Summer 8-8-2015

Fecal Microbiota Transplant (FMT) for the Treatment of Recurrent, Refractory Clostridium difficile Infection

Molly Beedles
Pacific University

Follow this and additional works at: http://commons.pacificu.edu/pa
Part of the Medicine and Health Sciences Commons

Recommended Citation

This Capstone Project is brought to you for free and open access by the Theses, Dissertations and Capstone Projects at CommonKnowledge. It has been accepted for inclusion in School of Physician Assistant Studies by an authorized administrator of CommonKnowledge. For more information, please contact CommonKnowledge@pacificu.edu.
Fecal Microbiota Transplant (FMT) for the Treatment of Recurrent, Refractory Clostridium difficile Infection

**Abstract**

**BACKGROUND**

According to the U.S. Center for Disease Control and Prevention, *Clostridium difficile* was responsible for 453,000 infections and approximately 29,000 deaths in the United States in 2011 alone. Newer, more virulent, antibiotic-resistant strains of *C. difficile* are increasing rates of relapse making the disease is more difficult to control than ever before. Efficacy of fecal microbiota transplant (FMT) for recurrent, refractory *C. difficile* infection (CDI) has been proven in case studies and reports, but the first RCTs using this treatment option have been published and will be analyzed in this systematic review.

**METHODS**

An exhaustive medical literature search was conducted using MEDLINE-Ovid, CINAHL, and Web of Science using the following keywords and searches: 1) fecal microbiota transplant and clostridium difficile and 2) clostridium difficile and feces and donor. The National Institute of Health clinical trials database was searched using the terms “fecal microbiota transplant,” “clostridium difficile and feces,” and “donor feces” for completed and published RCTs. Relevant articles for inclusion were assessed for quality using GRADE.

**RESULTS**

The search resulted in a total of 54 studies of which only two studies met inclusion criteria. The results from both the van Nood et al study and the Youngster et al study demonstrate the positive outcomes of treating recurrent, refractory CDI with fecal microbiota transplant (FMT). The van Nood et al study showed an overall cure in 15 of 16 patients (94%) with donor feces infusion compared to cure in 4 of 13 patients (31%) treated with vancomycin alone. According to the Youngster et al study, nasogastric tube (NGT) proves to be the safer, patient-preferred route of FMT administration and is comparably effective when compared to colonoscopy.

**CONCLUSION**

Based on the study results, FMT should be considered by clinicians as a safe and effective treatment option for certain patients with recurrent, refractory CDI. It also appears viable to spare patients risks of colonoscopy by administering the donor feces by upper GI route using NGT.

**KEYWORDS**

Fecal Microbiota Transplant (FMT), donor feces transplant, *Clostridium difficile*, *C. diff*, infection, diarrhea, humans, vancomycin, antibiotics, colonoscopy, NGT

**Degree Type**

Capstone Project

**Degree Name**

Master of Science in Physician Assistant Studies

This capstone project is available at CommonKnowledge: [http://commons.pacificu.edu/pa/506](http://commons.pacificu.edu/pa/506)
First Advisor
Professor Sommers

Keywords
Fecal Microbiota Transplant (FMT), donor feces transplant, Clostridium difficile, C. diff, infection, diarrhea, humans, vancomycin, antibiotics, colonoscopy, NGT

Subject Categories
Medicine and Health Sciences

Rights
Terms of use for work posted in CommonKnowledge.
Copyright and terms of use

If you have downloaded this document directly from the web or from CommonKnowledge, see the “Rights” section on the previous page for the terms of use.

If you have received this document through an interlibrary loan/document delivery service, the following terms of use apply:

Copyright in this work is held by the author(s). You may download or print any portion of this document for personal use only, or for any use that is allowed by fair use (Title 17, §107 U.S.C.). Except for personal or fair use, you or your borrowing library may not reproduce, remix, republish, post, transmit, or distribute this document, or any portion thereof, without the permission of the copyright owner. [Note: If this document is licensed under a Creative Commons license (see “Rights” on the previous page) which allows broader usage rights, your use is governed by the terms of that license.]

