A Narrative Review of the Current Evidence of Fecal Microbiota Transplant as Curative Therapy for Recurrent *Clostridioides difficile* Infection

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INTRODUCTION

The gastrointestinal tract is a reservoir for up to 10,000 to 100 trillion microorganisms, collectively known as the gut microbiota.[1] Among these colonizers, the dominant genera include *Bacteroides, Clostridioides, Fusobacterium, Eubacterium, Ruminococcus, Peptococcus, Peptostreptococcus*, and *Bifidobacterium*.[1] Although these microbes are mostly confined to the intestinal tract, they also play critical roles that extend beyond the gut (i.e., body weight, mental health, metabolism, and immune regulation).[2]

When the gut's microbiome gets disrupted, the term 'dysbiosis' can be adopted.[3] Factors causing such profound imbalance can be attributed to toxic insults from frequent antibiotic use, unwanted dietary changes, poor dental hygiene, and even physical and psychological stress.[4] In the event of deteriorating microbial diversity in persons with diarrhea, there is an excess amount of free amino acids, especially proline, and a lack of inhibitory bile acids.[3] Together, they create the ideal environment for dysbiosis-related pathologies as seen in an initial *Clostridioides difficile* infection (CDI) – the world's leading hospital-acquired illness.[5] Patients with CDI can be diagnosed with a positive PCR result for CDI toxin and a clinical presentation of more than three episodes of diarrhea, abdominal pain (that only resolves with defecation), mild fever, and leukocytosis.[6]

Current guidelines to treat CDI include mono- and combination therapies with vancomycin and fidaxomicin.[1] Of the existing dosage regimens, pulsed dosing of these first-line agents has starkly reduced recurrence rates compared with standard protocols. Unfortunately, even after the recommended treatment, recurrence is still seen in up to 10–20% of patients after the initial visit – with up to 40–65% of previously treated patients experiencing further recurrences after the second visit.[5] In 30% of the cases with severe, refractory CDI, colectomy becomes the last resort for treatment despite many of its feared complications: toxic megacolon, septicemia, and multiorgan failure.[7]

In the last few decades, there has been a surge in interest to revamp and revolutionize an ancient procedure known as fecal microbiota transplant (FMT) to correct the dysbiosis responsible for refractory *Clostridioides difficile* Infection (rCDI).[8] Unfortunately, because FMT meets the legal definition of a drug and biological product, it remains unqualified for regular use until it gets accepted through the investigational new drug (IND) approval.[9] However, this clause's exception emerges under 'enforcement discretion', which allows FMT for patients who are refractory to standard therapy with proper consent in order.[9]

FMT is a procedure that essentially involves a sophisticated administration of fecal matter obtained from a healthy, screened donor to a qualified recipient suffering from rCDI. The procedure's outcome most often results in the recipient altering his or her gut microbiota so that it closely resembles that of the stool donors' profile, which paves the way for its imminent success.[10] The American guidelines suggest a primary endpoint as the resolution of symptoms and the absence of CDI within 8 weeks of FMT as a secondary endpoint.[10] Currently, the cure for rCDI has been seen within hours to 4–5 days in struggling patients post-FMT.[9] This article aims to evaluate and analyze current and reliable sources of evidence

[1] Non-inferior to vancomycin; however, it is not studied in severe/fulminant cases of CDI.[17]

that support FMT as an optimal method to conventional therapy for resolving rCDI.

METHODS

Search Strategy

This literature review was executed according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA). PubMed, Medscape, and Cochrane Review searches consisted of titles of relevance, sorted by publication dates from 2010 to 2020. The PubMed search used the following filters: free full text, clinical trial, meta-analysis, randomized control trial, and systematic review. Search criteria were studies that were representative of the sustainability of FMT in treating rCDI in adults. Articles were retrieved from online databases using a combination of the key phrases: fecal microbiota transplant, donor feces infusion, fecal transplant, FMT, *Clostridium difficile* infection, *Clostridioides difficile* infection, *C. difficile colitis*, and CDI.

