

Fecal microbiota transplantation for recurrent *Clostridioides difficile*, safety, and pitfalls

Avnish Sandhu  and Teena Chopra

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Abstract: *Clostridioides difficile* infection (CDI) is one of the leading causes of hospital-acquired infection attributing to substantial morbidity, mortality, and healthcare cost. Recurrent CDI (rCDI) is common and occurs after effective treatment of first episode. Treatment of rCDI is based on accurate diagnoses, due to difficulty in distinguishing between colonization of *C. difficile* spores or CDI; coronavirus disease 2019 (COVID-19) added to the complexity of diagnoses as both entities can co-occur. It is difficult to eradicate rCDI, and there remains a critical gap regarding treatment of rCDI. The treatment goal of rCDI is to reestablish normal microbiota. Fecal microbiota transplantation (FMT) is suggested as a treatment for second episode of rCDI. Based on the collective evidence of all randomized controlled trials, FMT was reported more efficacious compared with vancomycin or fidaxomicin; however, these trials had limited number of patients and all patients were pre-treated with vancomycin prior to FMT. Furthermore, when comparing various routes of instillation and types of preparation of fecal microbiota, no difference was observed in cure rate. Despite the success rate of FMT, there remains a concern for transmission of infectious agents, such as Gram negative bacteremia or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), adverse events (diarrhea and abdominal pain), and reports of new diagnoses (inflammatory bowel disease, weight gain and irritable bowel syndrome). To lessen the risk of transmissible infections, donor screening should be performed, which includes screening for medical comorbidities and infectious pathogens in blood and feces. Scheduling complexities and reimbursement places an additional roadblock for using FMT. Microbiome-based therapies are being developed to eliminate the logistical challenges related to FMT. Large prospective and placebo-controlled studies are needed to evaluate the efficacy and long-term safety of FMT, so its use can be justified in clinical practice.

Keywords: *Clostridioides difficile*, fecal microbiota transplantation

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Introduction

Clostridioides difficile infection (CDI) is recognized as an urgent public health threat by Centers for Disease Control and Prevention (CDC), contributing to 223,900 hospitalizations, 12,800 associated deaths in the United States, and approximately US\$1 billion in attributable health care cost in 2017.¹ A population-based surveillance study conducted by CDC emerging infection program in 10 sites within United States from 2011 to 2017 reported a 24% decrease in

hospital onset *C. difficile* but found no decrease in community onset or first recurrence of *C. difficile*.²

Recurrent CDI (rCDI) is defined as CDI that relapses after initial successful treatment; rCDI is associated with an annual cost of approximately US\$2.8 billion.^{3,4} Nearly, one in six patients with CDI will experience recurrent infection in the following 2 to 8 weeks.² Patients with rCDI often experience additional recurrences, with reports

Correspondence to:

Teena Chopra
Department of Internal
Medicine, Division of
Infectious Disease, Wayne
State University School of
Medicine, Detroit Medical
Center Detroit, Harper
University Hospital, 3990
John R street, Detroit, MI,
48201, USA
tchopra@med.wayne.edu

Avnish Sandhu
Department of Internal
Medicine, Division of
Infectious Disease, Wayne
State University School of
Medicine, Detroit Medical
Center Detroit, MI, USA

estimating that 50–65% of patients have at least two or more incidence of rCDI.⁵ Increased incidence of rCDI was noted from 2001 to 2012; 1.07 to 3.09 cases per 100,000 person-years.⁶ Recurrent CDI (rCDI) poses a significant treatment challenge, given it is difficult to eradicate and often require escalation in treatment.