Inquiries regarding further use of these materials should be addressed to: CommonKnowledge Rights, Pacific University Library, 2043 College Way, Forest Grove, OR 97116, (503) 352-7209. Email inquiries may be directed to: copyright@pacificu.edu

This capstone project is available at CommonKnowledge: http://commons.pacificu.edu/pa/506
NOTICE TO READERS

This work is not a peer-reviewed publication. The Master’s Candidate author of this work has made every effort to provide accurate information and to rely on authoritative sources in the completion of this work. However, neither the author nor the faculty advisor(s) warrants the completeness, accuracy or usefulness of the information provided in this work. This work should not be considered authoritative or comprehensive in and of itself and the author and advisor(s) disclaim all responsibility for the results obtained from use of the information contained in this work. Knowledge and practice change constantly, and readers are advised to confirm the information found in this work with other more current and/or comprehensive sources.

The student author attests that this work is completely his/her original authorship and that no material in this work has been plagiarized, fabricated or incorrectly attributed.
Fecal Microbiota Transplant (FMT) for the Treatment of Recurrent, Refractory Clostridium difficile infection

Comparison of FMT administration routes and cure of C. difficile colitis using FMT versus standard antibiotic therapy

Molly Beedles
BIOGRAPHY

Molly Beedles was born and raised in Lawrence, Kansas. She stayed in her hometown to obtain her Bachelor of Science degree at The University of Kansas. She worked as a Patient Care Technician in an Orthopedic Clinic upon graduation. She then moved to New York City for a new adventure and found employment in a Physical Therapy office and as a Personal Trainer. After a short period, she moved back to Lawrence to complete prerequisite courses for Physician Assistant programs as well as work as a Medical Assistant in a Pediatric Clinic. She is thankful to have gotten into her top preferred PA program at Pacific University and is eager for an exciting future career as a Physician Assistant.
ABSTRACT

BACKGROUND
According to the U.S. Center for Disease Control and Prevention, Clostridium difficile was responsible for 453,000 infections and approximately 29,000 deaths in the United States in 2011 alone. Newer, more virulent, antibiotic-resistant strains of C. difficile are increasing rates of relapse making the disease is more difficult to control than ever before. Efficacy of fecal microbiota transplant (FMT) for recurrent, refractory C. difficile infection (CDI) has been proven in case studies and reports, but the first RCTs using this treatment option have been published and will be analyzed in this systematic review.

METHODS
An exhaustive medical literature search was conducted using MEDLINE-Ovid, CINAHL, and Web of Science using the following keywords and searches: 1) fecal microbiota transplant and clostridium difficile and 2) clostridium difficile and feces and donor. The National Institute of Health clinical trials database was searched using the terms “fecal microbiota transplant,” “clostridium difficile and feces,” and “donor feces” for completed and published RCTs. Relevant articles for inclusion were assessed for quality using GRADE.

RESULTS
The search resulted in a total of 54 studies of which only two studies met inclusion criteria. The results from both the van Nood et al study and the Youngster et al study demonstrate the positive outcomes of treating recurrent, refractory CDI with fecal microbiota transplant (FMT). The van Nood et al study showed an overall cure in 15 of 16 patients (94%) with donor feces infusion compared to cure in 4 of 13 patients (31%) treated with vancomycin alone. According to the Youngster et al study, nasogastric tube (NGT) proves to be the safer, patient-preferred route of FMT administration and is comparably effective when compared to colonoscopy.

CONCLUSION
Based on the study results, FMT should be considered by clinicians as a safe and effective treatment option for certain patients with recurrent, refractory CDI. It also appears viable to spare patients risks of colonoscopy by administering the donor feces by upper GI route using NGT.

KEYWORDS
Fecal Microbiota Transplant (FMT), donor feces transplant, Clostridium difficile, C. diff, infection, diarrhea, humans, vancomycin, antibiotics, colonoscopy, NGT
ACKNOWLEDGEMENTS

To Dr. Mark Pedemonte: Thank you for not only being an amazing professor during our didactic PA education, but also for being an invested student advisor. I appreciate all the time you spent outside class hours to answer questions about the material and to help get me through periods of personal turbulence during the intense didactic year.

To my parents: Thank you for supporting me through all of my personal and career endeavors. I appreciate your tough love during my schooling because it made me strong enough to keep pushing forward. You have been the most amazing role models—demonstrating both ambition and tenacity. You also instilled in your children a desire to help and empathize with others.