Inclusion and Exclusion Criteria

For all selected literature, the study population of interest was moderate to high-risk adults (age ≥ 18 years) of any demographic who had at least one incidence of recurrent *C. difficile* infection. Studies were also included if the following inclusion criteria were met: (1) participants with recurrent CDI supported by a clinical diagnosis and/or laboratory parameters and (2) subjects with recurrent CDI having received FMT through any method of administration. Studies were excluded if there were: (1) scoring <6 on controlled intervention studies and cohort studies; (2) scoring <4 on systematic reviews and meta-analyses; (3) lacking standard treatment of care for primary CDI before FMT; (4) evaluating FMT in the immunocompromised or patients with or without severe comorbid conditions; (5) including pediatric patients; (6) testing small (<15 subjects) and nondiverse sample sizes; (7) duplicated studies; (8) not in English.

Outcomes of Interest

The primary outcome of interest is clinical and bacteriologic resolution of CDI with FMT versus conservative treatment at least 4 weeks after the final FMT treatment – as most treatment failures with FMT occurred before this time point. Secondary outcomes of interest included the following: (1) treatment success and failure after single versus multiple infusions of FMT in the posttreatment phase; (2) long-term implications post-FMT; and (3) efficacy of mono- and/or adjunctive therapy with common antibiotics (vancomycin vs. fidaxomicin) for CDI and rCDI.

Data Extraction

All full texts were independently reviewed by the primary investigator to ascertain that each source contained information on the topic of choice. Following a meticulous search, a total of 106 articles met the selection criteria – out of which only 8 were independently selected based on providing the most valuable insight into the efficacy of FMT over antimicrobial treatments in the management of rCDI (see Fig. 1 and Table 1).

Quality Assessment and Risk of Bias of Individual Studies Assessment

The primary investigator independently evaluated all the included studies with ≥ 4 patients using the National Institute of Health (NIH) Study Quality Assessment Tools.[11] The score range for controlled intervention studies and cohort studies is between 0 and 14, where a score <6 was identified as poor in quality. The score range for systematic reviews and meta-analyses is between 0 and 8, where a score <4 was considered as poor in quality. Studies that were deemed poor in quality were excluded from this literature review. Additionally, with the help of the Risk of Bias in Nonrandomized Studies of Interventions tool (ROBINS-I) and the Risk of Bias tool for randomized control trial, the primary investigator also thoroughly assessed the risk of bias of each study.[12,11] The scores were classified to be either low, moderate, serious, or critical. Studies that were categorized as serious or critical were immediately excluded.

RESULTS

The search strategy identified 106 unique studies, of which 8 met the inclusion criteria. Of these, 2 were systematic reviews and meta-analyses, 4 were randomized controlled trials, and 2 were retrospective cohort studies (see Fig. 1 and Table 1). Table 1 highlights the notable components of each literature source, including the following: (1) name of the first author; (2) research design; (3) year of publication; (4) independent and dependent variables; (5) data collection method; (6) pertinent

