo M, Valerio M, Vázquez-Cuesta S, Alcalá L, Marín M, Muñoz P, Bouza E. Fecal microbiota transplantation for recurrent Clostridium difficile infection: Experience, protocol, and results. Rev Esp Quimioter 2018; 31: 411-418.
81. Zhang S, Chen Q, Kelly CR, Kassam Z, Qin H, Li N; Shanghai Tongji FMT Working Group; Tian H, Yang B, Zhao D, Ye C, Lin Z, Cui J, Zhou S, Chen X, Lv X, Yang R. Donor Screening for Fecal Microbiota Transplantation in China: Evaluation of 8483 Candidates. Gastroenterology 2022; 162: 966-968.e3.
82. Wang JW, Kuo CH, Kuo FC, Wang YK, Hsu WH, Yu FJ, Hu HM, Hsu PI, Wang JY, Wu DC. Fecal microbiota transplantation: Review and update. J Formos Med Assoc 2019; 118: S23-S31.
83. Ianiro G, Masucci L, Quaranta G, Simonelli C, Lopetuso LR, Sanguinetti M, Gasbarrini A, Cammarota G. Randomised clinical trial: faecal microbiota transplantation by colonoscopy plus vancomycin for the treatment of severe refractory Clostridium difficile infection-single versus multiple infusions. Aliment Pharmacol Ther 2018; 48: 152-159.
84. Tixier EN, Verheyen E, Ungaro RC, Grinspan AM. Faecal microbiota transplant decreases mortality in severe and fulminant Clostridioides difficile infection in critically ill patients. Aliment Pharmacol Ther 2019; 50: 1094-1099.
85. Marcella C, Cui B, Kelly CR, Ianiro G, Cammarota G, Zhang F. Systematic review: the global incidence of faecal microbiota transplantation-related adverse events from 2000 to 2020. Aliment Pharmacol Ther 2021; 53: 33-42.
86. Gundacker ND, Tamhane A, Walker JB, Morrow CD, Rodriguez JM. Comparative effectiveness of faecal microbiota transplant by route of administration. J Hosp Infect 2017; 96: 349-352.
87. Varga A, Kocsis B, Sipos D, Kása P, Vigvári S, Pál S, Dembrovszky F, Farkas K, Péterfi Z. How to Apply FMT More Effectively, Conveniently and Flexible - A Comparison of FMT Methods. Front Cell Infect Microbiol 2021; 11: 657320.
88. Ramai D, Zakhia K, Fields PJ, Ofosu A, Patel G, Shahnazarian V, Lai JK, Dhaliwal A, Reddy M, Chang S. Fecal Microbiota Transplantation (FMT) with Colonoscopy Is Superior to Enema and Nasogastric Tube While Comparable to Capsule for the Treatment of Recurrent Clostridioides difficile Infection: A Systematic Review and Meta-Analysis. Dig Dis Sci 2021; 66: 369-380.
89. Li Y, Yang Y, Yang N, Wu Q, Yang J, Guo J, Zhang H. Recent advances in fecal microbiota transplantation for Clostridium difficile infection-associated diarrhea after kidney transplantation. Front Microbiomes 2024; 3: 1409967.
90. Navalkele BD, Polistico J, Sandhu A, Awali R, Krishna A, Chandramohan S, Tillotson G, Chopra T. Clinical outcomes after faecal microbiota transplant by retention enema in both immunocompetent and immunocompromised patients with recurrent Clostridioides difficile infections at an academic medical centre. J Hosp Infect 2020; 106: 643-648.
91. Chehri M, Christensen AH, Halkjær SI, Günther S, Petersen AM, Helms M. Case series of successful treatment with fecal microbiota transplant (FMT) oral capsules mixed from multiple donors even in patients previously treated with FMT enemas for recurrent Clostridium difficile infection. Medicine 2018; 97: e11706.
92. Furuya-Kanamori L, Doi SA, Paterson DL, Helms SK, Yakob L, McKenzie SJ, Garborg K, Emanuelsson F, Stollman N, Kronman MP, Clark J, Huber CA, Riley TV, Clements AC. Upper Versus Lower Gastrointestinal Delivery for Transplantation of Fecal Microbiota in Recurrent or Refractory Clostridium difficile Infection: A Collaborative Analysis of Individual Patient Data From 14 Studies. J Clin Gastroenterol 2017; 51: 145-150.
93. Verdier C, Denis S, Gasc C, Boucinha L, Uriot O, Delmas D, Dore J, Le Camus C, Schwintner C, Blanquet-Diot S. An Oral FMT Capsule as Efficient as an Enema for Microbiota Reconstruction Following Disruption by Antibiotics, as Assessed in an In Vitro Human Gut Model. Microorganisms 2021; 9: 358.