Treatment of CDI is based on initial or recurrent episode and degree of severity. Initial episode of nonsevere or severe CDI can be treated with oral vancomycin or fidaxomicin for 10 days; fulminant initial episode of CDI is treated with intravenous metronidazole along with oral and rectal vancomycin.⁷ The first episode of rCDI can be treated with oral vancomycin or fidaxomicin for 10 days, or prolong taper of pulse oral vancomycin.⁷ Second or subsequent rCDI are treated with either prolong taper of pulsed oral vancomycin regimen, fidaxomicin, and vancomycin for 10 days followed by Rifaximin for 20 days, or fecal microbiota transplantation (FMT).⁷

Treatment of rCDI can be further complicated by diagnoses. Recognizing individuals with true rCDI can be challenging given the limitations of diagnostic testing. A common diagnostic test used widely for *C. difficile* diagnosis is nucleic acid amplification testing (NAAT), which is overly sensitive and unable to differentiate between colonization and CDI. Due to this diagnostic dilemma, enzyme immunoassay (EIA) toxin test along with glutamate dehydrogenase (GDH) or NAAT can be used as a part of a multistep algorithm for diagnoses of CDI.⁷ In addition, it is imperative to consider the diagnosis of post-infectious inflammatory bowel syndrome (PI-IBS) for patients that present with persistent diarrhea following CDI treatment. In a retrospective study of 205 post-CDI patients, 25.4% of patients ($n = 52$) developed IBS 6 to 9 months after CDI.^{8,9} Given that both entities (CDI and PI-IBS) present with diarrhea, testing for rCDI should be performed through active toxin rather than NAAT, as NAAT can lead to inaccurate diagnosis of rCDI further leading to unnecessary treatment.^{8,9}

Further complicating the CDI diagnosis is the presence of *C. difficile* coinfection with coronavirus disease 2019 (COVID-19). Clinicians should be aware of this co-infection as both entities can present with diarrhea, as shown by two reports Sandhu *et al.*¹⁰ and Lakkasani *et al.*¹¹ The co-infection was attributed to increased diarrhea and antibacterial

use leading to disruption in immune system, resulting in alteration of gut microbiome perpetuating the ability to activate *C. difficile* spores.^{10,11}

A healthy microbiota protects against colonization of *C. difficile* spores through restoring gut barrier defenses by stimulating mucosal immune system and transforming primary bile acids to secondary bile acids which inhibits *C. difficile* spore germination and growth.^{12,13} It is the vicious cycle of dysbiosis (imbalance of gut bacteria) that causes rCDI.¹² A treatment option to counteract dysbiosis is fecal microbiota transplant (FMT). FMT is a process of harvesting stool from healthy donor and transplanting into the colon of the patient, various routes of delivery can be used (nasogastric, colonoscopy, or capsules). The donor stool microbiota competes with *C. difficile* bacteria in recipient gut, allowing for restoration of secondary bile acids and stimulation of the mucosal immune system to help reinstate the microbiome of the patient.^{13,14} A prospective study conducted by Barberio *et al.* analyzed stool samples for metagenomic analysis pre- and post-FMT at 1 week and 6 and 12–24 months.¹⁵ The study reported significant change in microbiota toward eubiotic status at all time points analyzed.¹⁵ In particular, there was a decrease in protobacteria which is related to dysbiosis and normalization of *Faecalibacterium parusnitizii* 1 year post FMT again favoring eubiotic state achieved by FMT.¹⁵

When compared with standard oral antibiotic treatment, FMT has demonstrated survival benefit. A prospective cohort study conducted by Ianiro *et al.* analyzed 290 rCDI patients, of which 109 received FMT and 181 received antibiotics (pulsed oral vancomycin, oral metronidazole plus pulsed oral vancomycin, fidaxomicin, or oral metronidazole).¹⁶ These results demonstrated a higher, 90-day overall survival in the FMT group, which remained true in propensity score-matched cohort; a 32% increase in overall survival.¹⁶ Within the cohort treated with FMT there was higher proportion of patients with severe CDI (32%) compared with antibiotic group.¹⁶ Similarly, another retrospective study conducted among 111 severe CDI patients, 66 received FMT and 45 received antibiotics alone (vancomycin, metronidazole, vancomycin plus metronidazole, or fidaxomicin), FMT improved survival in severe cases; $p = 0.001$.¹⁷