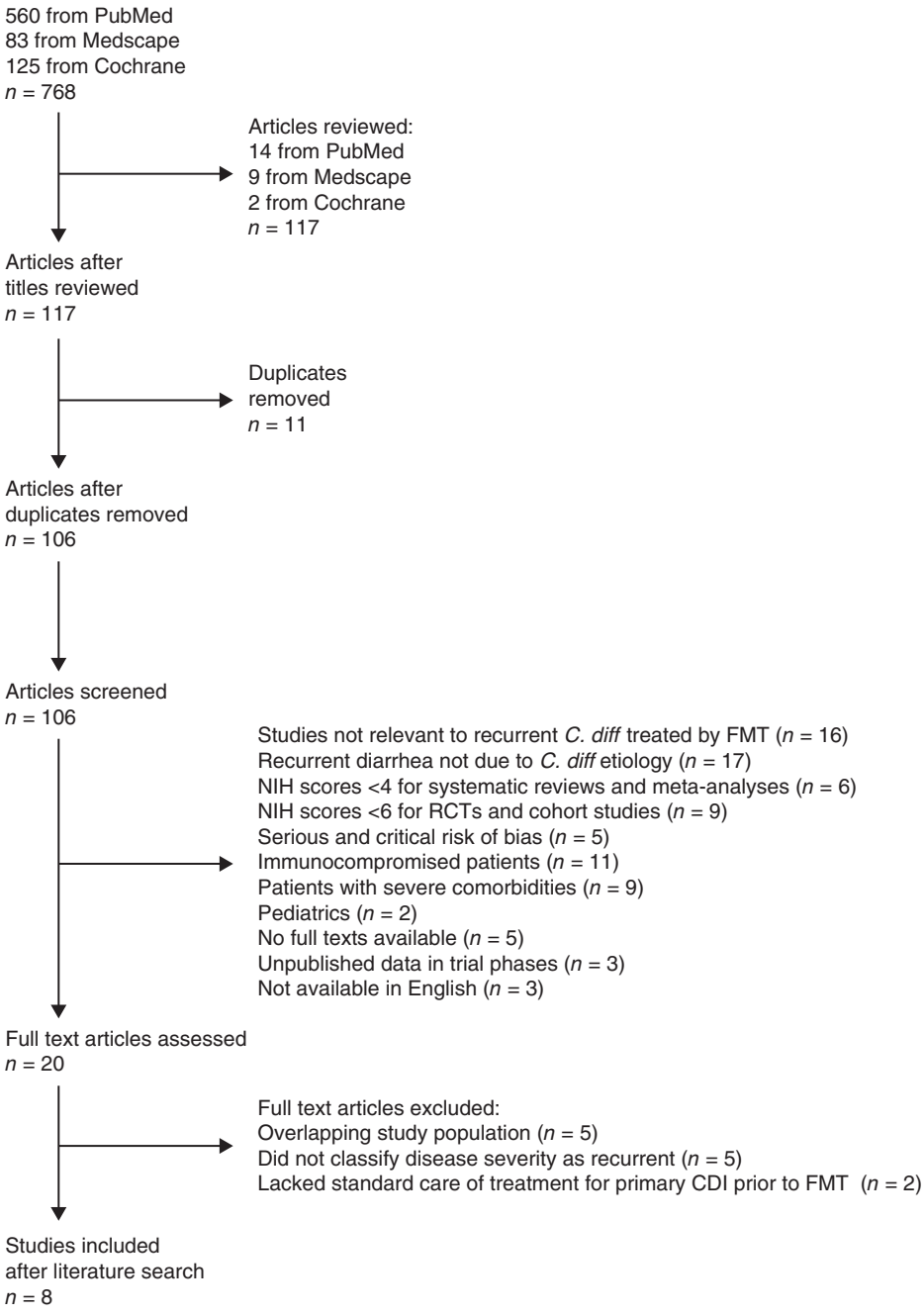

Figure 1. Flowchart outlining the selection strategy during the literature search.

findings; (7) strengths; (8) weaknesses; (9) NIH scores; (10) ROBINS-I scores; (11) level of study based on the Evidence-Based Medicine Pyramid.

M.N. Quraishi and colleagues did a systematic review and meta-analysis on the efficacy of FMT of different delivery methods and preparation in the treatment of rCDI.[13] Of the 37 studies, 34 reported positive responses to FMT with a cure rate of 84%; 25 case series and 7 RCTs demonstrated that the lower gastrointestinal route was superior to the upper gastrointestinal route (95 vs. 88%)

Table 1. Evidence table.