94. Zain NMM, Ter Linden D, Lilley AK, Royall PG, Tsoka S, Bruce KD, Mason AJ, Hatton GB, Allen E, Goldenberg SD, Forbes B. Design and manufacture of a lyophilised faecal microbiota capsule formulation to GMP standards. J Control Release 2022; 350: 324-331.
95. Urbonas T, Ianiro G, Gedgaudas R, Sabanas P, Urba M, Kiudelis V, Kiudelis G, Petkevicius V, Vitkauskiene A, Cammarota G, Gasbarrini A, Kupcinskas J. Fecal Microbiome Transplantation for Recurrent Clostridioides difficile Infection: Treatment Efficacy, Short and Long-term Follow-up Results from Consecutive Case Series. J Gastrointestin Liver Dis 2021; 30: 470-476.
96. van Lingen EE, Baunwall SSMD, Lieberknecht SSC, Benech NN, Ianiro GG, Sokol HH, Gasbarrini AA, Cammarota GG, Eriksen MMK, van der Meulen-de Jong AAE, Terveer EEM, Verspaget HHW, Vehreschild MM, Hvas CCL, Keller JJJ. Short- and long-term follow-up after fecal microbiota transplantation as treatment for recurrent Clostridioides difficile infection in patients with inflammatory bowel disease. Ther Adv Gastroenterol 2023; 16: 17562848231156285.
97. Mintz M, Khair S, Grewal S, LaComb JF, Park J, Channer B, Rajapakse R, Bucobo JC, Buscaglia JM, Monzur F, Chawla A, Yang J, Robertson CE, Frank DN, Li E. Longitudinal microbiome analysis of single donor fecal microbiota transplantation in patients with recurrent Clostridium difficile infection and/or ulcerative colitis. PloS One 2018; 13: e0190997.
98. Brandt LJ, Aroniadis OC, Mellow M, Kanatzar A, Kelly C, Park T, Stollman N, Rohlke F, Surawicz C. Long-term follow-up of colonoscopic fecal microbiota transplant for recurrent Clostridium difficile infection. Am J Gastroenterol 2012; 107: 1079-1087.
99. Zhang F, Zuo T, Yeoh YK, Cheng FWT, Liu Q, Tang W, Cheung KCY, Yang K, Cheung CP, Mo CC, Hui M, Chan FKL, Li CK, Chan PKS, Ng SC. Longitudinal dynamics of gut bacteriome, mycobiome and virome after fecal microbiota transplantation in graft-versus-host disease. Nat Commun 2021; 12: 65.
100. Nooij S, Vendrik KEW, Zwittink RD, Ducarmon QR, Keller JJ, Kuijper EJ, Terveer EM; Netherlands Donor Feces Bank study group. Long-term beneficial effect of faecal microbiota transplantation on colonisation of multidrug-resistant bacteria and resistome abundance in patients with recurrent Clostridioides difficile infection. Genome Med 2024; 16: 37.
101. Aroniadis OC, Brandt LJ, Greenberg A, Borody T, Kelly CR, Mellow M, Surawicz C, Cagle L, Neshatian L, Stollman N, Giovanelli A, Ray A, Smith R. Long-term Follow-up Study of Fecal Microbiota Transplantation for Severe and/or Complicated Clostridium difficile Infection: A Multicenter Experience. J Clin Gastroenterol 2016; 50: 398-402.
102. Di Bella S, Sanson G, Monticelli J, Zerbato V, Principe L, Giuffrè M, Pipitone G, Luzzati R. Clostridioides difficile infection: history, epidemiology, risk factors, prevention, clinical manifestations, treatment, and future options. Clin Microbiol Rev 2024; 37: e0013523.
103. Martinez-Gili L, McDonald JAK, Liu Z, Kao D, Allegretti JR, Monaghan TM, Barker GF, Miguéns Blanco J, Williams HRT, Holmes E, Thursz MR, Marchesi JR, Mullish BH. Understanding the mechanisms of efficacy of fecal microbiota transplant in treating recurrent Clostridioides difficile infection and beyond: the contribution of gut microbial-derived metabolites. Gut Microbes 2020; 12: 1810531.
104. Yadegar A, Pakpoor S, Ibrahim FF, Nabavi-Rad A, Cook L, Walter J, Seekatz AM, Wong K, Monaghan TM, Kao D. Beneficial effects of fecal microbiota transplantation in recurrent Clostridioides difficile infection. Cell Host Microbe 2023; 31: 695-711.
105. Rakotonirina A, Galperine T, Allémann E. Fecal microbiota transplantation: a review on current formulations in Clostridioides difficile infection and future outlooks. Expert Opin Biol Ther 2022; 22: 929-944.