To Cyrus Beedles, my husband: I could not have made it through this program without your unwavering love and support. You have been my provider, my cheerleader, my lunch-maker, my housekeeper, my event planner... my rock. I can never do or say enough to thank you.
TABLE OF CONTENTS

BIOGRAPHY .................................................................................................................. 2
ABSTRACT ..................................................................................................................... 3
ACKNOWLEDGEMENTS ............................................................................................... 4
LIST OF TABLES ............................................................................................................ 6
LIST OF ABBREVIATIONS .......................................................................................... 6
BACKGROUND ............................................................................................................ 7
METHODS .................................................................................................................. 10
RESULTS ..................................................................................................................... 11
DISCUSSION ............................................................................................................... 17
REFERENCES .............................................................................................................. 23
TABLE I. GRADE QUALITY ASSESSMENT OF STUDIES ........................................ 25
LIST OF TABLES

TABLE I. GRADE QUALITY ASSESSMENT OF STUDIES

LIST OF ABBREVIATIONS

CDC – Center for Disease Control and Prevention
CDI – Clostridium difficile Infection
FMT – Fecal Microbiota Transplant
GI – Gastrointestinal
GRADE – Grading of Recommendations, Assessment, Development and Evaluations
HAI – Healthcare Associated Infection
IMT – Intestinal Microbiota Transplantation
NGT – Nasogastric Tube
RCT – Randomized Controlled Trial
RR – Relative Risk
Fecal Microbiota Transplant (FMT) for the Treatment Of Recurrent, Refractory *Clostridium difficile* Infection: Comparison of FMT administration routes and cure of *C. difficile* colitis using FMT versus standard antibiotic therapy

**BACKGROUND**

*Clostridium difficile*—a gram-positive, spore-forming bacillus most prevalent in hospitals and chronic-care facilities—1—is responsible for increased rates of morbidity and mortality in patients nationwide and is an increased burden to healthcare providers due to the high rate of recurrence. According to the U.S. Center for Disease Control and Prevention, *C. difficile* was responsible for 453,000 infections and approximately 29,000 deaths in the United States in 2011 alone. In the last 15 years, the incidence of infections due to *C. difficile* has tripled. In some parts of the United States, it has even been suggested by data from 2011 that *C. difficile* infections are the most common etiology of healthcare-associated infections (HAIs)—even more than the infamous methicillin-resistant *Staphylococcus aureus* infections. Though the U.S. Department of Health and Human Services set a goal to reduce facility-onset *C. difficile* infections and hospitalizations with *C. difficile* by 30% individually, data revealed only a 2% reduction in facility-onset CDI and a 17% increase in hospitalizations from baseline.

Not only do clinicians need to consider the increasing incidence of CDI, but also the increasing severity of the disease. A new strain of *Clostridium difficile* was discovered in the 1980s and has been followed more closely since CDI epidemics in the U.S. and Canada from 2000 to 2003 were linked with the strain. This new strain—referred to as restriction
enzyme analysis Type BI, North American PFGE type 1 or PCR-ribotype 027 (NAP1/027)\(^2,8,9\) — is not only a hyperproducer of toxins, but is also resistant to fluoroquinolone antimicrobials.\(^2,9\) It has been shown to be responsible for lower cure rates of CDI and increased recurrence rates when compared to other \textit{C. difficile} strains.\(^8\) Their development is likely linked in part to increased antibiotic use — especially in healthcare settings, where the majority (at least 80\%) of cases are contracted.\(^1,2\)

Clinicians are constantly being reminded of the issues concerning antibiotic-resistance and our contributing role by overprescribing antibiotics. The CDC reports that half of all hospitalized patients get antibiotics at some point during their stay despite studies showing that 30-50\% of antibiotics prescribed in hospitals are unnecessary or incorrect.\(^2\) One study revealed that 85\% of patients with \textit{C. difficile} infection received antibiotics within 30 days of symptom onset.\(^10\) By prescribing broad-spectrum antibiotics for most bacterial infections, both pathologic and non-pathologic microbiota are killed, thus disrupting the balance of the sensitive human fecal microbiome.\(^11\) This dysbiosis facilitates infection by \textit{C. difficile} either by overgrowth of indigenous spores (normally held to low quantities by native gut flora) or nosocomial acquisition of \textit{C. difficile}.\(^12\) Current treatment of CDI using the standard antibiotics results in perpetuation of microbiome disturbance and put the patient at risk for recurrent or relapsing infection.\(^1,3\)