1st Author	M.N. Quaraishi	Wenjia Hui	G. Ianiro	Colleen R. Kelly	Christian Lodberg Hvas	Louie TJ	J. Jalanka	Jae Hyun Shin
Research design	**Systematic review and meta-analysis**	**Systematic review and meta-analysis**	**RCT**	**RCT**	**RCT**	**RCT**	**Retrospective cohort study**	**Retrospective cohort study**
Pub. Yr. Ind. V.	**2017**	**2019**	**2016** 1(a). Donor FMT 1(b). Autologous FMT	**2018** 2(a). FMT-S group 2(b). FMT-M group	**2019** 1(a). FMTv (n = 24) 2(b). Fidaxomicin b.i.d. (n = 24) 2(c). Vancomycin q.i.d. (n = 16)	**2012** 1(a). Vancomycin-treated patients (n = 44) 1(b). Fidaxomicin-treated patients (n = 45)	**2018** 1(a). FMT group 1(b). Antibiotic group (AB)	**2019** 1(a). Lower GI-FMT delivery 1(b). Upper GI-FMT delivery 2(a). Non-FMT tx
Dep. V.			Clinical cure within 8 weeks after FMT or at the time of early withdrawal	Clinical cure within 8 weeks after FMT or at the time of early withdrawal	Clinical cure in the intention-to-treat population 8 weeks after FMT or at the time of early withdrawal	Spore counts and *C. difficile* cytotoxin B titers at study entry; on days 4,10,14,21,28; on days 38–42	Clinical cure in the intention-to-treat population 8 weeks after FMT or at the time of early withdrawal	CDI recurrence within 3 months of FMT or since initial visit
Data collection method	37 papers: 7 RCTs and 30 case series	Researchers chose 8 studies using electronic database search and compiled data from each	46/179 patients were randomly assigned: (a). Donor (n = 22) (b). Autologous (n = 24)	56 enrolled subjects (a). FMT-S (n = 28) (b). FMT-M (n = 28)	64/120 adults w/rCDI were seen at a gastro clinic in Denmark between 5/5/16 and 6/10/18 and randomly assigned	89/629 patients were randomly assigned to a 10-day course of: (a). Vancomycin 125mg q.i.d. OR (b). Fidaxomicin 20 mg b.i.d.	(a). FMT (n = 45); (b). AB (n = 39)	FMT = 52/113; done at the CDCC from 6/2012 to 3/2015
Findings	Single FMT infusion cure rate = 84% (better than abx tx)	The 8 studies yielded 273 patients, of which 243 had clinical resolution	Donor FMT = 91% cure rate (20/22); Autologous FMT = 63% cure rate (15/24); Crossed over to donor FMT = 9	FMT-S: 21/28 cured; 7 retreated and cured but 1/7 died. FMT-M: 28/28 cured	Clinical resolution: FMT = 92% (n = 24); Fidaxomicin = 42% (n = 24); Vancomycin = 19% (n = 24)	Recurrence was observed in 23% (10/44) in vancomycin-treated patients versus 11% (5/44) in fidaxomicin-treated patients	↑ Bowel fxn: 53.3 versus 25.6% ↑ Mental health 31.1 versus 8.9% Upper GI pain 31.3 versus 51.3% FMT readiness 97.6 versus 60%	Recurrence rate: FMT = 4.5 versus Non-FMT = 16.7%
Strengths	Stringent section criteria	8 high-quality RCTs updated to 9/20/18	Double-blinded, multicenter design	Use of expert endoscopist	Appropriate statistical analysis	Double-blinded; 10 samples from healthy controls were analyzed via qPCR	~3.8 years observational period post-FMT	Use of CDI-focused clinic
Weaknesses	Lacks adverse event data	Not generalizable	Not generalizable	No double-blinding	No double blinding	No quality assessment	Questionnaires	Telephone surveys
NIH score	6	6	9	8	10	9	8	7
ROBINS-I	Low	Low	Low	Moderate	Moderate	Moderate	Moderate	Low
Level of study[1]	**1**	**1**	**1**	**1**	**1**	**1**	**3**	**3**

[1] Level 1 includes RCT, systematic review of RCTs ± meta-analysis of RCTs; Level 3 includes retrospective cohort studies.

GI, gastrointestinal; qPCR, quantitative polymerase chain reaction.