Randomized controlled trials comparing FMT to antibiotic therapy

There are four randomized controlled trials (RCTs) that compare FMT with oral vancomycin; of these, only one trial compared FMT with fidaxomicin and oral vancomycin. Van Nood *et al.* compared vancomycin for initial 4 days followed by bowel lavage with FMT with standard vancomycin regimen for 14 days or standard vancomycin regimen with bowel lavage¹⁸ FMT with bowel lavage demonstrated 81% efficacy compared with 31% with vancomycin alone, and 23% with vancomycin given with bowel lavage.¹⁸ Repeat FMT was offered to three patients and 66% had no reoccurrence.¹⁸ Cammarota *et al.* compared initial vancomycin for 3 days followed by FMT with vancomycin for 10 days with taper for 3 weeks; FMT showed 90% resolution of CDI with overall odds ratio of cure rate 25.2 compared with 26% of resolution of CDI seen in vancomycin group.¹⁹ Hota *et al.* compared initial therapy with vancomycin for 14 days plus FMT to 6 week taper of oral vancomycin; FMT showed resolution of CDI in 43.8% compared with 58.3% in oral vancomycin group.²⁰ Fidaxomicin was compared with FMT in only one trial by Hvas *et al.*; the study population received oral vancomycin for initial 4–10 days followed by FMT, fidaxomicin for 10 days, or vancomycin for 10 days.²⁰ Resolution of CDI was observed in 71% of patients treated with FMT compared with 33% in patients treated with oral fidaxomicin and 18% in patients treated with oral vancomycin.²¹ Apart from these RCTs, there are several retrospective studies that evaluate the effectiveness of FMT; however, due to significant heterogeneity among the studies it is difficult to draw meaningful conclusion. A systematic review and meta-analysis of nine RCTs and 36 cohort studies showed 91% cure rate for FMT at week 8 and number needed to treat (NNT) of 1.5 compared with standard antibiotic therapy.²²

Effectiveness of different route and type of fecal microbiota preparation used

A concern always remains among clinicians whether effectiveness of FMT depends on route of administration and/or type of preparation (frozen, fresh, or lyophilized). There are five RCTs that compare different routes and preparations of fecal microbiota in patients with rCDI. Youngster *et al.* compared administration of frozen stool

FMT through colonoscopy *versus* nasogastric tube (NG) and no difference was observed in cure rate based on route of administration.²³ Jiang *et al.* compared fresh, lyophilized product and frozen donor stool administered through colonoscopy; cure rate was highest for fresh product (100%), intermediate for frozen (83%), and were lowest for lyophilized product (78%).²⁴ A single-center RCT compared oral lyophilized FMT with frozen FMT by enema.²⁵ Equivalent efficacy was seen for oral lyophilized FMT (84%) compared with frozen FMT (88%), $p = 0.76$ and the route of delivery had no effect on adverse outcomes.²⁵ Lyophilized microbiota are being considered because of easier storage, longer stability of frozen lyophilized product, and ability to be administered orally.^{24,25} Lee *et al.* conducted a noninferiority double-blind RCT that compared frozen and fresh FMT administered through enema, and clinical resolution was 83.5% for frozen FMT compared with 85.1% for fresh FMT; $p = 0.01$.²⁶ No difference was observed in proportion of adverse events.²⁶ Kao *et al.* conducted a noninferiority, unblinded randomized clinical trial at three academic centers in Alberta, Canada comparing FMT delivered by capsule or colonoscopy, cure rate of 96.2% was achieved in both groups, with $p < 0.01$.²⁷

However, these RCTs do not offer substantial data to formulate a standardized protocol for administration and preparation of FMT. A recent meta-analysis of 15 studies demonstrated that infusion through colonoscopy, multiple infusions, and higher fecal dosage had higher efficacy rates; a lower fecal amount ≤ 50 g was associated with lower efficacy.²⁸ In addition, meta-analysis demonstrated type of infused material has no influence on efficacy outcomes of FMT.²⁸ This meta-analysis provides a framework for the clinicians to develop a standardized protocol at their respective institutions.