With the newer, antibiotic-resistant NAP1/027 strain of \textit{C. difficile} becoming more prevalent, the incidence of recurrent or relapsing CDI should be of great concern to clinicians. The rate of recurrence or relapse varies in the research, but clinicians should expect 15-35\% of patients to have a second episode of CDI after treatment of the first
episode with appropriate antibiotic regimen—with most reinfections occurring within 8 weeks of initial infection.⁴,¹³ Rates of failure after antibacterial therapy were comparable between the two antibiotics used for CDI treatment over the last 25 years—vancomycin and metronidazole.³,¹⁴

*Clostridium difficile* infection is increasing in prevalence, severity, and rates of recurrence or relapse despite—and often in correspondence to—antibiotic therapy. Thus, investigators are finally beginning to think outside the box for improved treatment of CDI. Administration of fecal enema was initially used in 1958 as a therapeutic method in the treatment of “fulminant, life-threatening pseudomembranous enterocolitis.”¹⁵ As we learn more about the importance of maintaining a balanced gut microbiome, there has been growing interest in restoring the microbiota through instillation of healthy, donor feces.¹⁶ Right now, the concentration on microbiota restoration is targeted at patients with refractory CDI because of the presumed link between continued antibiotic treatments and increased displacement of normal gut flora in these individuals. A systematic review of 317 patients across 27 case series and reports revealed disease resolution in 92% of cases after intestinal microbiota transplantation (IMT)—89% were cured after a single IMT treatment.¹⁷ Though many case studies have shown positive treatment outcomes with use of fecal bacteriotherapy, randomized controlled trials (RCTs) have been lacking on the subject. This systematic review aims to answer questions using data from recent RCTs as to the superiority, safety, and feasibility of treating refractory CDI with fecal microbiota transplant versus standard antibiotic therapy, in addition to the most successful route of administration.
METHODS

Literature Search

An exhaustive medical literature search was conducted using the databases MEDLINE-Ovid, CINAHL, and Web of Science using the following keywords and searches: 1) fecal microbiota transplant and clostridium difficile and 2) clostridium difficile and feces and donor. The search was then limited to include human-only studies in the English language. Abstracts were reviewed in search of randomized controlled trials with a comparison of interest. The National Institute of Health clinical trials database was also searched using the terms “fecal microbiota transplant,” “clostridium difficile and feces,” and “donor feces” for completed and published RCTs. Bibliographies of meta-analysis articles reviewing FMT treatment for C. difficile were also searched for any inclusions of RCTs.

Eligibility Criteria

Articles included in this analysis were those designed as a randomized controlled trial comparing two different interventions regarding FMT as treatment for C. difficile with the primary outcomes being cure of C. difficile infection and prevention of relapse. The population of interest included patients of any age who experienced relapsing C. difficile colitis. Most patients in the studies had C. difficile infection refractory to a standard regimen of antibiotics, but this was not a requirement for analysis. Due to the low number of RCTs completed and published on this subject, no RCTs found were excluded from this systematic review.
Study Validity

Selected studies were analyzed for validity and risk of bias in addition to the overall quality assessment using Grading of Recommendations, Assessment, Development and Evaluation (GRADE). \(^{20}\) Selection bias was addressed by looking at randomization and concealing of study groups. Performance bias and detection bias were assessed through study blinding procedures. Attrition bias was addressed by whether or not the studies discussed and accounted for any missing outcome data. Lastly, reporting bias was assessed by reviewing articles for any significant, yet unreported, differences between the groups.

RESULTS

Search Results

The first keyword search on MEDLINE-Ovid resulted in 16 studies. The second keyword search on MEDLINE-Ovid resulted in 38 studies. After applying limitations and eligibility criteria, two randomized controlled trials \(^{21,22}\) were included in this systematic review. (See Table I.)

The van Nood et al Study

This randomized, controlled trial \(^{21}\) compared infusion of donor feces (FMT) to standard antibiotic regimen in the treatment of recurrent, refractory Clostridium difficile infection. The study had three treatment groups: 1) donor feces infusion, preceded by a 4-day vancomycin regimen with bowel lavage, 2) 14-day vancomycin regimen, 3) 14-day vancomycin regimen with bowel lavage. This study took place in Amsterdam, The Netherlands, at the Academic Medical Center between January 2008 and August 2010. The
study planned to enroll a total of 120 patients—40 in each treatment arm. Patients were enrolled internally and also admitted from other hospitals based on physician referral with a visit by a study physician to confirm eligibility.²¹