(*p = 0.02*). Fresh FMT revealed a cure rate of 85% and a lower cure rate of 68% with frozen FMT; however, neither was statistically significant (*p = 0.10*). However, FMT still appeared promising as an effective and safe treatment choice for rCDI, as seen in controlled and uncontrolled studies.

A systematic review and a meta-analysis were executed to confirm the efficacy of fresh FMT in the clinical resolution of rCDI. Two of the researchers, W.J. Hui and Ting Li, independently extracted articles with stringent eligibility criteria that resulted in eight RCT studies.[14] The pooled relative risks were calculated with a 95% confidence interval (CI), and the heterogeneity between studies was assessed using the I2 statistic; 537 patients met the inclusion criteria and were divided into the fresh FMT group (*n* = 273) and control group (*n* = 264). The control groups included antibiotic therapy or placebo, frozen FMT, and capsule groups. The eight studies determined that 243 out of the 273 patients experienced clinical resolution from rCDI through FMT (RR = 0.38, *p = 0.02*) with a high heterogeneity (I2 = 67%) between them. The recurrence rate of clinical diarrhea in the control group was significantly higher compared with the fresh FMT group (24.6% or 65/264 vs. 11.0% or 30/273; $p \leq 0.05$). Like previous findings, multiple infusions showed greater improvement in the remission rate (RR = 0.24; *p = 0.001*). The combination of self-limiting adverse events and high-quality RCTs provides overpowering evidence to endorse FMT as a curative treatment for rCDI.

An open-labeled RCT at the Gemelli University Hospital was carried out by G. Ianiro et al to compare single infusion (FMT-S) with multiple infusions (FMT-M) of FMT in the treatment of rCDI.[15] Using randomization software, a total of 56 subjects were enrolled and randomly assigned to either FMT-S (*n* = 28) or FMT-M (*n* = 28). Outcome data were assessed using the Student's *t*-test and Fisher's exact test, according to the intention-to-treat principle. All statistical tests were 2-sided, and a *p*-value <0.01 was considered statistically significant and analyzed using an online calculator; 21 of the 28 subjects in the FMT-S group had shown clinical resolution. All 7 remaining in the FMT-S group received further infusions and resulted in 100% cure. Ultimately, the cure rate was greater with FMT-M than FMT-S (100 vs. 75%), favoring FMT as an effective alternative for resolving rCDI.

Colleen R. Kelly et al conducted a double-blinded RCT at the University of Minnesota in Minneapolis to compare the clinical outcome of autologous FMT to donor FMT.[16] Patients were enrolled between 11/15/2012 and 03/10/2015 at two academic hospitals in New York (NY) and Rhode Island (RI). Stool specimens of both the donor and the patient were collected 1 h before the scheduled FMT procedure; 46 patients were randomly allocated to either the donor group (*n* = 22) or autologous FMT group (*n* = 24). Baseline demographic and clinical data were described, and groups were assessed using Stata (version 12), SAS (version 9.4), and a 2-sample *t*-test. Clinical resolution was seen in 90.9% (*p = 0.042*) in the donor FMT group and 62.5% in the autologous group. Although the donor FMT group was statistically superior to the autologous FMT group, the interaction between NY and RI was not statistically significant for treatment effects (*p = 0.24*). One of the two treatment failures from the donor FMT group was cured after the second donor stool infusion. Nine patients who had recurrence after autologous FMT switched over to treatment with donor FMT and were cured.