106. Segal JP, Mullish BH, Quraishi MN, Iqbal T, Marchesi JR, Sokol H. Mechanisms underpinning the efficacy of faecal microbiota transplantation in treating gastrointestinal disease. Ther Adv Gastroenterol 2020; 13: 1756284820946904.
107. Millard SA, Vendrov KC, Young VB, Seekatz AM. Host origin of microbiota drives functional recovery and Clostridioides difficile clearance in mice. mBio 2025; 16: e0110825.
108. Ríos Colombo NS, Paul Ross R, Hill C. Synergistic and off-target effects of bacteriocins in a simplified human intestinal microbiome: implications for Clostridioides difficile infection control. Gut Microbes 2025; 17: 2451081.
109. Frisbee AL, Petri WA Jr. Considering the Immune System during Fecal Microbiota Transplantation for Clostridioides difficile Infection. Trends Mol Med 2020; 26: 496-507.
110. Calvigioni M, Mazzantini D, Celandroni F, Ghelardi E. Animal and in vitro models as powerful tools to decipher the effects of enteric pathogens on the human gut microbiota. Microorganisms 2023; 12: 67.
111. Bublitz A, Brauer M, Wagner S, Hofer W, Müsken M, Deschner F, Lesker TR, Neumann-Schaal M, Paul LS, Nübel U, Bartel J, Kany AM, Zühlke D, Bernecker S, Jansen R, Sievers S, Riedel K, Herrmann J, Müller R, Fuchs TM, Strowig T. The natural product chlorotonil A preserves colonization resistance and prevents relapsing Clostridioides difficile infection. Cell Host Microbe 2023; 31: 734-750.e8.
112. Bruno G, Gagliardi A, Oliva A, Trancassini M, Macone A, Cicerone C, D'Abramo A, Iebba V, Auria S, Bonfiglio G, Zingaropoli MA, D'Ettorre G, Badiali D, Vullo V, Corazziari ES, Schippa S. Fecal Microbial Transplantation impact on gut microbiota composition and metabolome, microbial translocation and T-lymphocyte immune activation in recurrent Clostridium difficile infection patients. New Microbiol 2019; 42: 221-224.
113. Lahoud C, Habib T, Kalta D, Dimachkie R, El Sayegh S, Deeb L. Intestinal Microbiota and Fecal Transplantation in Patients with Inflammatory Bowel Disease and Clostridioides difficile: An Updated Literature Review. J Clin Med 2025; 14: 5260.
114. Zuo T, Wong SH, Lam K, et al. Bacteriophage transfer during faecal microbiota transplantation in Clostridium difficile infection is associated with treatment outcome. Gut 2018; 67: 634-643.
115. Soveral LF, Korczaguin GG, Schmidt PS, Nunes IS, Fernandes C, Zárate-Bladés CR. Immunological mechanisms of fecal microbiota transplantation in recurrent Clostridioides difficile infection. World J Gastroenterol 2022; 28: 4762-4772.

116. Zuo T, Wong SH, Cheung CP, Lam K, Lui R, Cheung K, Zhang F, Tang W, Ching JYL, Wu JCY, Chan PKS, Sung JJY, Yu J, Chan FKL, Ng SC. Gut fungal dysbiosis correlates with reduced efficacy of fecal microbiota transplantation in Clostridium difficile infection. Nat Commun 2018; 9: 3663.
117. Jain N, Umar TP, Fahner AF, Gibietis V. Advancing therapeutics for recurrent clostridioides difficile infections: an overview of vowst's FDA approval and implications. Gut Microbes 2023; 15: 2232137.
118. Khanna S, Assi M, Lee C, Yoho D, Louie T, Knapple W, Aguilar H, Garcia-Diaz J, Wang GP, Berry SM, Marion J, Su X, Braun T, Bancke L, Feuerstadt P. 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: 1527-1538.
119. Zhang Y, Saint Fleur A, Feng H. The development of live biotherapeutics against Clostridioides difficile infection towards reconstituting gut microbiota. Gut Microbes 2022; 14: 2052698.
120. Cruz KCP, Enekegho LO, Stuart DT. Bioengineered Probiotics: Synthetic Biology Can Provide Live Cell Therapeutics for the Treatment of Foodborne Diseases. Front Bioeng Biotechnol 2022; 10: 890479.
121. Vinderola G, Sanders ME, Salminen S. The concept of postbiotics. Foods 2022; 11: 1077.
122. Isaac-Bamgboye FJ, Mgbechidinma CL, Onyeaka H, Isaac-Bamgboye IT, Chukwugozie DC. Exploring the Potential of Postbiotics for Food Safety and Human Health Improvement. J Nutr Metab 2024; 2024: 1868161.
123. Wang S, Xiang L, Li F, Deng W, Lv P, Chen Y. Butyrate protects against Clostridium difficile infection by regulating bile acid metabolism. Microbiol Spectr 2023; 11: e0447922.