Of the 102 patients initially screened, only 43 participants were included in the study based on eligibility criteria. Inclusion criteria was outlined as being at least 18-years-old with a life expectancy of at least 3 months and history of relapsing CDI despite at least one course of standard antibiotic therapy (i.e., vancomycin 125 mg four times daily for at least 10 days or metronidazole 500 mg three times daily for at least 10 days.) *C. difficile* infection was defined as 3 or more loose or watery stools per day for at least 2 days, or 8 or more loose stools in 48 hours, as well as a positive *C. difficile* toxin in stool. Criteria for exclusion included compromised immunity (i.e., recent chemotherapy, HIV infected with CD4 count less than 240, chronic use of prednisone in quantities greater than or equal to 60 mg per day); antibiotic use other than for CDI; current pregnancy; requirement of vasopressors; or admission to an ICU.²¹

Randomization was achieved by using an automated biased coin minimization. There was neither blinding nor concealment of allocation per the study design. Patients were initially stratified on whether they would be inpatient or outpatient and by the number of recurrent infections at the start of the trial. Of the 43 total subjects at the time of randomization, 17 were assigned to receive the donor feces infusion, 13 were assigned to receive vancomycin only, and 13 were assigned to receive vancomycin plus bowel lavage.²¹

Patients in the first treatment group received 4 days of vancomycin (500 mg four times daily), followed by bowel lavage using macrogol solution on the last day of
vancomycin treatment. The following day, they received an infusion through nasogastric tube (NGT) administration with a mean of 141+/−71 g of fresh donor feces. Exact methods for monitoring safety, quality, and preparation of donor feces infusion was outlined in the article but will not be discussed in this review. Patients in this treatment group were given a second donor feces infusion if they developed a recurrent *C. difficile* infection. Patients in the second treatment group received vancomycin 500 mg four times daily for 14 days. Patients in the third treatment group received the same vancomycin regimen as the second group, but also received a bowel lavage with macrogol solution on day 4 or 5 of the regimen. Patients with continued *C. difficile* in the antibiotic control groups were offered donor feces infusion off protocol. Results were compiled using stool diaries kept by the patients and study follow up was concluded 10 weeks after administration of treatment.

The primary outcome of the study was cure of CDI without relapse within 10 weeks of treatment administration. Secondary outcome was cure of CDI without relapse after 5 weeks. Cure was defined as absence of diarrhea and three consecutive negative stool tests for *C. difficile* toxin. Relapse was defined as presence of diarrhea with positive stool test for *C. difficile* toxin. The study was terminated early by the data and safety monitoring board due to the unexpected low rates of cure and increased relapse in both vancomycin groups. Of 43 participants initially randomized into study arms, 41 patients completed the study protocol—one lost from the infusion group and one from the vancomycin-only group.

Cure of CDI without relapse occurred in 13 (81%) of the 16 patients in the donor feces group after the first treatment. After a subsequent treatment with a different donor feces sample, another 2 patients were cured, which gave an overall resolution of infection
in 15 of 16 patients (94%) in the group receiving the donor feces infusion. Cure in the vancomycin-only group occurred in 4 of 13 patients (31%, P<0.001) with relapse in 8 of 13 patients (62%). In the group receiving vancomycin plus bowel lavage, 3 of 13 patients (23%, P<0.001) were cured with relapse in 7 of 13 (54%). The main adverse events that occurred in the donor-feces infusion group included diarrhea (94%), cramping (31%) and belching (19%)—all of which subsided within 3 hours of administration. Three patients in this group (19%) reported constipation during follow up.21

The diversity of fecal microbiota of the participants receiving donor feces infusion was assessed before and after treatment using The Simpson’s Reciprocal Index of diversity. Prior to infusion, the diversity was low across this study arm, but it increased a three-fold average to the same level of diversity as the donors within 2 weeks of infusion. It was also shown that this increased level of diversity remained consistent through follow up. Overall, the authors of this randomized, controlled trial conclude that infusion of donor feces has a superior treatment outcome when compared to vancomycin in patients with recurrent, refractory *C. difficile* infection—likely due to improvement in microbial diversity.21

**The Youngster et al Study**

This randomized, controlled trial22 adds important, supported protocol for preferred administration and cure of relapsing *Clostridium difficile* infection using FMT. The study was conducted at Massachusetts General Hospital between the dates of December 2012 and May 2013. Primary outcome of interest was resolution of diarrhea (<3 bowel movements per 24 hours) and cure of CDI while off antibiotics, without relapse for 8 weeks after
treatment. Secondary endpoints included subjective improvement in well-being by the participants and any adverse events that occurred with treatment.22