An open-labeled RCT was conducted at a gastroenterology clinic in Denmark by Christian Lodberg Hvas et al. to compare the combined clinical resolution of fresh FMT and non-FMT treatments (vancomycin and fidaxomicin).[17] Between 04/05/2016 and 06/10/2018, 64 of 120 adults with rCDI were randomly assigned to 1 of the 3 predetermined vancomycin courses or fidaxomicin before rescue FMT (*n* = 24); 24 patients were assigned to 4–10 days of vancomycin (125 mg 4 times daily), 24 patients were assigned to 10 days of fidaxomicin (200 mg twice daily), and 16 patients were assigned to 10 days of vancomycin (125 mg 4 times daily). Outcome data were assessed using chi-squared analysis and Kruskal–Wallis analysis of variance, and a *p*-value of 0.05 was decided to be clinically significant. At the eighth-week follow-up, combined clinical resolution and negative PCR test for CD toxin were observed in 17 of the 24 patients with rescue FMT (71%). After week eight, a clinical resolution was found in up to 22 patients (92%). In the case of fidaxomicin, a combined resolution was found in only eight of the 24 patients (33%), with an increase in clinical resolution to 10 patients after the eighth week (42%). Finally, only 3 of the 16 patients (19%) had combined resolution with vancomycin at week eight with no clinical resolution increase afterward. In summary, FMT showed greater efficacy to fidaxomicin (*p = 0.009*) and vancomycin (*p = 0.001*) than either of the antibiotics alone (*p = 0.31*).

Thomas J. Louis et al performed a double-blinded, multicenter RCT at the Foothills Medical Center (Calgary,

Canada) to compare the efficacy of a 10-day course of vancomycin 125 mg q.i.d. versus fidaxomicin PO 200 mg b.i.d. in the treatment of rCDI.[18] Using the randomization software, a total of 89 out of 629 subjects were registered and randomly assigned to either vancomycin ($n = 44$) or fidaxomicin ($n = 45$). The primary outcome was to assess for the reduction of both *C. difficile* toxin reexpression and rCDI during and after treatment through the collection of fecal samples (>10 g/samples) on days 1, 4, 10, 21, 28, 38–42. Quantification of target bacterial DNA in fecal samples was performed using real-time quantitative polymerase chain reaction (qPCR) and was log-transformed. Vancomycin-treated patients experienced more recurrence than fidaxomicin-treated patients (10/44 or 23% vs. 5/44 or 11%, $p = 0.03$). Similarly, vancomycin-treated patients had more toxin reexpression in fecal samples than fidaxomicin-treated patients (29/94 or 28% vs. 13/91 or 11%, $p = 0.03$). Provided the results, it can be presumed that fidaxomicin encompasses microflora-sparing properties that make it more potent against rCDI compared with its competitor, vancomycin.

A retrospective cohort study was instigated by Jae Hyun Shin and colleagues in all patients' medical records that received FMT between June 2012 and March 2015 at the University of Virginia Complicated *C. difficile* Clinic (CCDC).[19] Patient follow-up for recurrence data occurred through telephone contact at 1 week, 1 month, 3 months, 6 months, and 1 year post-FMT. Of the 113 patients who were reviewed, 52 patients who had three or more CDC recurrences were eligible to be treated with FMT. Of the remaining, 25 patients were deferred, and 36 patients who had fewer than two recurrences received non-FMT treatment. Outcome data were assessed using the chi-squared analysis, the Fisher's exact test, or the Student's *t*-test. When treated with standard non-FMT treatment, there was a higher recurrence (16.7 vs. 8.8%, $p = 0.05$) and mortality (12.5 vs. 6%, $p = 0.05$) rates than FMT treatment. In contrast, FMT-treated patients had fewer recurrence (4.5 vs. 8.8%, $p = 0.05$) and mortality (7 vs. 6%, $p = 0.05$) rates – findings suggest that patients with greater than three recurrences benefit from FMT regardless of route of delivery.

DISCUSSION

Donor versus Autologous FMT

Even though modern technologies are still not capable of determining the fecal composition responsible for both the positive and negative responses to FMT, progress still has been made in distinguishing the safety and efficacy of autologous versus heterologous FMT. According to the findings of Colleen R. Kelly et al., 90.1% ($p = 0.042$) of the patients experienced clinical resolution with donor FMT versus only 62.5% seen with autologous FMT.[16]