Limitations of all RCTs

Overall, FMT was shown to be more effective in treating rCDI compared with oral antibiotic therapy (vancomycin and/or fidaxomicin) and remains efficacious regardless of route or preparation used; however, there remains several limitations among these studies that prohibit clinicians from using FMT as the standard of care (SOC) for treatment of rCDI.

All of the RCTs had small sample sizes and repeated FMT infusions were often required to achieve cure but repeat challenge with vancomycin was not allowed.^{18–27,29–32} All patients received oral vancomycin at varied duration preceding FMT with most of the studies including patients with three or more episodes of rCDI, but *C. difficile* treatment guidelines suggest using FMT for second recurrence.^{7,18–27,29–32} In addition, there are no RCTs that compare pulsed regimen of fidaxomicin to FMT; EXTEND trial demonstrated that extended pulse regimen of fidaxomicin had better outcomes compared with vancomycin alone.^{21,33} All the RCTs reviewed above lack data on immunocompromised patients.^{18–21} Navalkele *et al.* conducted a retrospective cohort study that consisted of largest population of immunocompromised patients; FMT was given as definitive treatment through retention enema in 50 patients; of which 17 were immunocompromised, the cure rate was 81% after first FMT and 91% after the second FMT.³⁴ Furthermore, all the RCT trials above were conducted in Europe and the United States and therefore limits generalizability to patients residing in Asia and other regions.²⁹ Finally, it is important to note that each study used different testing methods for diagnosis of CDI with a variable time frame to assess clinical cure, and mean duration of antibiotics administered since CDI first diagnosis differed potentially confounding the results.^{18–27,29–32}

Fecal microbiota transplant and bezlotoxumab

Bezlotoxumab, a human monoclonal antibody, is a new emerging therapy for rCDI.³⁵ The drug binds and neutralizes *C. difficile* toxin B.³⁵ MODIFY 1 and MODIFY 11 were double-blind, placebo-controlled RCTs conducted in 30 centers to evaluate the safety and efficacy of bezlotoxumab compared with placebo in patients being treated with SOC antibiotics (vancomycin, metronidazole, or fidaxomicin) for primary or rCDI.³⁵ The results demonstrated a statistically significant reduction in CDI recurrence using bezlotoxumab compared with placebo 17% versus 28% in MODIFY 1 and 16% versus 26% in MODIFY 11; $p < 0.001$.³⁵ Furthermore, a *post hoc* analysis of hospitalization data from both MODIFY 1 and 11 trials showed that bezlotoxumab also resulted in reduction in cumulative inpatient days and CDI-associated re-hospitalizations.^{36,37}

In addition, a retrospective multicenter cohort study conducted across 34 outpatient infusion centers in the United States evaluated 200 patients with rCDI or at risk of rCDI.³⁸ Patients that received SOC antibiotics (vancomycin, metronidazole, or fidaxomicin) plus bezlotoxumab demonstrated a successful prevention of rCDI in 84.1% of patients.³⁸ The timing of bezlotoxumab infusion relative to SOC antibiotics and type of SOC antibiotics used did not affect the outcome.³⁸ There are no RCTs that compare bezlotoxumab to FMT; however, a meta-analysis that reviewed 1003 articles (seven RCTs) reported no difference between single or multiple infusions of FMT compared with single infusion of bezlotoxumab; nevertheless FMT had higher rate of nonserious diarrhea.³⁹ In addition, there is a case report published that demonstrated success in combining third FMT with bezlotoxumab to prevent rCDI in a patient after failure with SOC and two trials of FMT.⁴⁰ Based on these studies, bezlotoxumab can be considered as adjunctive therapy in addition to SOC antibiotics among patients with rCDI or at risk of rCDI.

What is the data on long-term follow-up after FMT?

Long-term follow-up of patients who receives FMT still remains a concern. To date, there are no RCTs that evaluate long-term efficacy and safety of FMT. There are few meta-analysis, retrospective, and prospective studies that evaluated long term follow up.