After assessing 37 patients for study eligibility, a total of 20 patients were included in the study. Participants between the ages of 7 and 90 were included if they had relapsing (at least 3 episodes of CDI with vancomycin and/or other alternative antibiotic taper) or refractory (at least 2 episode of CDI resulting in hospitalization and significant morbidity) C. difficile infection. Patients were excluded if there was an anatomic contraindication to NGT or colonoscopy procedure; recurrent aspirations or delayed gastric emptying syndrome; immunosuppression (defined fully in article); pregnancy; more than 40 mg of oral prednisone daily; history of significant allergies to food.22

Patients were assigned to treatment arms based on a computer-generated randomization in blocks of 4. There was no blinding or allocation concealment per study design. All participants discontinued any antibiotics at least 48 hours prior to treatment administration. Donor feces was prepared fresh and suspended with saline and 10% glycerol prior to being frozen for use as study inoculum. Complete specifics of screening, obtaining, and preparing donor fecal inoculum were detailed in the article and will not be reviewed here.22

The first treatment arm received FMT via NGT. They were given up to 20 mg of omeprazole 48 hours before the procedure and were given a total of 90 cc of the fecal inoculum for the procedure itself. The second treatment arm received FMT via endoscopic insertion into the right colon. This group underwent bowel preparation with polyethylene glycol prior to the procedure. A total of 90 cc of fecal inoculum was diluted to 160 cc for
pediatric patients and 250 cc for adults. Participants were instructed to retain the inoculum for as long as possible and were given one dose of loperamide to facilitate this instruction. Patients in both groups who showed no improvement after the first treatment were offered a second treatment by their preferred route of administration.22

Patients were followed for a total of 6 months after treatment administration with questionnaires reporting their stool frequency and consistency, their overall well-being, and any adverse events. After the first donor feces treatment, 14 of the 20 participants were cured: 6 in the NGT group and 8 in the colonoscopy group. Of the 6 patients who continued to have symptoms after the first treatment, 5 chose to get a second treatment with the route of their choosing. All 5 chose to get their second treatment via NGT and 4 of the 5 were subsequently cured. This resulted in an overall 90% cure rate (80% in the NGT group and 100% in the initial colonoscopy group) without relapse after receiving FMT administration with donor feces for recurrent or refractory CDI.22

Secondary outcomes measuring subjective improvement in well-being was assessed with a standardized questionnaire with ratings from 1-10, with 10 being “your best recent health baseline.” Patients in the NGT group had a median score of 4 prior to FMT administration, which increased to a score of 7 at the 8-week follow up point. Similarly, the colonoscopy group had a median score of 5 prior to FMT administration, which increased to a score of 8 at the 8-week follow up point.22

Adverse events related to treatment administration included mild abdominal discomfort and bloating in 4 patients (20%), but there was no delineation as to the treatment route that these patients were assigned. They did report that one child in the
colonoscopy group had a fever of 38.8 degrees on day 2 after treatment, but it was transient and resolved spontaneously. Other adverse events occurred but were not associated with donor feces transplant. These included 2 deaths from unrelated health conditions, 1 cancer diagnosis and 1 hospitalization for Fournier gangrene.\textsuperscript{22}

Lastly, fecal microbiota from recipients was compared to that of donors at 44 different time points after FMT administration. Though the recipients had consistently low microbiota diversity at the prior to treatment, the diversity after FMT increased to a level comparable to that of the donor feces. As it showed in the trial’s chosen Shannon diversity index, the route of administration (NGT vs. colonoscopy) to increase native microbiota resulted in a negligible difference. Overall, the authors of this randomized, controlled trial\textsuperscript{22} conclude that the efficacy of FMT by route of NGT to treat recurrent CDI is comparable to colonoscopic infusion but with less associated risks.\textsuperscript{22}

**DISCUSSION**

Fecal Microbiota Transplant using donor feces has been proven effective in producing cure of refractory CDI across several case studies and case reports.\textsuperscript{17} However, the existing variability in these published results with regard to patient and donor populations, protocol for donor feces inoculum preparation, and route of administration leave many questions for clinicians and researchers. This is why the two recently published RCTs discussed in this review are an important step in researching the novel, functional approach to *Clostridium difficile* infection management that FMT provides.
Outcomes