Normally, during remission periods with rCDI, the patient's stool is 'banked' for FMT use before starting the patient on any antibiotic therapy.[20] Following antimicrobial treatment, when the patient is increasingly vulnerable to recurrences with CDI, the patient's stool could serve as a rapid approach to reinstate the possibly depleted commensal organisms using FMT. Unlike heterologous FMT, autologous FMT is shown to have little to no improvement from prior dietary changes[2] due to the already weakened microbiome of the patient. However, because it is better tolerated with a higher safety profile, it reduces the need for strict screening methodologies, thus increasing the patients' and physicians' willingness to opt for autologous over heterologous FMT in those suffering from rCDI.[21]

Even so, as determined by the findings of Colleen R. Kelly et al., the results with donor FMT have been more promising due to the effectiveness of more protective microbes that are most often scarce from the patients' stool: *Bacteroides* and *Firmicutes*.[16,22] The basis for the higher therapeutic potential seen with heterologous FMT can be attributed to the fact that the donors' feces are better equipped with microbes that are more favorably anti-inflammatory and diverse.[22] For such reasons, donor FMT necessitates only a *partial* rather than complete engraftment of the donor's feces to resolve rCDI.[22] Of course, donor FMT still carries a greater risk of exposing the individual to potentially pathogenic microorganisms that could lead to possible autoimmune complications; however, with more definite screening protocols in place, heterologous FMT's feasibility seems to be of reasonable value over autologous FMT. In both situations, regardless of their distinct favorable and unfavorable features, it can be said that FMT possibly proves advantageous to standard treatments of care, namely, vancomycin and fidaxomicin, as the objective is deemed at restoring the microflora necessary to resolve the recurring infection versus ridding the body of the pathogenic strains in the symptomatic period.

[2] Protein consumption has a positive correlation with overall microbial diversity.[8]

Fresh versus Frozen FMT

Similar outcomes were also seen in another systematic meta-analysis by Wenjia Hui et. al.[14] The study has shown that there is a higher recurrence rate of diarrhea within the control group compared with the fresh FMT group (24.6 vs. 11.0%, $p = 0.05$), which leads to the presumption that, despite the difficulty involved with its preparation, fresh FMT is more efficacious in preventing recurrent bouts of diarrhea associated with rCDI. Although frozen FMT has been known to decrease the number and frequency of donor screenings and expenses with application in healthcare settings, the study could not detect a significant clinical difference with frozen FMT compared with its counterparts, including antibiotic treatment ($p = 0.79$) and capsule forms ($p = 0.45$).[23] Although the ideal form of FMT remains unknown, one may still argue that both fresh and frozen FMT serve as beneficial alternatives to antimicrobial therapies in the prevention of recurrent bouts of CDI, especially following the initial clinical resolution of CDI with typical mainstays of treatment.

Multiple versus Single Infusion of FMT

Irrespective of delivery modality, multiple rather than a single infusion of FMT seemed to have assured a better prognosis of rCDI after initial treatment failure with FMT. In the comparison between donor FMT and autologous FMT by Colleen R. Kelly et al., multiple infusions increased the overall cure rate to 93.5%.[16] Similarly, in the study conducted by G. Ianiro et al., there was complete resolution in the FMT-M group compared with the FMT-S group (100 vs. 75%).[15] In both cases, the patient's response to FMT was concentration-dependent, favoring its efficacy in preventing recurrent episodes of CDI. Then again, it is worth mentioning that more adverse events were recorded in the FMT-M group than in the FMT-S group (7 vs. 19) in the investigation led by G. Ianiro and colleagues, which questions the safety profile of the stool specimens utilized.[15] Regardless, while antibiotics attempt to cure the disease course of CDI during the first episode itself, many of the relapsing cases can be attributed to the depleted microbiome profile of the patients. Thus, in cases of critical exhaustion of patients' microflora, more than a single infusion of FMT may be required to acquire the desired effects of the novel procedure.

