

# Accepted Manuscript

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

Divya Lakshmi Yerramsetty, Dipendra R. Pandeya, Ph.D.

DOI: 10.15404/msrj/09.2021.218

Reference: MSRJ

To appear in: *Medical Student Research Journal*

Received Date: 8 January 2021

Revised Date: 27 August 2021

Accepted Date: 1 September 2021

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

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

Divya Lakshmi Yerramsetty, Dipendra R. Pandeya, Ph.D.

Medical University of the Americas, Devens, MA, USA

**Corresponding author:**

Divya Lakshmi Yerramsetty, BS

[yerrams1@msu.edu](mailto:yerrams1@msu.edu)

## Introduction

The gastrointestinal tract is a reservoir for up to 10,000 to 100 trillion microorganisms<sup>[10]</sup>, collectively known as the gut microbiota. Amongst these colonizers, the dominant genera include *Bacteroides*, *Clostridioides*, *Fusobacterium*, *Eubacterium*, *Ruminococcus*, *Peptococcus*, *Peptostreptococcus*, and *Bifidobacterium*<sup>[10]</sup>. Though 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, immune regulation, etc.)<sup>[11]</sup>.

When the gut's microbiome gets disrupted, the term "dysbiosis"<sup>[2]</sup> can be adopted. 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<sup>[27]</sup>. 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<sup>[2]</sup>. 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<sup>[4]</sup>. 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<sup>[1]</sup>.

Current guidelines to treat CDI include mono- and combination therapies with vancomycin and fidaxomicin<sup>1</sup>. Of the existing dosage regimens, pulsed dosing of these first-line agents has starkly reduced recurrence rates compared to standard protocols. Unfortunately, even after the recommended treatment, recurrence is still seen in up to 10 to 20 percent<sup>[4]</sup> of patients after the initial visit – with up to 40 to 65 percent<sup>[4]</sup> of previously treated patients experiencing further recurrences after the second visit.

---

<sup>1</sup> Non-inferior to vancomycin; however, it is not studied in severe/fulminant cases of CDI<sup>[6]</sup>

In 30 percent<sup>[3]</sup> 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<sup>[3]</sup>.

In the last few decades, there has been a surge in interest to revamp and revolutionize an ancient<sup>[25]</sup> procedure known as Fecal Microbiota Transplant (FMT) to correct the dysbiosis responsible for rCDI. 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<sup>[13]</sup>. However, this clause's exception emerges under "enforcement discretion"<sup>[13]</sup>, which allows FMT for patients who are refractory to standard therapy with proper consent in order.

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<sup>[15]</sup>, which paves the way for its imminent success. 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<sup>[15]</sup>. Currently, the cure for rCDI has been seen within hours to 4-5 days<sup>[13]</sup> in struggling patients post-FMT. This paper aims to evaluate and analyze current and reliable sources of evidence 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). A 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 ( $\geq 18$  years old) 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: (a) participants with recurrent CDI supported by a clinical diagnosis and/or laboratory parameters; (b) subjects with recurrent CDI having received FMT through any method of administration. Studies were excluded if there were: (a) scoring  $< 6$  on controlled intervention studies and cohort studies; (b) scoring  $< 4$  on systematic reviews and meta-analyses; (c) lacking standard treatment of care for primary CDI before FMT; (d) evaluating FMT in the immunocompromised or patients with or without severe comorbid conditions; (e) including pediatric patients; (f) testing small ( $< 15$  subjects) and non-diverse sample sizes; (g) duplicated studies; (h) 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: (a) treatment success and failure after single versus multiple infusions of FMT in the post-treatment phase; (b) long-term implications post-FMT; (c) efficacy of mono- and/or adjunctive therapy with common antibiotics (vancomycin versus 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 Figure 1 and Table 1).

### **Quality Assessment and Risk of Bias of Individual Studies Assessment**

The primary investigator independently evaluated all the included studies with  $\geq 4$  patients using the National Institute of Health (NIH) Study Quality Assessment Tools<sup>[14]</sup>. 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 non-randomized Studies of Interventions tool<sup>[22]</sup> (ROBINS-I) as well as the Risk of Bias tool for randomized control trial<sup>[14]</sup>, the primary investigator also thoroughly assessed the risk of bias of each study. The scores were classified to be either low,

moderate, serious, or critical. Studies that were categorized as serious or critical were immediately excluded.