The results from both the van Nood et al study\textsuperscript{21} and the Youngster et al study\textsuperscript{22} demonstrate the positive outcomes of treating recurrent, refractory CDI with FMT. The van Nood et al study\textsuperscript{21} showed cure of recurrent CDI in 13 of 16 patients (81%) after initial donor feces infusion and an overall cure in 15 of 16 patients (94%) after re-treatment with FMT for refractory CDI. This was a much more favorable response rate when compared to both vancomycin alone (cure in 4 of 13 patients—31%) and vancomycin plus bowel lavage (cure in 3 of 13 patients—23%). The relative risk (RR) of treatment with FMT versus vancomycin alone was approximately 3, which means that there was a three-fold increase in rate of cure without relapse at 10 weeks post-treatment with FMT compared to vancomycin. Similarly, the Youngster et al study\textsuperscript{22} showed cure in 14 of 20 patients (70%) after initial FMT—using either NGT or colonoscopy—and cure in 18 of 20 patients (90%) after second infusion. In fact, the success of FMT compared to both control arms in the van Nood et al study\textsuperscript{21} led to early termination and closed enrollment after only 43 of the planned 120 patients completed the study. Though these two RCTs\textsuperscript{21,22} had small sample sizes, the results provide depth and consistency to the meta-analysis of case studies and reports demonstrating resolution of recurrent CDI in 92% of cases.\textsuperscript{17}

Not only was the overall efficacy of FMT studied, but also the important comparison of effective and preferred route of administration of FMT—NGT or colonoscopy.\textsuperscript{22} It was demonstrated that both routes were comparably effective, especially when taking into consideration that one patient in the NGT group refused to undergo subsequent treatment after initial FMT treatment failure. It is of interest that the other 5 patients without cure
after first FMT administration in the Youngster et al study\textsuperscript{22} chose (per study protocol) to receive their second treatment via NGT administration. Additionally, no complications of vomiting or aspiration occurred with this upper GI route. Therefore, NGT proves to be the safer, comparably effective, and preferred route of FMT administration when compared to colonoscopy. This finding will save patients from unnecessary sedation and undesirable bowel prep.\textsuperscript{22}

Secondary outcomes observed include increased subjective well-being by the participants in both FMT treatment arms of the Youngster et al study\textsuperscript{22} and common, yet mild and transient, adverse gastrointestinal events in both studies.\textsuperscript{21,22} These adverse events reported do not outweigh the benefits of considering donor feces infusion for patients with recurrent or refractory CDI who fit the eligibility criteria of these RCT study participants.\textsuperscript{21,22} Though bacterial diversity was not an explicit outcome of interest in either study, both studies did include this assessment in their study design and research results. Using a diversity index calculator, both studies showed that study recipients of donor feces had decreased fecal bacterial diversity prior to FMT and had markedly increased levels comparable to donors immediately after FMT. Of great importance is that these levels had sustained elevation even two weeks after treatment. This finding adds additional evidence to the physiologic basis supporting FMT that assumes the donor bacteria occupies niches in the gut, which leads to restoration of the structure and function of the gut microbiome as a host defense.\textsuperscript{21,22,23}
Limitations

Though the resultant evidence from these two trials\textsuperscript{21,22} is promising, it is not without both clinical and logistical flaws. The first thing that the clinician needs to consider when assessing FMT for clinical use is the fact that these two RCTs had a narrow study population that excluded groups most likely to have severe CDI: immunodeficient patients, ICU patients, and patients requiring concurrent antibiotics for reasons other than CDI\textsuperscript{21,22}. The greatest incidence of CDI occurs in patients 65 years of age or older\textsuperscript{2,4}, but other known risk factors include severity of comorbidities, previous gastrointestinal surgery, antacid treatment, use of electronic rectal thermometers, and enteral tube feeding—all extremely prevalent characteristics across patient populations\textsuperscript{1}. Taking into consideration the excluded populations, in addition to patients with any of the above risk factors, the risk-benefit assessment could be much different. Therefore, adapting FMT as a treatment option given the current research must be at the discretion of individual providers.