124. Walsh L, Lavelle A, O'Connor P, Hill C, Ross R. Comparison of fidaxomicin, thuricin CD, vancomycin and nisin highlights the narrow spectrum nature of thuricin CD. Gut Microbes 2024; 16: 2342583.
125. Nale JY, Thanki AM, Rashid SJ, Shan J, Vinner GK, Dowah ASA, Cheng JKJ, Sicheritz-Pontén T, Clokie MRJ. Diversity, Dynamics and Therapeutic Application of Clostridioides difficile Bacteriophages. Viruses 2022; 14: 2772.
126. Fujimoto K, Uematsu S. Phage therapy for Clostridioides difficile infection. Front Immunol 2022; 13: 1057892.
127. Raeisi H, Noori M, Azimirad M, Mohebbi SR, Asadzadeh Aghdaei H, Yadegar A, Zali MR. Emerging applications of phage therapy and fecal virome transplantation for treatment of Clostridioides difficile infection: challenges and perspectives. Gut Pathog 2023; 15: 21.
128. Mondal SI, Draper LA, Ross RP, Hill C. Bacteriophage endolysins as a potential weapon to combat Clostridioides difficile infection. Gut Microbes 2020; 12: 1813533.
129. Cho Y, Park K, Park J, An J, Myung H, Yoon H. Exploring the therapeutic potential of endolysin CD27L_EAD against Clostridioides difficile infection. Int J Antimicrob Agents 2024; 64: 107222.
130. Fujimoto K, Kimura Y, Shimohigoshi M, Satoh T, Sato S, Tremmel G, Uematsu M, Kawaguchi Y, Usui Y, Nakano Y, Hayashi T, Kashima K, Yuki Y, Yamaguchi K, Furukawa Y, Kakuta M, Akiyama Y, Yamaguchi R, Crowe SE, Ernst PB, Miyano S, Kiyono H, Imoto S, Uematsu S. Metagenome Data on Intestinal Phage-Bacteria Associations Aids the Development of Phage Therapy against Pathobionts. Cell Host Microbe 2020; 28: 380-389.e9.
131. Gondil VS, Chhibber S. Bacteriophage and endolysin encapsulation systems: a promising strategy to improve therapeutic outcomes. Front Pharmacol 2021; 12: 675440.
132. Wang M, Deng Z, Li Y, Ma Y, Wang J. Design and characterization of a novel lytic protein against Clostridium difficile. Appl Microbiol Biotechnol 2022; 106: 4511-4521.
133. Sandhu A, Chopra T. Fecal microbiota transplantation for recurrent Clostridioides difficile, safety, and pitfalls. Ther Adv Gastroenterol 2021; 14: 17562848211053105.
134. Yadegar A, Bar-Yoseph H, Monaghan TM, Pakpour S, Severino A, Kuijper EJ, Smits WK, Terveer EM, Neupane S, Nabavi-Rad A, Sadeghi J, Cammarota G, Ianiro G, Nap-Hill E, Leung D, Wong K, Kao D. Fecal microbiota transplantation: current challenges and future landscapes. Clin Microbiol Rev 2024; 37: e0006022.
135. DeFilipp Z, Bloom PP, Torres Soto M, Mansour MK, Sater MRA, Huntley MH, Turbett S, Chung RT, Chen YB, Hohmann EL. Drug-Resistant E. coli Bacteremia Transmitted by Fecal Microbiota Transplant. N Engl J Med 2019; 381: 2043-2050.
136. Grosen AK, Povlsen JV, Lemming LE, Jørgensen SMD, Dahlerup JF, Hvas CL. Faecal Microbiota Transplantation Eradicated Extended-Spectrum Beta-Lactamase-Producing Klebsiella pneumoniae from a Renal Transplant Recipient with Recurrent Urinary Tract Infections. Case Rep Nephrol Dial 2019; 9: 102-107.
137. 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: 1367.
138. Burstiner LS, Silver J, Burstiner LJ, Teymoorian A, Pallav K, Jones D, Owings A, Glover S. Escherichia coli O157: H7 sepsis following fecal microbiota transplant in an IgA-deficient inflammatory bowel disease patient. Gastroenterol Rep (Oxf) 2021; 10: goab041.
139. Rapoport EA, Baig M, Puli SR. Adverse events in fecal microbiota transplantation: a systematic review and meta-analysis. Ann Gastroenterol 2022; 35: 150-163.
140. Rasmussen TS, Mao X, Forster S, Larsen SB, Von Münchow A, Tranæs KD, Brunse A, Larsen F, Mejia JLC, Adamberg S, Hansen AK, Adamberg K, Hansen CHF, Nielsen DS. Overcoming donor variability and risks associated with fecal microbiota transplants through bacteriophage-mediated treatments. Microbiome 2024; 12: 119.