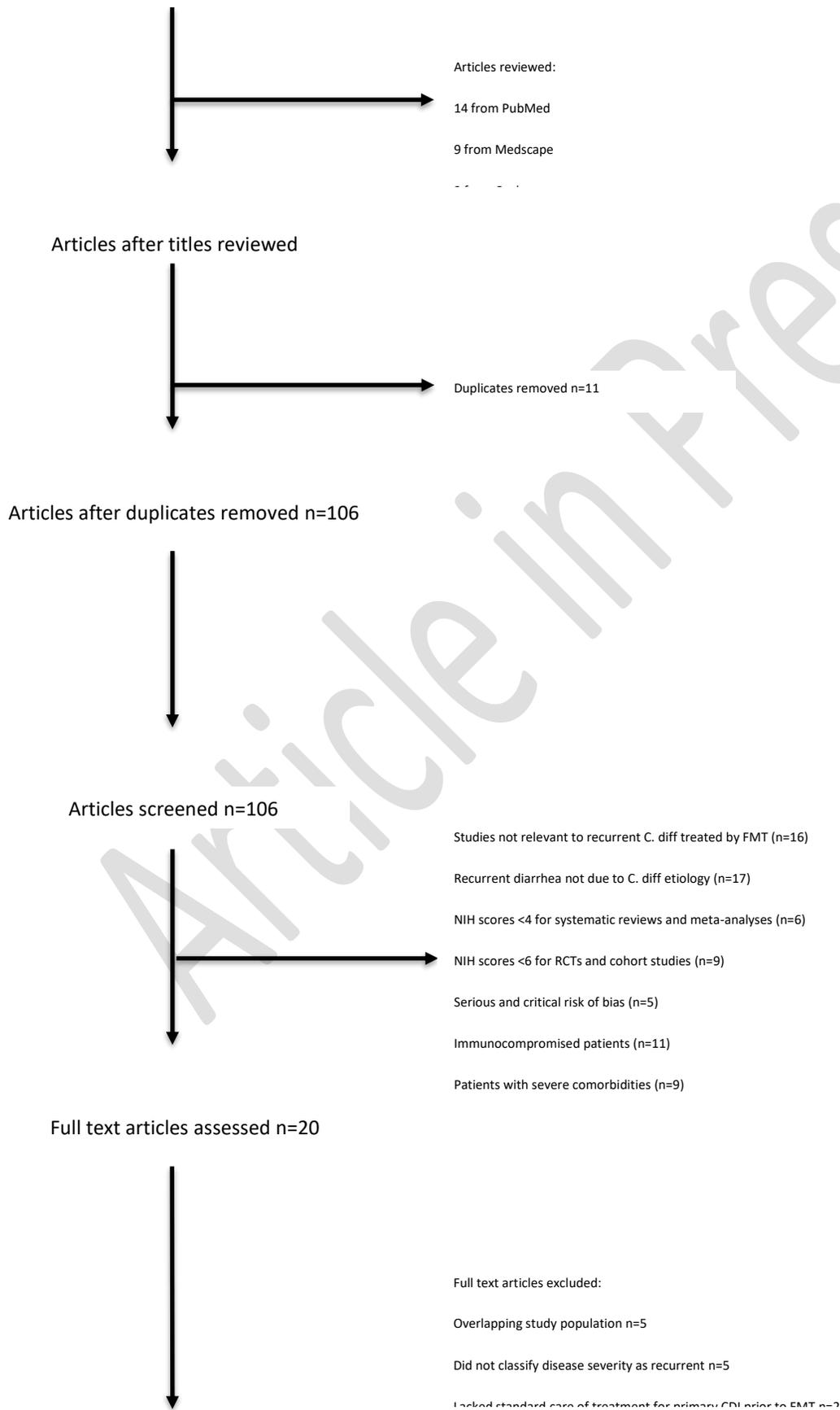
**Table 1. Evidence Table**

Article in Press

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

	560 from PubMed	Hui	G. Ianiro	Colleen R. Kelly	Christian Lodberg Hvas	Louie TJ	J. Jalanka	Jae Hyun Shin
1 <sup>st</sup> Re	83 from Medscape	atic & analysis	RCT	RCT	RCT	RCT	Retrospective Cohort Study	Retrospective Cohort Study
Pub. Yr.	analysis	analysis	2016	2018	2019	2012	2018	2019
Ind. V.		2019	1(a). Donor FMT 1(b). Autologous FMT	2(a). FMT-S group 2(b). FMT-M group	1(a). FMTv (n=24) 2(b). Fidaxomicin b.i.d. (n=24) 2(c). Vancomycin q.i.d. (n=16)	1(a). Vancomycin-treated pts (n=44) 1(b). Fidaxomicin-treated pts (n=45)	1(a). FMT group 1(b). Antibiotic group (AB)	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 & 30 case series	Researchers chose 8 studies using electronic database search and compiled data from each	46/179 pts 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 b/w 5/5/16 and 6/10/18 and randomly assigned	89/629 pts were randomly assigned to a 10d course of: (a). Vancomycin 125mg q.i.d. OR (b). Fidaxomicin 20mg 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 pts, 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 pts vs 11% (5/44) in fidaxomicin-treated pts	<u>IBowel fxn:</u> 53.3%vs25.6% <u>IMental health</u> 31.1% vs 8.9% <u>Upper GI pain</u> 31.3%vs51.3% <u>FMT readiness</u> 97.6% vs 60%	<u>Recurrence rate:</u> FMT=4.5% vs. 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 <sup>2</sup>	1	1	1	1	1	1	3	3

<sup>2</sup> Level 1 includes RCT, systematic review of RCTs +/- meta-analysis of RCTs; Level 3 includes retrospective cohort studies





Studies included after literature search n=8

### **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 Figure 1 and Table 1). Table 1 highlights the notable components of each literature source, including: (a) name of the first author; (b) research design; (c) year of publication; (d) independent and dependent variables; (e) data collection method; (f) pertinent findings; (g) strengths; (h) weaknesses; (i) NIH scores; (j) ROBINS-I scores; (k) level of study based on the Evidence-Based Medicine Pyramid.

M.N. Quraishi and colleagues<sup>[15]</sup> did a systematic review and meta-analysis on the efficacy of FMT of different delivery methods and preparation in the treatment of rCDI. Of the 37 studies, 34 reported positive responses to FMT with a cure rate of 84%. The 25-case series and 7 RCTs demonstrated that the lower gastrointestinal route was superior to the upper gastrointestinal route (95% vs. 88%) ( $p = 0.02$ ). 