Another factor to consider is that patients included in the van Nood et al study\textsuperscript{21} had an average of 2-3 relapses of CDI with prior antibiotic treatment at study initiation. Therefore, it is plausible to assume that the CDI in the van Nood et al study\textsuperscript{21} may be resistant to repeated vancomycin therapy, which led to decreased treatment effects. This demonstrated lack of cure with repeated antibiotic therapy should make clinicians more willing to consider treatment with FMT after a second or third relapse of refractory CDI\textsuperscript{21}.

A GRADE quality assessment was performed in this systematic review to analyze limitations and applicability of the studies\textsuperscript{20}. (See Table I.) The major limitations that led to quality downgrades were no blinding or allocation concealment in either study, as well as
small sample sizes. There was also no control group in the Youngster et al study. Study limitations downgraded these RCTs to Low. However, the studies were then upgraded in quality by one level based on large RR values for the following outcomes: 1) Cure of CDI without relapse within 8-10 weeks of initial therapy and 2) Relapse within 5 weeks of initial therapy. Improvement in subjective well-being, as studied by Youngster et al, did show improvement across study arms and is a patient-important outcome to consider. Adverse GI symptoms (though mild and short-lived) were common in both studies, but sample size limited the quality of evidence of this outcome. In the end, the GRADE assessment for the critical outcomes of interest in this systematic review resulted in overall Moderate quality.

**Further Research**

This area of research is already quickly emerging and several additional trials are underway to further validate and standardize FMT as a treatment for *C. difficile* infection. It will be important that this research include RCTs with better study design quality—including larger sample sizes, set control groups, and proper blinding and allocation concealment. There should be emphasis placed on protocol for donor feces inoculum preparation, as well as cost-effective and efficient solutions for procuring donor feces. The overall costs associated with mainstream FMT should be included in further research, but studies must compare it to the current costs of CDI management (estimated at an annual $3.2 billion dollars nationally as reported in 2005 US dollars). For FMT to be a viable treatment option adopted in clinics it need not only be proven safe and effective, but also easily accessible and aesthetically tolerable to patients.
CONCLUSION

Fecal microbiota transplant proves to be a groundbreaking treatment option for the growing problems associated with recurrent or relapsing *C. difficile* infection refractory to initial antibiotic therapy. It improves patient-important outcomes including cure of CDI without relapse at 8-10 weeks after treatment, subjective improvement in well-being, and increased fecal bacterial diversity. These results were obtained with an acceptable level of adverse events due to FMT. Furthermore, it appears that NGT offers an accessible, effective, and patient-preferred route of administration at this time. These practices are both safe and effective for certain patient populations that must be assessed individually by clinicians.

These findings are of vital significance in the current climate of newer, more virulent, antibiotic-resistant strains of *C. difficile* that are at the forefront of the disease progression. Though RCTs are just starting to emerge on the subject, there is enough quality evidence published that CDI treatment guidelines\(^{14,24}\) are suggesting that clinicians consider FMT for patients with recurrent CDI based on the likelihood that the native gut microbiome is disrupted. Clinicians must also accept their role in *Clostridium difficile* disease prevention by implementing better practices of prescribing antibiotics. This should include restriction of unnecessary antibiotic prescriptions, decreased frequency and duration of prescriptions, and more targeted antimicrobials to local epidemiology. Though fecal therapy for similar colonic diseases is over 50 years old, new light on the use of FMT will likely facilitate improved CDI management by clinicians for decreased disease morbidity and mortality.
REFERENCES


TABLE I. GRADE QUALITY ASSESSMENT OF STUDIES

<table>
<thead>
<tr>
<th>QUALITY ASSESSMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Downgrade Criteria</td>
</tr>
<tr>
<td>No. of Studies</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Cure of CDI without relapse within 8-10 weeks of initial therapy</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>Relapse within 5 weeks of initial therapy</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>Presence of adverse events</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>Improvement in subjective well-being</td>
</tr>
<tr>
<td>1</td>
</tr>
</tbody>
</table>


\(^a\) No blinding in either study\(^{21}\)\(^{22}\)
\(^b\) No allocation concealment in either study\(^{21}\)\(^{22}\) due to trial procedures
\(^c\) No control group by design in Youngster et al study\(^{22}\)
\(^d\) The van Nood et al study\(^{21}\) was stopped early because of large magnitude of treatment effects noted.
\(^e\) There were small sample sizes in both studies,\(^{21}\)\(^{22}\) however there were large magnitude of treatment effects noted which maintained precision. The adverse events were a secondary outcome and require larger trials.

\(^f\) Upgraded one level due to RR > 2