FMT versus Antibiotics

Additionally, the results of both Christian Lodberg Hvas et al. and Jae Hyun Shin et al. conveyed the increased ineffectiveness of both antibiotics in curing rCDI and how useful FMT is as a rescue treatment following initial failures with traditional approaches.[17,19] For instance, in the open-labeled RCT by Christian Lodberg Hvas et al., FMT showed greater efficacy to fidaxomicin ($p = 0.009$) and vancomycin ($p = 0.001$) than either of the antibiotics alone ($p = 0.31$) after the eighth-week follow-up.[17] Even in the retrospective cohort study executed by Jae Hyun Shin et al., the non-FMT treatment showed higher recurrence (16.7 vs. 8.8%) and mortality (12.5 vs. 6%) rates with rCDI than what was seen with FMT.[19] Given that data were collected from a CDI-focused clinic, there was an intensive evaluation of the patient at the initial admission to determine their FMT qualification. With such strict inclusion and exclusion selection criteria in place, it gives way for increased generalizability of FMT's outcome data to patients suffering from severe cases of rCDI.

In another comparison with antibiotics, FMT contributed to better gastrointestinal health in the long run. With very few studies following patients post-FMT for even a year, the retrospective cohort study by Jalanka et al. had managed to observe patients for almost 3.8 years to determine the worst- and best-case scenarios of FMT's practical use for rCDI.[24] The findings disclose more upper gastrointestinal pain and overall discomfort post-antibiotic treatment than what was seen with FMT (25.6 vs. 11.1%, $p = 0.06$). In fact, better bowel function was reported with FMT than with antibiotics (53.3 vs. 25.6%, $p = 0.016$). There was up to 31.1% of patients who experienced improved mental health than the patients in the antibiotics group (8.9%, $p = 0.06$). For the reasons mentioned, the study also supported the patients' increased readiness to consider FMT as an initial treatment for rCDI over antibiotics for the extraintestinal benefits (FMT = 97.6%, AB = 60%). With further research underway, it can be understood that patients are more likely to fend for its regular use with the emergence of more favorable clinical outcomes irrespective of its unappealing esthetics.

Then again, a reasonable argument should still be made for the efficacy of antibiotics. For example, the RCT study by Louie et al investigates the distinct effectiveness of fidaxomicin and vancomycin during and after the treatment of CDI. In the study, fidaxomicin proved to be more superior to vancomycin, especially in its pursuit to reduce recurrence and toxin reexpression in the intestinal microbiome. Statistically speaking, while reappearance of

toxin in collected fecal samples was observed in 28% of vancomycin-treated patients (29 of 94 patients, $p = 0.03$), only 14% was observed in fidaxomicin-treated patients (13 of 91 patients, $p = 0.03$). Similarly, while 23% of vancomycin-treated patients (10 of 44 patients) experienced rCDI, only 11% of fidaxomicin-treated patients had a recurrence. Collectively, it can be understood that compared with vancomycin, fidaxomicin may serve as a robust choice of treatment during both the pretreatment and posttreatment phases of FMT, making way for a higher treatment prognosis in the event of using FMT as a rescue modality in refractory cases of CDI.

LIMITATIONS

As far as limitations are concerned, this article is flawed by its intent to solely focus on publications where FMT was more successful; hence, minimal consideration was given to those reporting poor treatment outcomes, despite comparing its efficacy to standard antibiotic therapies. For instance, this article failed to assess rCDI patients infected by the CD ribotype 027 strain, which is commonly associated with the poorest outcomes.[11] Thus, FMT results might not be completely representative of patient populations with a high frequency of this strain.

This article also does not focus heavily on the mentioned adverse events caused by FMT nor the efficacies of different delivery modalities of FMT due to the lack of information available; hence, it calls for future studies that can help compensate for these deficits using bigger sample sizes in more controlled testing environments.

Despite the limitations, there is still considerable evidence that supports FMT's role in ridding the patient of rCDI without the need for detrimental rescue treatments involving antimicrobials and elective surgeries. However, before declaring the novel procedure as the best form of medical practice, future studies should have a stronger emphasis on diverse non-FMT treatments outside of vancomycin to allow for a more accurate assessment of FMT's therapeutic role.

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