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 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<sup>[5]</sup>, independently extracted articles with stringent eligibility criteria that resulted in eight RCT studies. The pooled relative risks were calculated with a 95% CI, and the heterogeneity between studies was assessed using the I<sup>2</sup> 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 ( $I^2 = 67\%$ ) between them. The recurrence rate of clinical diarrhea in the control group was significantly higher compared to the fresh FMT group (24.6% or 65/264 vs. 11.0% or 30/273;  $p = <0.05$ ). 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 provide 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.*<sup>[7]</sup> to compare single (FMT-S) to multiple infusions (FMT-M) of FMT in the treatment of rCDI. 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 *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.*<sup>[9]</sup> conducted a double-blinded RCT at the University of Minnesota in Minneapolis to compare the clinical outcome of autologous FMT to donor FMT. Patients were enrolled between 11/15/2012 and 03/10/2015 at two academic hospitals in New York (NY) and Rhode Island (RI). Both the donor and patient stool specimens were collected one hour 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-label RCT was conducted at a gastroenterology clinic in Denmark, Christian by Christian Lodberg Hvas *et al.* [6] to compare the combined clinical resolution of fresh FMT and non-FMT treatments (vancomycin and fidaxomicin). 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.* <sup>[12]</sup> 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. Using 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 reduction of both *C. difficile* toxin re-expression 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 qPCR and was log-transformed. Vancomycin-treated patients experienced more recurrence than fidaxomicin-treated patients Compared (10/44 or 23% vs 5/44 or 11%,  $p = 0.03$ ). Similarly, vancomycin-treated patients had more toxin re-expression 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 to its competitor, vancomycin.