Kelly *et al.* conducted a prospective multicenter observational trial among North American participants that evaluated cure and safety profile at 1 month and 6 months post FMT.⁴¹ Among 222 patients, 200 (90%) showed cure at 1 month follow-up; of these, 197 (98%) received only one FMT.⁴¹ At 1 month follow-up post FMT, diarrhea and abdominal pain was reported by five (2%) and four (2%) patients, respectively.⁴¹ Among 112 patients, four (4%) patients had rCDI at 6 month follow-up; new diagnoses of irritable bowel syndrome was made in two (1%) patients and inflammatory bowel disease in two (1%) patients.⁴¹ The national registry is ongoing; so, more data will be available in the near future.⁴¹ Multicenter study by Brandt *et al.* evaluated long-term follow-up at 17 months for patients who received FMT through colonoscopy; primary cure rate was 91% (defined as resolution within 3

months) and secondary cure rate 98% (defined as resolution with an additional course of vancomycin with or without FMT).⁴² Li *et al.* performed a meta-analysis of observational studies that evaluated long-term (≥ 90 days) efficacy and recurrence rate.⁴³ A total of 611 patients were evaluated and the overall cure rate of FMT was 91.2%; recurrence rate for < 90 days was 2.7% and 1.7% for ≥ 90 days.⁴³ A prospective survey-based study from September 2012 to June 2018 evaluated 609 patients to determine long-term safety of FMT.⁴⁴ One year follow-up demonstrated that $> 60\%$ patients reported diarrhea and $< 33\%$ had constipation and 9.5% reported rCDI; at long-term follow-up (median 3.7 years), 73 new diagnoses were reported: 13% gastrointestinal, 10% weight gain, and 11.8% new infections that were unrelated to FMT.⁴⁴ This study further stresses the importance for future studies evaluating long-term follow-up given new diagnoses reported.⁴⁴

Furthermore, there are limited studies that evaluate the potential of transmission of procarcinogenic bacteria post FMT. Drewes *et al.* demonstrated transmission and clearance of procarcinogenic bacteria in patients with rCDI post FMT by measuring stool samples for bacterial virulence factors (*Bacteriodes fragilis* toxin, *fusobacterium adhesin*, and *Escherichia coli*) through polymerase chain reaction (PCR) from 11 pediatric patients and their respective donors prior to FMT as well as from recipients post FMT at (2–10 weeks, 10–20 weeks, 6 months).⁴⁵ Of these 11 patients, four had sustained acquisition of procarcinogenic bacteria if the donor stool was from a patient with positive virulence factor; transmission was demonstrated by performing whole genome sequencing (WGS) on isolate from one donor/recipient as *E. coli* strain present in the donor was also present in recipient after FMT.⁴⁵ On the contrary, this study also showed that FMT from a donor whose stool is negative for procarcinogenic bacteria contributed to eradication of procarcinogenic bacteria in a recipient who is positive.⁴⁵ Another retrospective study conducted among 49 rCDI patient treated with FMT screened patients via fecal metagenomics for procarcinogenic *E. coli* demonstrated that patients with rCDI due to dysbiosis have higher levels of procarcinogenic *E. coli*; among these patients, FMT promoted the persistence of procarcinogenic bacteria in a recipient if donor is positive but eradication if donor is negative.⁴⁶ However, this study found no clear evidence of donor to

patient transmission of procarcinogenic bacteria.⁴⁶ Both of these studies further highlight the importance for the need of additional studies regarding appropriate screening process and long-term effects of FMT.

Is the screening process for FMT standardized?

There is a lack of standardized screening process for FMT; Bafeta *et al.* in 2017 performed a systematic review, which highlighted the lack of universal standardization in published studies with respect to criteria for donor selection, screening process, and methodology pertaining to stool collection and preservation.⁴⁷ In 2019, an international consensus guideline regarding selection and screening of donors along with collection, preparation, and storage of feces were developed by Cammarota *et al.*⁴⁸ FMT has not been accepted as a widely used treatment given lack of regulation by Food and Drug Administration (FDA); FMT does not require an Investigational New Drug (IND) application from physicians who offer FMT as a treatment option for rCDI.⁴⁹ There are logistical challenges involved in donor screening process, as often there are delays in finding suitable donors that pass the screening process, the cost related to screening process, and some donors are lost to follow-up during the screening process.⁵⁰ Despite this, screening process is necessary given the risk of transmitting infectious agent from donor stool to the recipient.