An open-label RCT was conducted at a gastroenterology clinic in Denmark by Christian Lodberg Hvas *et al.* <sup>[6]</sup> to compare the combined clinical resolution of fresh FMT and non-FMT treatments (vancomycin and fidaxomicin). Between 04/05/2016 and 06/10/2018, 64 out of 120 adults with rCDI were randomly assigned to one of the three 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 8 of 24 patients (33%), with an increase in clinical resolution to 10 patients after the eighth week (42%). Finally,

only 3 of 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 ( $p = 0.31$ ).

A retrospective cohort study was instigated by Jae Hyun Shin and colleagues<sup>[18]</sup> j all patients' medical records that received FMT between June 2012 to March 2015 at the University of Virginia Complicated *C. difficile* Clinic (CCDC). 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 chi-squared analysis, 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 that suggest that patients with greater than three recurrences benefit from FMT regardless of route of delivery.

## **Discussion**

### **Donor vs. 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.* <sup>[9]</sup>, 90.1% ( $p = 0.042$ ) of the patients experienced clinical resolution with donor FMT versus only 62.5% seen with autologous FMT.

Normally, during remission periods with rCDI, the patient's stool is "banked"<sup>[23]</sup> for FMT use before starting the patient on any antibiotic therapy. 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.<sup>3</sup> 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, increases the patients' and physicians' willingness to opt for autologous over heterologous FMT in those suffering from rCDI <sup>[21]</sup>.

Even so, as determined by the findings of Colleen R. Kelly *et al.* <sup>[9]</sup>, 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 <sup>[26]</sup>: *Bacteroides*, *Firmicutes*. 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 <sup>[26]</sup>. For such reasons, donor FMT necessitates only a *partial* rather than complete engraftment of the donor's feces to resolve rCDI <sup>[26]</sup>. 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

---

<sup>3</sup> Protein consumption has a positive correlation with overall microbial diversity<sup>[25]</sup>

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.

### **Fresh vs. Frozen FMT**

Similar outcomes were also seen in another systematic and meta-analysis by Wenjia Hui *et al.*<sup>[5]</sup> The study has shown that there is a higher recurrence rate of diarrhea within the control group compared to 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<sup>[16]</sup>, the study could not detect a significant clinical difference with frozen FMT compared to its counterparts, including antibiotic treatment ( $p = 0.79$ ) and capsule forms ( $p = 0.45$ ). 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 vs. 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.*<sup>[9]</sup>, multiple infusions increased the overall cure rate to 93.5%. Similarly, in the study conducted by G. Ianiro *et al.*<sup>[7]</sup>, there was complete resolution in the FMT-M group compared to the FMT-S group (100% vs. 75%). 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<sup>[7]</sup>) in the investigation led by G. Ianiro and colleagues<sup>[7]</sup>, which questions the safety profile of the stool specimens utilized. 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 vs. Antibiotics**

Additionally, the results of both Christian Lodberg Hvas *et al.*<sup>[6]</sup> and Jae Hyun Shin *et al.*<sup>[10]</sup> convey the increased ineffectiveness of both antibiotics in curing rCDI and how useful FMT is as a rescue treatment following initial failures with traditional approaches. For instance, in the open-label RCT by Christian Lodberg Hvas *et al.*<sup>[6]</sup>, 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. Even in the retrospective cohort study executed by Jae Hyun Shin *et al.*<sup>[18]</sup>, 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. Given that data was 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.*<sup>[8]</sup> 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. 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 the 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 aesthetics.

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 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,  $p = 0.03$ ), only 14% was observed in fidaxomicin-treated patients (13 of 91,  $p = 0.03$ ). Similarly, while 23% of vancomycin-treated patients (10 of 44) experienced rCDI, only 11% of fidaxomicin-treated patients had a recurrence. Collectively, it can be understood that compared to vancomycin, fidaxomicin may serve as a robust choice of treatment during both pretreatment and post-treatment 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 paper 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 paper failed to assess rCDI patients infected by the CD ribotype 027 strain<sup>[14]</sup>, which is commonly

associated with the poorest outcomes. Thus, FMT results might not be completely representative of patient populations with a high frequency of this strain.

This paper 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.

**References:**

- [1] Bagdasarian N, Rao K, Malani PN. Diagnosis and Treatment of *Clostridium difficile* in Adults: A Systematic Review. *JAMA*. 2015;313(4):398–408. doi:10.1001/jama.2014.17103.
- [2] Battaglioli, E. J. et al. (2018). Clostridioides difficil amino acids associated with gut microbial dysbiosis in a subset of patients with diarrhea. *Science Translational Medicine*, 10(464). doi:10.1126/scitranslmed.aam7019.
- [3] Cheng, Y., Fischer, M. (2020). Clinical management of severe, fulminant, and refractory Clostridioides difficile infection. *Expert Review of Anti-infective Therapy*, 18(4), 323-333. doi:10.1080/14787210.2020.1730814.
- [4] Feuerstadt, P et al. (2020). Healthcare resource utilization and direct medical costs associated with index and recurrent Clostridioides difficile infection: A real-world data analysis. *Journal of Medical Economics*, 23(6), 603-609. doi:10.1080/13696998.2020.1724117
- [5] Hui, Wenjia et al. "Fecal Microbiota Transplantation for Treatment of Recurrent C. Difficile Infection: An Updated Randomized Controlled Trial Meta-Analysis." *PLOS ONE*. 23 Jan. 2019, pp. 1–14., doi:https://doi.org/10.1371/journal.pone.0210016.
- [6] Hvas, Christian Lodberg et al. "Fecal Microbiota Transplantation Is Superior to Fidaxomicin for Treatment of Recurrent Clostridium Difficile Infection." *Gastroenterology*, vol. 156, no. 5, 2 Jan. 2019, pp. 1324–1332., doi:https://doi.org/10.1053/j.gastro.2018.12.019.
- [7] Ianiro, G et al. "Faecal Microbiota Transplantation by Colonoscopy Plus Vancomycin for the Treatment of Severe Refractory Clostridium Difficile." *Alimentary Pharmacology & Therapeutics*, 2018, pp. 152–159. *Medscape*, www.medscape.com/viewarticle/898739\_3.

- [8] Jalanka, J et al. "The Long-Term Effects of Faecal Microbiota Transplantation for Gastrointestinal Symptoms and General Health in Patients with Recurrent Clostridium Difficile Infection." *Alimentary Pharmacology & Therapeutics*, 2018, pp. 371–379. *Medscape*, [www.medscape.com/viewarticle/891293\\_2](http://www.medscape.com/viewarticle/891293_2).
- [9] Kelly, Colleen R et al. "Effect of Fecal Microbiota Transplantation on Recurrence in Multiply Recurrent Clostridium difficile Infection: A Randomized Trial." *Annals of internal medicine* vol. 165,9 (2016): 609-616. doi:10.7326/M16-0271
- [10] Lawson, R.D., Coyle, W.J. The Noncolonic Microbiome: Does it Really Matter?. *Curr Gastroenterol Rep* 12, 259–262 (2010). <https://doi.org/10.1007/s11894-010-0111-6>.
- [11] Littman, D., & Pamer, E. (2011). Role of the Commensal Microbiota in Normal and Pathogenic Host Immune Responses. *Cell Host & Microbe*, 10(4), 311-323. doi:10.1016/j.chom.2011.10.004
- [12] Louie TJ, Cannon K, Byrne B, Emery J, Ward L, Eyben M, Krulicki W. Fidaxomicin preserves the intestinal microbiome during and after treatment of Clostridium difficile infection (CDI) and reduces both toxin reexpression and recurrence of CDI. *Clin Infect Dis*. 2012 Aug;55 Suppl 2(Suppl 2):S132-42. doi: 10.1093/cid/cis338. PMID: 22752862; PMCID: PMC3388020.
- [13] Mullish, Benjamin H et al. "The Use of Faecal Microbiota Transplant as Treatment for Recurrent or Refractory Clostridium Difficile Infection and Other Potential Indications: Joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) Guidelines." *Journal of Hospital Infection*, vol. 100, no. Supplement 1, 2018, pp. S1–S31., doi:<https://doi.org/10.1016/j.jhin.2018.07.037>.