COVID-19 pandemic further complicated the FMT screening process, as guidelines needed to be updated to address possible transmission of severe acute respiratory syndrome virus 2 (SARS-CoV-2). Ianiro *et al.* provide a framework for stool donation during the COVID-19 pandemic to ensure safety for patients and providers.⁵¹ According to the recommendation, donors should be asked the regular health questionnaire needed for FMT and be assessed for COVID-19 symptoms, previous diagnosis of COVID-19, and household exposure for COVID-19 at each donation visit.⁵¹ Donors who have positive screening process must be excluded from donation. In addition, donors with positive COVID-19 diagnosis and/or symptoms who donated stool 4 weeks prior should have their stool discarded, as evidence suggests that SARS-CoV-2 can remain in stools 4 weeks post-infection.^{51–53}

Once the donors pass the questionnaire screening process described above, standard blood and stool lab testing needs to be completed in addition a nasopharyngeal swab and serology for SARS-CoV-2.⁵¹ If swab or IgM serology is positive, donor is excluded; however, if only IgG positive, questionnaire and stool testing for SARS-CoV-2 should be done after 30 days of positive IgG.⁵¹ If regular lab testing, swab, and serology tests are negative, then the stool can be processed for storage and quarantine or rapid donation if a rapid stool assay performed for common pathogens and SARS-CoV-2.⁵¹ If the stool is stored, the donor screening with testing for SARS-CoV-2 at 8–12 weeks by polymerase chain reaction (PCR) and serology (IgM and IgG only if previously negative) can be repeated.⁵¹ If the test yield negative results, the donation can be used for clinical use.⁵¹ Any positive stool should be discarded.⁵¹

Serious adverse events related to FMT

Placebo-controlled trials evaluating FMT do not report serious adverse events (SAEs) related to transmission of infectious agents. A systematic review assessing the efficacy and safety of FMT in immunocompromised patients observed similar rate of adverse events among both immunocompromised and immunocompetent patients.⁵⁴ A total of four studies reported Gram-negative bacteremia post FMT. In three of four cases, the bacteremia was attributed to events unrelated to FMT and the fourth case was related to aspiration of feculent material after upper endoscopic FMT.^{55–58} In 2019, there was a brief report that described extended-spectrum-beta-lactamase (ESBL) *E. coli* among two immunocompromised patients who received stool from the same donor, of which one of the patient died.⁵⁹ Given the transmission of this multi-drug-resistant organism in two patients, FDA implemented new requirements for donor screening in July 2019.⁶⁰ Another report published by Kassam *et al.* in 2019 also highlighted the importance of donor screening to alleviate the risk of transmission of infectious organisms.⁶¹ In April 2020, a safety alert was published by the FDA, due to transmission of enteropathogenic *E. coli* (EPEC) and Shigatoxin-producing *E. coli* (STEC) post FMT among six patients; two patients had EPEC and four had STEC. Among the four patients who had STEC, two died from the infection.^{62,63} A retrospective review by Navalke *et al.* reported one case of vancomycin-resistant Enterococcus

(VRE) bacteremia among 50 patients; however, FMT was not identified as a definite cause.³⁴ In the midst of COVID-19 pandemic, one needs to consider the potential of transmission of severe acute respiratory syndrome virus 2 (SARS-CoV-2) from donor stool post FMT given prolonged viral shedding in stool even after recovery of respiratory symptoms.^{52,53} All of these cases stress the importance of informing the patient of potential risk and obtaining informed consent prior to administration of FMT.