- [14] National Institute of Health. Study Quality Assessment Tools.  
<https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools>. [cited October 24, 2021].
- [15] Pan, D., & Yu, Z. (2013). Intestinal microbiome of poultry and its interaction with host and diet. *Gut Microbes*, 5(1), 108-119. doi:10.4161/gmic.26945
- [16] Paknikar, Raghavendra. "Fecal Microbiota Transplantation for the Management of Clostridium Difficile Infection." *Surgical Infections*, 5 Dec. 2018, pp. 785–791. *PubMed*, doi:10.1089/sur.2018.221.
- [17] Quraishi, M. N. et al. "Systematic Review with Meta-Analysis: The Efficacy of Faecal Microbiota Transplantation for the Treatment of Recurrent and Refractory Clostridium Difficile Infection." *Alimentary Pharmacology & Therapeutics*, vol. 46, no. 5, 14 July 2017, pp. 479–493., doi:<https://doi.org/10.1111/apt.14201>.
- [18] Ramai, D. (2018). Fecal microbiota transplantation: Donor relation, fresh or frozen, delivery methods, cost-effectiveness. *Annals of Gastroenterology*, 32(1), 30-38.  
doi:10.20524/aog.2018.0328.
- [19] Rosa, Rossana M. et al. "Preventing Recurrent CDI: New, Old, and Really Old Strategies ." *Society for Healthcare Epidemiology of America (SHEA)*, 15 June 2017. *Medscape*, [www.medscape.com/viewarticle/881379](http://www.medscape.com/viewarticle/881379).
- [20] Shin, Jae Hyun et al. "Outcomes of a Multidisciplinary Clinic in Evaluating Recurrent Clostridioides Difficile Infection Patients for Fecal Microbiota Transplant: A Retrospective

Cohort Analysis." *Journal of Clinical Medicine*, vol. 8, no. 7, 16 July 2019, pp. 1–11.,  
doi:<https://doi.org/10.3390/jcm8071036>.

- [21] Singh, R.K., Chang, H.W., Yan, D. *et al.* Influence of diet on the gut microbiome and implications for human health. *J Transl Med* 15, 73 (2017). <https://doi.org/10.1186/s12967-017-1175-y>.
- [22] Staley, C. (2016). Complete Microbiota Engraftment Is Not Essential for Recovery from Recurrent *Clostridium difficile* Infection following Fecal Microbiota Transplantation. *MBio*, 7(6), 1-9. doi:10.1128/mbio.01965-16.
- [23] Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: A tool for assessing risk of bias in non-randomized studies of interventions. *BMJ* 2016;355:i4919.
- [24] Sterne JAC, Savovic J, Page MJ, et al. RoB 2: A revised tool for assessing risk of bias in randomized trials. *BMJ* 2019;366:l4898.
- [25] Taur, Y. (2018). Reconstitution of the gut microbiota of antibiotic-treated patients by autologous fecal microbiota transplant. *Science Translational Medicine*, 10(460), 1-8. doi:10.1126/scitranslmed.aap9489.
- [26] Wilson, Brooke C. "The Super-Donor Phenomenon in Fecal Microbiota Transplantation." *Frontiers in Cellular and Infection Microbiology*, vol. 9, no. 2, 21 Jan. 2019, pp. 1–11. *PubMed*, doi:10.3389/fcimb.2019.00002.
- [27] Woodworth, M. H. (2017). Challenges in fecal donor selection and screening for fecal microbiota transplantation: A review. *Gut Microbes*, 8(3), 225-237. doi:10.1080/19490976.2017.1286006

Article in Press