A recent meta-analysis analyzed 20-year period data from 20 RCTs and 109 non-RCTs and demonstrated that 19% of patients experienced FMT-related adverse events (AE) and 1.39% of patient experienced FMT-related SAE.⁶⁴ Among the AE, most commonly reported was diarrhea (10%); abdominal discomfort (7%); and nausea, vomiting, and flatulence (3.3%); with regard to SAE, bacteremia and death was reported in 0.09% of patients; commonly seen in patients with mucosal barrier injury than without mucosal barrier injury ($p < 0.05$).⁶⁴ In addition, patients undergoing FMT through upper route experienced higher degree of AE; 80% of reported deaths were among patients who had FMT through endoscope procedures.⁶⁴

Reimbursement and scheduling complexities

Hospital administration often face challenges with respect to reimbursement of FMT. There are three studies that have demonstrated cost-effectiveness of FMT compared with oral vancomycin therapy.^{65–67} However, reimbursement for FMT is variable and often does not cover the cost involved in donor screening or purchase cost of FMT dose from stool bank.⁶⁸ Scheduling FMT is also complex. It has to be scheduled as the last case of the day to limit the spread of the disease, donor stool needs to be ordered as most hospital pharmacies do not keep abundant stock given cost issues (US\$1695 for each donor sample from OpenBiome),⁶⁹ coordination between pharmacy staff and provider has to be completed prior to the procedure for appropriate thawing, and appropriate cleaning of the room needs to be scheduled per *C. difficile* protocol after the procedure. Adding to these scheduling intricacies is uncertainty about patient canceling or arriving late for the appointment, as this can lead to thawed sample being discarded further adding to

the hospital cost. Limited providers offer FMT through retention enema as an outpatient procedure in clinic, which involves the same logistical challenges described above. Due to these challenges, often patient prefers FMT oral capsule which can be ordered through OpenBiome; however, that requires physician orientation to be administered and is also associated with a higher cost of US\$2050.⁶⁹

New therapies

Microbiota-based treatments are being sought out for FMT given the role intestinal microbiome plays in colonization of CDI. FMT can re-establish normal microbiota, but concern remains regarding variation treatment approaches and risk of pathogen transmission from donor stool. A multicenter double-blind placebo-controlled trial evaluated the efficacy and safety of one or two doses of RBX2660 to prevent rCDI at 8 weeks following treatment.⁷⁰ One RBX2660 dose was superior to placebo and overall efficacy was 88.8%.⁷⁰ No difference was seen among AE between groups.⁷⁰ A larger phase III clinical trial is ongoing to give more insight about RBX2600.⁷⁰

Other therapies such as ‘RePOOPulating’ the gut attempt to treat rCDI developing a synthetic stool by culturing the microbial diversity from healthy donor stool.⁷¹ Petrof *et al.* treated two patients with rCDI with a synthetic stool created by 33 different isolates of commensal species identified by 16s ribosomal nucleic acid (rRNA) delivered by colonoscopy.⁷¹ Both patients returned to normal bowel pattern within 2 to 3 days and remained symptom free at 6 months.⁷¹ This pilot study demonstrates that synthetic stool is a reasonable alternative for treatment of rCDI. Similarly, another phase I open-label trial assessed the safety and tolerability of microbial ecosystem therapeutic (MET-2), oral encapsulated formulation of 40 lyophilized bacterial species.⁷² The oral MET-2 treatment was offered to 19 adult patients with two episodes of CDI and resolution of CDI was measured at day 40 after treatment; 79% of patients achieved resolution after first treatment, which increased to 95% after second treatment.⁷²

Conclusion

FMT is a testament to science; however, given the heterogeneity involved within the donor stools and lack of adequate long-term safety data, FMT

is yet to be approved as a standardized product by FDA. This further prohibits clinicians from using FMT confidently both in the inpatient and outpatient setting among patients with rCDI. A strong collaboration among hospital administrators and clinicians is needed to overcome logistical challenges related to FMT.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Author contributions

Avnish Sandhu: Conceptualization; Data curation; Investigation; Writing-original draft; Writing-review & editing.

Teena Chopra: Conceptualization; Supervision; Validation; Writing-review & editing.

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ORCID iD

Avnish Sandhu  <https://orcid.org/0000-0003-0880-3898>

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